Cloherty and Stark's Manual of Neonatal Care

South Asian Edition

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Ann R. Stark

SAE Editor
Naveen Jain

Adapted for Local Practices, Conditions, and Therapeutics

Wolters Kluwer

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Dedication

To the former editor and inspiration for the manual John P. Cloherty,
to my teachers, to my students, to my family,
and to the many babies and parents
we have cared for

Preface to the International Edition

This edition of the *Manual of Neonatal Care* has been completely updated and extensively revised to reflect the changes in fetal, perinatal, and neonatal care that have occurred since the seventh edition. In addition, we welcome Camilia R. Martin from Harvard as a new editor and collaborator.

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 added a section of key points to each chapter.

We acknowledge the efforts of many individuals to advance the care of newborns and recognize, in particular, our teachers, colleagues, and trainees at Harvard, where the editors all trained in newborn medicine and practiced in the neonatal intensive care units (NICUs). We are indebted to Clement Smith and Nicholas M. Nelson for their insights into newborn physiology and to Stewart Clifford, William D. Cochran, John Hubbell, and Manning Sears for their contributions to the care of infants at the Boston Lying-In Hospital and all the former and current leaders of the Newborn Medicine Program at Harvard.

This would have been an impossible task without the administrative assistance of Ashley Park. We also thank Ashley Fisher of Wolters Kluwer for her invaluable help and patience.

We dedicate this book to Dr. Mary Ellen Avery for her contributions to the care of infants all over the world and to the personal support and advice she has provided to so many, including the editors. We also dedicate this book to our founding editor, Dr. John P. Cloherty, whose collaboration with current editor Dr. Ann R. Stark led to the first edition more than three decades ago, and is acknowledged in the revised 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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Preface to the South Asian Edition

Cloherty and Stark's Manual of Neonatal Care has been my first and best teacher in neonatology from way back in 1996, when I joined my pediatrics training. Cloherty has been the bedside guide for neonatal training across India and am sure it is the same for most of the students and practicing doctors across the world.

It is a proud privilege to contribute to the South Asian edition of this book. We have attempted to make this edition simple and enjoyable for students and practicing pediatricians of our region without changing the spirit and content of the great book that has grown in respect over the decades. One of the most important need for an Asian adaptation is the major difference in resources and trained manpower available for sick newborns. There are ethnic differences in a few conditions especially infections, fetal growth restriction, neonatal jaundice, and many more.

India and South Asia have grown as a neonatal power in the last decade. We have seen an exponential increase in trained neonatal specialists and neonatal nurses. They have improved care of normal and sick newborns through evidence-based practices. Availability of infrastructure, equipment, easy access to knowledge through internet, and growing awareness of quality and safety in health care has improved intact survival of extreme preterm and sick babies. As an editor, with the help of these neonatal specialists and nurses in Asia and across the world, I have attempted to showcase the scientific prowess and stature of Asian region, especially India. Asia-specific data and publications have been included, wherever available. Guidelines for practice have been adapted, understanding well the significant differences in processes within India (and Asia) at various levels of health care.

The popularity of the manual is testimony to the untiring work of the editors and authors of the previous editions.

The opportunity to update and adapt the best neonatal care manual to region-specific needs was an immense responsibility, yet not too difficult. I had the help from almost 80 experts and a similar number of young neonatologists from India and abroad who have worked for a large part of their neonatal practice in Asian countries. Some of them are now part of most reputed academic organizations of the world. Many of the authors are busy clinicians and distinguished academicians rolled into one, thus making the manual a true bedside companion.

Care of a newborn starts *in-utero*. Fetal well-being assessment has seen significant changes to less invasive and more accurate methods of evaluation. Restricted use of oxygen, delivery room CPAP, change in management of meconium passage *in-utero*, thermoregulation in extreme preterm, delayed cord clamping, and therapeutic hypothermia have been updated in the Resuscitation chapter. Care of extremely preterm baby, development supportive care, discharge planning, follow up, and bronchopulmonary dysplasia have evolved into a new science altogether in the last few years. These topics have been appropriately revised in various chapters in the book.

Infections and antibiotic use distinguish tropical region from the rest of the world. Frequent infections in Asia include gram negative microbes in contrast to GBS, these have been discussed in detail, and a new chapter on antimicrobials in NICU has been included.

Advances in technology have improved outcomes of ventilation, PPHN, congenital heart disease, shock, and genetic diagnosis. These advances have been included in simple and easy to understand language.

The COVID-19 pandemic has changed almost everything we considered as normal starting from resuscitation in labor room to understanding of grave impact of viral infections. We have attempted to include as much knowledge as on date, although enough is not known and we are still battling the pandemic.

Early work of many pioneers has brought neonatology to its present level, but changing concepts necessitated deleting some of the older tables, facts, and guidelines. Every chapter has

been updated and adapted to Asian context. We hope the this edition will justify the efforts of the publishers to meet the growing demand of a regional neonatal manual of highest standards. This edition is not just an Asian adaptation, it is a completely updated manual. We have made best efforts to update diagnostics, therapeutics, and knowledge of disease processes.

Naveen Jain, DM

Acknowledgments

My thoughts of gratitude begin with my late father, Mr Anand Prakash, who despite his humble beginning, rose to a distinguished aerospace scientist for Indian Space Research Organization. He inspired me from early school years, by his perseverance and untiring pursuit, to understand the subject before memorizing it. My mother Sudha Jain, although an unassuming home maker, has shaped me to what I am today. My wife Neetu Gupta has been an honest critic and true life-partner. My children Muskan and Naman make life and work a song.

It would be impossible for me to list all the teachers who mentored me, but the years of training in Government Medical College, Trivandrum (for MBBS and MD Pediatrics) and PGIMER Chandigarh for Neonatology were polished by the safety and quality work culture of Kerala Institute of Medical Sciences (KIMS Health), where I practice and teach neonatology.

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My most sincere gratitude is to my colleagues and students who are also my dearest friends and extended family who taught me neonatology and lessons of life over the two decades.

Families who submitted their dearest babies to our care, bestowed faith in us have been the reason for improving my understanding of neonatal science.

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Contents

1 Fetal Well-Being Assessment and Prenatal Diagnosis

Stephanie Dukhovny, Louise E. Wilkins-Haug

KEY POINTS

- Prenatal screening for aneuploidy must be offered, after appropriate counseling, to all pregnant women.
- Fetal crown–rump length (measured in the first trimester) is the most accurate estimate of the gestational age.
- First trimester screening for aneuploidy includes a combination of maternal age, pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG), and nuchal translucency (NT).
- Second trimester screening for aneuploidy includes a combination of maternal serum α-fetoprotein (MSAFP), total or free β-hCG, unconjugated estriol (uE3), and inhibin A (quad test); it is less sensitive than first trimester screening.
- Integrated screening increases the detection rate of aneuploidy (trisomy 21) and decreases false-positive rates.
- Prenatal cell free DNA screening (non-invasive prenatal test) is recommended for women at a high risk for aneuploidy.
- Ultrasound screening for anomalies is a non-invasive, cost effective method and is available even in resource-limited settings.
- Diagnosis of aneuploidy can be confirmed by chorionic villus sampling.
- Amniocentesis is usually performed at 16 to 20 weeks of gestation—genetic, biochemical, and microbiological studies can be done.
- Fetal growth restriction (FGR) may be due to placental insufficiency or innate fetal causes.
- Early onset FGR is associated with severe placental insufficiency and risk of preeclampsia.
- Late-onset FGR is commoner and is associated with the risk of intrapartum fetal distress.
- Advances in fetal well-being assessment have significantly improved the management of high-risk pregnancies; at the same time, improper interpretation can result in unnecessary interventions.
- Fetal well-being in the antenatal period can be measured by umbilical artery Doppler, biophysical profile, and nonstress test, and in the intrapartum period by fetal heart rate monitoring and fetal blood sampling.

Perinatology and neonatology are branches of medicine which deal with early diagnosis of fetal and neonatal diseases and their appropriate management. These are discussed in detail in the 70 chapters of this book. Most often the treating physician, parents, and family

members are concerned mainly with physical aspects of fetal development *in utero*. But they forget that baby does not develop merely in terms of somatic growth. He/she develops holistically and undergoes a very rapid brain development during the whole pregnancy, and this continues for the first 3 years after birth.

Investing in early childhood development is good for everyone: communities, parents, and most importantly for children themselves. One must start from the first days of life and spend quality time with the baby (smiling, touching, talking, storytelling, music, reading books, and engaging in play). These build neural connections (synapses) that strengthen the baby's brain. ***Ideally positive parenting should begin even before birth.***

The development of the brain is sensitive to prenatal experiences. The epigenetic modulation may be as equally important as the genetic and biologic endowment. Scientists have employed various methods to prove the unimaginable learning abilities and awareness of prenates and their influences on mental development. Even an extreme preterm baby has abilities to perceive all the senses and have organized responses, either self-regulatory (cope with stress) or stress response. In fact, this knowledge has been the driving force behind *developmentally supportive care* in neonatal intensive care units. The baby in-utero begins to experience the world through touch as early as 8 weeks. Later in pregnancy, the fetus sequentially develops the other senses - taste, sound, smell, and sight. It is these senses that enable the baby to acquire information and learn from womb experiences. Developmentally supportive care of the premature and sick babies (family-centered care) is already central to neonatal intensive care units and surely must be extended to positive health of all unborn babies.

There is an ongoing debate regarding the extent to which these memories have impact on their mental function and personality. Proof of memory comes from tests that evaluate habituation. Habituation is the modification of responses to repeated stimuli. Vibro-acoustic habituation has been demonstrated as early as 22 weeks of gestation. Fetuses older than 34 weeks could reproduce learnt content after a period of 4 weeks. Fetuses remembered musical patterns and showed specific changes in heart rate frequency and motor activity in well-designed experiments. Although the process of learning is life long, the experiences in the earliest stages of brain development may create blueprints for future behaviors and abilities to adapt.

The nurturing framework should help parents-to-be and caregivers to ensure that every baby gets the best start in life. This "philosophical" start to "physiological" health may appear out of context to a manual of neonatal care. But one must remember that 'normal development' of the 'normal baby' (without diseases) is a science far more essential as compared to only management of medical conditions like gestational diabetes, hypertension, and aneuploidy.

I. GESTATIONAL AGE (GA) ASSESSMENT.

GA assessment is important to both the obstetrician and the neonatologist and must be made with a reasonable degree of precision. Elective obstetric interventions such as chorionic villus sampling (CVS) and amniocentesis must be timed accurately. When premature delivery is inevitable, GA is important with regard to prognosis and the initial neonatal treatment plan. Wrong dates and inaccurate assessment of GA can increase iatrogenic interventions.

The clinical estimate of GA is best made on the basis of the first day of the last menstrual period (LMP). LMP dating has accuracy in women with regular 28-day cycles. If there is a history of irregular cycles, pregnancy dating should be done by

early sonogram. Most of the clinical methods of calculating GA are of limited accuracy—first maternal perception of fetal movement, first auscultation of fetal heart sounds, and maternal physical examination (symphysiofundal height [SFH]). As per the American College of Obstetricians and Gynecologists (ACOG), ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm the GA. *Fetal crown–rump length (CRL) is the most accurate assessment of GA.* At <9 weeks of gestation, if the CRL and LMP dates differ by >5 days, then ultrasound is considered as the better estimate of GA. After 14 weeks, *measurement of the head circumference (HC) and femur length (FL) is used to estimate GA*. Additional fetal measurements, including biparietal diameter (BPD), abdominal circumference (AC), fetal long bones (i.e., femur, humerus, ulna, and tibia), and transverse cerebellar diameter, may also assist in the estimation of fetal GA. Owing to normal biological variability, the accuracy of GA estimated by biometry decreases with increasing GA.

II. PRENATAL DIAGNOSIS OF ANEUPLOIDIES. Universal prenatal screening for aneuploidies should be offered to all women, irrespective of their risk status and age, as majority of the chromosomal anomalies (especially trisomy 21) are seen in women younger than 35 years.

Two types of tests are available: screening and diagnostic tests.

A. Screening tests. These include ***serum tests in the mother, imaging, and cell-free fetal DNA in the maternal blood.***

1. Serum tests for aneuploidy. We will discuss the tests based on the period of pregnancy at which they are offered.

a. First trimester screening

b. Second trimester screening (STS) for aneuploidy

c. Combined first and second trimester screening for aneuploidy

a. First trimester screening (FTS). First trimester aneuploidy screening is performed between 11 and 13^{+6} weeks of pregnancy. It is done using a combination of maternal age, pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG), and nuchal translucency (NT) on ultrasound. Detection rates of trisomy 21 are around 90% to 94% with low false positives of only 3% to 5% (Table 1.1).

Maternal levels of two analytes, PAPP-A and β-hCG (either free or total), are altered in pregnancies with an aneuploid conception, i.e., trisomies 21, 13, and 18.

Besides aneuploidy, Besides aneuploidy, decrease levels of PAPP-A (<0.415 MOM) may be associated with fetal growth restriction (FGR), preterm labor, gestational hypertension, preeclampsia (PE), and ectopic pregnancy. PAPP-A is higher in twin pregnancies. Hence, abnormal PAPP-A is not specific to aneuploidy. Ideal timing for testing PAPP-A is 9 to 10 weeks.

Ultrasonographic assessment of the fluid collected at the nape of the fetal neck behind the cervical soft tissue, NT, is a sensitive marker for aneuploidy. It should be measured for a CRL between 45 and 84 mm. With

Table 1.1. Characteristics of Serum Screening Options for Aneuploidy

Screening Test	Detection Rate for Trisomy 21 (%)	Screen-Positive Rate (%)	Analytes and/or Measurements Obtained
First trimester screening	90	5	Nuchal translucency PAPP-A hCG (maternal age)
Quad screen	81	5	hCG AFP uE3 Inhibin A
Integrated screening	96	5	First trimester screen, then quad screen
Sequential screening			
Stepwise	95	5	First trimester screen, then quad screen for all
Contingent	88–94	5	First trimester screen, then quad screen only for intermediate/high risk
Cell-free fetal DNA	99	0.5	Molecular evaluation of cell-free fetal DNA within maternal serum

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein-A; uE3, unconjugated estriol.
Adapted from Committee on Practice Bulletins—Obstetrics, Committee on Genetics, Society for Maternal–Fetal Medicine. Practice bulletin no. 163: screening for fetal aneuploidy. *Obstet Gynecol* 2016;127(5):e123–e137.

optimization of image and quality control, studies indicate a 70% to 80% detection of aneuploidy in pregnancies with an increased NT. NT above the 95th centile for a particular CRL (2.1 mm for a CRL of 45 mm, and 2.7 mm for a CRL of 84 mm) is associated with an increased risk of aneuploidy and should be evaluated further. In addition to aneuploidy, some fetuses with structural abnormalities such as cardiac defects and lymphatic defects will also have an abnormal NT. Risk of other anomalies in the fetus with an increased NT includes single-gene defects, central nervous system (CNS) defects, and skeletal and abdominal wall defects. *Ultrasound for NT is best performed at 11 to 13^{+6} weeks.*

Other ultrasound findings in the first trimester fetus that may be associated with trisomy include absent or hypoplastic nasal bone, abnormal ductus venosus (DV) blood flow, and triscuspid regurgitation.

A combined screening and diagnostic test—one-stop clinic for assessment of risk (OSCAR)—is practiced in centers where biochemistry is performed by 11 weeks and scan at 11 to 12 weeks and risk assessed after scan. CVS is offered on the same day if risk is more than 1 in 100.

b. Second trimester screening (STS) for aneuploidy

i. Quadruple panel (quad test). Fetal chromosomal abnormalities are associated with altered values of maternal serum α-fetoprotein (MSAFP), hCG (free β or total), unconjugated estriol (uE3), and inhibin A. In a pregnancy (fetus) with trisomy 21, hCG (free β or total) and inhibin A levels are high, and MSAFP and uE3 levels are low. Trisomy 18 is typically signaled by low levels of all serum biochemical markers. A serum panel in combination with maternal age can estimate the risk of trisomy 21 for an individual woman with modest accuracy. Only 80% of the fetuses with trisomy 21 will have a "positive" quadruple screen (Table 1.1). *As this screen has a lower sensitivity than FTS, STS is not repeated as a second screen after FTS. A quad test is offered only to mothers who did not have FTS for aneuploidies.*

ii. MSAFP is best measured between 15 and 22 weeks. α-Fetoprotein (AFP) is secreted by the fetus and is present in the amniotic fluid and maternal serum. MSAFP elevated above 2.5 multiples of median (MOM) for the GA occurs in 70% to 85% of fetuses with open spina bifida and 95% of fetuses with anencephaly. High MSAFP is not specific for aneuploidy (Table 1.2); in half of the women with elevated levels, ultrasonic examination reveals a cause other than an abnormal fetus,

Table 1.2. Conditions Associated with Abnormal MSAFP Levels

Conditions with Elevated MSAFP Levels	Conditions with Reduced MSAFP Levels
Underestimated gestational age	Overestimated gestational age
Maternal low BMI	Trisomies
Multiple gestation	Fetal wastage
Open neural tube defects	Maternal diabetes
Open abdominal wall defects	Maternal obesity
Esophageal/intestinal obstruction	
Renal conditions such as renal agenesis/urinary tract dilatation/congenital nephrosis	
Cloacal exstrophy	
Skin conditions such as aplasia cutis	
Fetomaternal hemorrhage	
Sacrococcygeal teratoma	
Osteogenesis imperfecta	
Placental chorioangioma/accreta spectrum/abruption	
Maternal hepatic and ovarian tumors	

BMI, body mass index; MSAFP, maternal serum α-fetoprotein.

most commonly an error in GA estimate. Ultrasonography intracranial signs such as changes in the head shape (lemon sign) or deformation of the cerebellum (banana sign) point toward neural tube defect (NTD).

c. **Combined first and second trimester screening for aneuploidy.** Combined screening aims at increasing the sensitivity of screening for trisomy 21 (to miss no baby with Down's syndrome) while retaining a low screen-positive rate (unnecessary invasive tests). There are two approaches; they differ primarily in whether they disclose the first trimester results immediately after the test or disclose only after both first and second trimester testing are completed.

   i. **Integrated screening.** It involves a first trimester ultrasound and maternal serum screening in both the first and second trimesters. This approach achieves the highest detection rate of trisomy 21 (97%) at a low screen-positive rate (2%). This is a nondisclosure approach; the results of FTS are released only after the STS reports are available. Family anxiety is high for 3 to 4 weeks, while they are waiting.

   ii. **Sequential screening.** Results indicating a high risk of trisomy 21 in the first trimester are declared, but the entire population is screened in the second trimester (stepwise sequential). In another approach (contingent approach), low-risk patients do not return for further screening, as their risk of a fetus with Down's syndrome is low; only high-risk patients are further tested. 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%)

2. **Imaging for prenatal diagnosis**

   a. **Ultrasound in prenatal diagnosis.** Two-dimensional ultrasound allows direct imaging of fetal abnormalities. It is noninvasive, economical, and available even in resource-limited settings.

   Mid-trimester (targeted imaging for fetal anomalies (TIFFA)] scan, between 18 and 22 weeks, has traditionally enabled imaging to screen and detect fetal structural anomalies. With the advent of transabdominal and transvaginal high-frequency transducers, sonologists are now able to image the fetus in greater detail at all gestations. Some anomalies are detectable in the first trimester, e.g., anencephaly, holoprosencephaly, and conjoined twins. However, most anomalies (e.g., fetal heart anomalies) remain too subtle to be detected that early and require second trimester scanning. The introduction of color Doppler technology for fetal imaging has also improved the detection of fetal anomalies (fetal echocardiography). The introduction of three- and four-dimensional ultrasound has been reported to enhance the assessment of specific fetal anomalies, such as the brain, heart, face, and palate.

   Ultrasound is done in at-risk mothers, to look for anomalies, a normal ultrasound is reassuring—it decreases the a priori maternal age risk of Down's syndrome by 50% to 60%. Second trimester ultrasound following FTS for aneuploidy has likewise been shown to have value in increasing pickup rate of trisomy 21.

   Soft markers (Table 1.3) are sonographic findings with little or no pathological significance in isolation. They may be normal variants, with

Table 1.3. Soft markers for diagnosis of aneuploidy

Soft marker	Description	Positive Likelihood ratio	Negative Likelihood ratio	Likelihood ratio isolated marker
Ventriculomegaly	Dilatation of the lateral ventricle atrium ≥ 10 mm (Uni/ biventricular)	27.5	0.94	3.81
Thickened nuchal fold	≥ 6 mm thickness of skin and subcutaneous tissues on the posterior aspect of the fetal neck	23.3	0.8	3.79
Unossified nasal bone	Absent or Hypoplastic nasal bone i.e. nasal bone length <2.5 mm or < 0.75 MOM in the mid-sagittal section of the fetal profile	23.27	0.46	6.58
Aberrant right subclavian artery	Aberrant right subclavian artery arising most distally from the aortic arch	21.48	0.71	3.94
Echogenic bowel	Fetal bowel of similar or greater echogenicity than the surrounding bone	11.44	0.90	1.65
Pyelectaisis	Bilateral renal pelvic anteroposterior measurement in a transverse scanning plane of ≥4 mm from 16-28 Weeks and ≥7 mm from >28 Weeks	7.63	0.92	1.08
Intracardiac echogenic focus	Echogenic small spot inside the heart having brightness equivalent to that of the bone	5.83	0.80	0.95
Short humerus	Bone length <5th percentile for gestational age	4.81	0.74	0.78
Short femur	Bone length <5th percentile for gestational age	3.72	0.80	0.61

Source: Agathokleous M, Chaveeva P, Poon LCY, Kosinski P, Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2013 Mar;41(3):247–61.

no clinical importance. They are usually transient and mostly resolve with advancing gestation or after birth. But they may be markers for aneuploidy in high risk population.

Ultrasound potentially aids in taking a decision as to whether to pursue invasive testing or not.

b. Magnetic resonance imaging (MRI) in prenatal diagnosis. Ultrasonography has limitations in the detection of fetal anomaly. Image resolution may be limited by fetal positioning and movement, reduced amniotic fluid volume, maternal obesity, and the state of filling of the maternal bladder. MRI has emerged as a complementary imaging modality for assessing the fetus and is now widely available. MRI without contrast has been reported to have little or no adverse impact on the mother and fetus, although its safety in the first trimester has not been fully evaluated. Many studies have reported that fetal MRI allows more detailed observation than prenatal ultrasound and therefore provides additional information to confirm a diagnosis. There is an emerging evidence of this added benefit when assessing the fetal CNS, congenital diaphragmatic hernia, and abnormalities of the genitourinary system. It is, however, not recommended as a primary imaging modality but as an adjunct to ultrasound.

c. Fetal echocardiogram (ECHO) for prenatal diagnosis. Prenatal detection of congenital heart disease (CHD) helps in planning the place of birth (at a cardiac surgery center) and avoids transfer of an unstable newborn; these are associated with survival benefits. Initially, fetal echocardiography included only a four-chamber view (basic cardiac echocardiographic examination [BCEE]) of the heart, and then outflow tract view (OTV) and three-vessel trachea view (3VTV) were added to increase the accuracy of fetal echocardiography. Indications of fetal echocardiography could be as follows:

i. Fetal—suspected CHD on screening ultrasonography, fetal chromosomal anomaly—fetal extracardiac anatomic anomaly, fetal cardiac arrhythmia - persistent bradycardia or tachycardia, irregular rhythm, and nonimmune hydrops fetalis

ii. Maternal—maternal metabolic diseases, e.g., overt diabetes, phenylketonuria, systemic lupus erythematosus, maternal exposure to alcohol, and intake of cardiac teratogenic medications

Coarctation of aorta, small ventricular and atrial septal defects, partial anomalous pulmonary venous return, and mild aortic or pulmonary stenosis are abnormalities that may be missed by fetal echocardiography.

3. Cell-free fetal DNA screening for aneuploidy. Cell-free fetal DNA is a non-invasive prenatal test (NIPT). Newer technology has allowed analysis of cell-free fetal DNA from the maternal serum.

Cell-free fetal DNA screening for aneuploidy is not recommended in the general obstetric population and currently is *recommended only for women at a high risk for aneuploidy*—women who are >35 years old, have a history of a fetus or newborn with aneuploidy, are carriers of a balanced translocation, or have a positive traditional screening test. It is important to note that cell-free fetal DNA *targets specific aneuploidies and will miss abnormalities in other chromosomes and those with a mosaic karyotype*. NIPT allows detection of trisomies

13, 18, and 21, sex chromosomal aneuploidies, and some microdeletion syndromes. Fetal DNA detected in the maternal serum is placental in origin and is released from apoptotic trophoblasts. Circulating DNA fragments detect both maternal and placental cf DNA. The ratio of placental to total (consisting of maternal and placental) cfDNA is known as the fetal fraction, which increases with advancing pregnancy. Fetal cell fraction is a major determinant of a good NIPT—a minimum of 4.5% is needed. Testing of cfDNA is generally performed *starting from the 10th week of gestation*, since this is the time when the fetal fraction in the maternal circulation reaches the minimum amount needed for an accurate test result.

Sensitivity of cfDNA for trisomy 21 is reported at 99.3% and specificity at 99.8%. For trisomy 18, the sensitivity is 97.4% and specificity is 99.8%. Sensitivity is lower for trisomy 13 (91%) with a specificity of 99.6%.

Maternal chromosomal abnormalities or malignancy may result in nonreportable or false-positive results. Other possible sources of false-positive results include vanishing twins or confined placental mosaicism. Failed NIPT can occur in cases of maternal obesity and very early GA. Cell-free fetal DNA 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.

B. Diagnostic tests for aneuploidy. Positive screening tests for aneuploidy in the first or second trimester must be followed up by diagnostic tests, before any medical decisions are made. Diagnostic tests include ***chorion villus sampling (CVS), amniocentesis, percutaneous umbilical blood sampling (PUBS), and preimplantation genetic diagnosis (PGD)***.

When a significant malformation or a genetic disease is diagnosed prenatally, the information gives the obstetrician and pediatrician time to counsel the parents, discuss options, and establish an initial neonatal treatment plan before the infant is delivered. In some cases, treatment may be initiated *in utero*. Detailed counseling should precede any invasive procedure; it should cover the expected benefits, risks, and technical aspects of the test.

Indications for invasive prenatal diagnosis are as follows:

- Increased risk of fetal aneuploidy from a serum screening test and abnormal ultrasound findings
- Obstetric history (previous fetus or child affected by aneuploidy)
- Increased risk for a known genetic or biochemical disease of the fetus
- Family history (parental carrier of chromosomal balanced translocation or inversion, parental aneuploidy or mosaicism for aneuploidy)
- Maternal transmittable infectious disease
- Under certain circumstances, maternal request

Conception by assisted reproductive technique itself is not considered a valid indication for invasive prenatal diagnosis. However, in pregnancies conceived by intracytoplasmic sperm injection because of oligospermia, the prospective parents should be informed that there is an increased risk of chromosomal anomalies in the sperm causing infertility which may be transmitted to male offspring.

When an invasive diagnostic test is performed for a *structural abnormality* detected on ultrasound, a *chromosomal microarray* (CMA) is indicated, which will detect aneuploidy as well as smaller chromosomal deletions and duplications.

If an invasive test is performed secondary to a positive screening test for aneuploidy, either a CMA or a karyotype can be offered.

1. **Diagnostic tests - chorion villus sampling (CVS).** Performed at or after 11 weeks of gestation (till 13+6 weeks), CVS provides the earliest possible confirmation of a genetically abnormal fetus through analysis of trophoblast cells. Under ultrasonographic guidance, a sample of placental tissue is obtained through a catheter placed through either a transcervical or a transabdominal route. The possible complications of amniocentesis and CVS are similar. Technical improvements in ultrasonographic imaging and in the CVS procedure have brought the pregnancy loss rate very close to the loss rate after second-trimester amniocentesis, 0.5% to 1.0%. CVS, if performed before 10 weeks of gestation, can be associated with an increased risk of fetal limb reduction defects and oromandibular malformations.

   CVS allows for diagnostic analyses, including fluorescence *in situ* hybridization (FISH), karyotype, microarray, molecular testing, and gene sequencing. Direct preparations of rapidly dividing cytotrophoblasts can be prepared, making a full karyotype analysis available in 2 days. Even though direct preparations minimize maternal cell contamination, most centers analyze cultured trophoblast cells, before reporting, which are embryologically closer to the fetus. This procedure takes an additional 8 to 12 days.

   In approximately 2% of CVS samples, a mosaic diagnosis is made, which indicates that both karyotypically normal and abnormal cells are identified in the same sample. Because CVS-acquired cells reflect placental constitution, in these cases, amniocentesis is typically performed as a follow-up study to analyze fetal cells. Only about one-third of CVS mosaicisms are confirmed to be present in the fetus.

2. **Diagnostic study - amniocentesis.** Amniotic fluid around the fetus is aspirated through a needle guided by ultrasound. The removed amniotic fluid (~20 mL) is replaced by the fetus rapidly within 24 hours. Amniocentesis can technically be performed as early as 10 to 14 weeks of gestation, although early amniocentesis (<13 weeks) is associated with a pregnancy loss rate of 1% to 2% and an increased incidence of clubfoot. Loss of the pregnancy following an ultrasonography-guided second trimester amniocentesis (16 to 20 weeks) is lower, at 0.5% to 1.0% in most centers.

   Amniotic fluid analysis. The amniotic fluid contains desquamated cells from the fetal skin, bladder, and gastrointestinal tract. They can be used for enzymatic/biochemical, genetic, and microbiological studies.

   a. **Enzymatic/biochemical analysis of amniotic fluid.** 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. Assessment of fetal lung maturity by LS ratio (lecithin/sphingomyelin ratio) or measurement of MSAFP in the amniotic fluid for NTD or bilirubin in Rhesus D (RhD) isoimmunization is seldom done these days.

b. Genetic analysis. The choice of the genetic test to be performed on the cells obtained via amniocentesis (the same genetic tests can be performed on CVS samples) depends on the indication for testing.

- **Chromosomal analysis** (i.e., karyotype) reports are available after 7 to 14 days.
- **FISH.** Interphase *FISH* provides a limited karyotype within 24 to 48 hours; the most frequently used probes detect aneuploidy of chromosomes 13, 18, 21, X, and Y, which are the most common causes of aneuploidy. Metaphase FISH allows the identification of large chromosomal abnormalities, including deletions, duplications, and translocations, as well as smaller chromosomal microdeletions and duplications.
- **Chromosomal microarray analysis (CMA)** increases the diagnostic yield over conventional karyotyping because it can delineate microdeletions and microduplications. It has a faster turnaround time because studies can be performed directly on high-quality DNA extracted from isolated cells so time for culture is not required (results take 3 to 5 days with direct testing and 10 to 14 days when cultured cells are used).
- **Polymerase chain reaction (PCR).** DNA methodologies can be used when the gene sequence producing the disease in question is known. Disorders secondary to deletion of DNA (e.g., beta-thalassemia, Duchenne and Becker muscular dystrophy, cystic fibrosis) can be detected by the altered size of DNA fragments. Direct detection of a DNA mutation can also be accomplished by allele-specific oligonucleotide (ASO) analysis. ASO hybridization involves the placing ("spotting") of denatured PCR-amplified DNA onto a membrane and subsequent hybridization with short allele-specific, labeled probes. Under optimal hybridization and washing conditions, hybridization will occur only if the probe sequence is perfectly complementary to the single-stranded sample DNA.
- **DNA sequencing** for many genetic disorders has revealed that a multitude of different mutations within a gene can result in the same clinical disease. For example, cystic fibrosis can result from >1,000 different mutations. Therefore, for any specific disease, prenatal diagnosis by DNA testing may require parental as well as fetal DNA. Trio analysis, consisting of the proband and both biological parents, is preferred to singleton (fetus only) or duo (fetus and one parent) analysis. It consistently shows greater diagnostic yield compared with nontrio analysis. It allows for the immediate identification of *de novo* variants, determination of phase for biallelic variants, and confirmation of carrier status of both parents if a homozygous variant is detected.
- Next generation sequencing (NGS) including whole genome sequencing (WGS) or whole exome sequencing (WES) may be considered for a fetus with ultrasound anomalies when standard CMA analysis and karyotype analysis have failed to yield a definitive diagnosis. At present, there are no data supporting its clinical use for other reproductive indications such as the identification of sonographic markers suggestive of aneuploidy or a history of recurrent unexplained pregnancy loss.

3. **Diagnostic tests - percutaneous umbilical blood sampling (PUBS)** is performed under ultrasonic guidance from the second trimester until term. It 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 is associated with a 1% to 2% risk of fetal loss and 5% risk of preterm delivery.
4. **Diagnostic tests - preimplantation genetic diagnosis (PGD).** During an *in vitro* fertilization process, early in gestation (at the eight-cell stage in humans), prior to transfer, one or two cells can be removed without known harm to the embryo. PGD is useful for a wide range of autosomal recessive, dominant, and X-linked molecular diagnoses. For couples at risk, testing allows for identification of embryos that carry the disorder in question, and transfer of unaffected embryos can be planned. In women who are at risk for X-linked recessive disorders, determination of XX-containing embryos by FISH can enable transfer of only female embryos. When one member of a couple carries a balanced translocation, only those embryos that screen negative for the chromosomal abnormality in question are transferred. When more cells are needed for molecular diagnoses, biopsy on day 5 is considered. An alternative approach is analysis of the second polar body, which contains the same genetic material as the ovum. Preimplantation genetic screening (PGS) to assess preimplantation embryos for aneuploidy is not currently considered to provide reproductive advantage to women of advanced maternal age or poor reproductive histories.

Genetic counseling is a must, before any screening/diagnostic test is interpreted to a mother. Patients must ideally be referred to a genetic counselor, who is formally trained. A genetic counseling visit entails obtaining a detailed medical and family history, including the age and health status of first-degree, second-degree, and third-degree relatives. For the prenatal patient, additional information such as genetic screening results, ultrasound findings, and possible teratogenic exposures is discussed. This information allows for a targeted discussion regarding the likelihood of developing disease, testing options for the condition, the impact that an illness could have on the patient and family, and the possible interventions available to modify the disease. Ideally, antenatal counseling is provided in a nondirective manner, emphasized on counseling the patient on his or her options and the consequences of those options.

III. FETAL SIZE AND GROWTH RATE ABNORMALITIES

may have significant implications for perinatal prognosis and care (see Chapter 7). Appropriate fetal growth assessment is important in establishing a diagnosis and a perinatal treatment plan. The fetuses may be smaller that expected (growth restricted) or larger than average (macrosomia).

A. Fetal growth restriction (FGR) may be due to the following:

1. Placental insufficiency
2. Problems intrinsic to the fetus

1. **Placental insufficiency.** These are constitutionally normal fetuses whose growth is impaired. Because their risk of mortality is increased several-fold before and during labor, FGR fetuses may need preterm intervention for best survival rates.

Table 1.4. Early and Late-Onset FGR

Early FGR	Late FGR
GA <32 weeks, in absence of congenital anomalies	GA ≥32 weeks, in absence of congenital anomalies
Less common (20%–30%) of all FGR	Common (70%–80%) of all FGR
Placental insufficiency (severe) Umbilical artery Doppler abnormal High risk of PE	Placental insufficiency (mild) Umbilical artery Doppler normal Low risk of PE
Severe hypoxia Systemic cardiovascular adaptation	Mild hypoxia Central cardiovascular adaptation (cerebro-placental ratio, middle cerebral artery Doppler abnormal)
Immature fetus (higher tolerance to hypoxia)	Mature fetus (lower tolerance to hypoxia)
Longer natural history/progression in pregnancy/sequence of changes allows planning	Shorter natural history/rapid deterioration intrapartum/lack of sequence of changes posing diagnostic challenge
Higher mortality	Lower mortality (accounts for late pregnancy deaths), poor long-term outcomes

FGR, fetal growth restriction; GA, gestational age; PE, preeclampsia.
Adapted from Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016;48(3):333–339.

FGR may be classified into two phenotypes—early onset and late-onset FGR (Table 1.4).

a. The early onset FGR (less common, 20% to 30% of all fetal FGR) is associated with severe, chronic fetal hypoxia and has a high association with preeclampsia (PE); it may require very preterm delivery. The umbilical artery Doppler worsens over weeks followed by changes in DV Doppler; this progression over weeks allows planning of the timing of the delivery.

b. The late-onset FGR is far common (70% to 80% of all FGR), has mild placental insufficiency (umbilical artery Doppler may be normal), and is associated with a low risk of PE. There is a risk of intrapartum fetal distress, late pregnancy deaths, or severe neonatal acidosis. Late FGR is associated with rapid deterioration and does not have the cascade of fetal deterioration that is associated with early FGR.

2. **Problems intrinsic to the fetus** include chromosomal abnormalities (such as trisomies, microdeletions, or duplications), congenital malformations, and congenital infections (e.g., cytomegalovirus, toxoplasmosis, varicella, or rubella). Prenatal genetic assessment should be considered if there is severe FGR before 24 weeks or when structural anomalies or soft markers for aneuploidy are present. Investigation by cell-free DNA versus a karyotype/microarray or

DNA diagnostic studies is individualized to the specific findings of the case. Prior knowledge that a fetus has a malformation (e.g., anencephaly) or chromosomal 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.

Diagnosis of FGR. Clinical examination by measuring the SFH detects about two-thirds of cases and incorrectly diagnoses FGR in about 50% of cases. Ultrasonography improves the sensitivity and specificity to >80%. From the large Prospective Observational Trial to Optimize Pediatric Health Trial in Intrauterine Growth Restriction (PORTO) study, the greatest risk for morbidity/mortality was among those fetuses below the third percentile for estimated fetal weight (EFW) with abnormal umbilical Doppler perfusion and delayed serial growth trajectory.

B. Macrosomia. Macrosomic fetuses (>4,000 g) are at an increased risk for shoulder dystocia and traumatic birth injury. Conditions such as maternal diabetes, post-term pregnancy, genetic overgrowth syndromes, and maternal obesity are associated with an increased incidence of macrosomia. Fetal macrosomia can be determined clinically, by abdominal palpation using Leopold maneuvers, or by ultrasound examination; both of these two techniques appear to be equally accurate. EFW measurements are less accurate in large (macrosomic) fetuses than in normally grown fetuses, and factors such as low amniotic fluid volume, advancing GA, maternal obesity, and the position of the fetus can compound these inaccuracies. Unfortunately, efforts to use a variety of measurements and formulas have met with only modest success in predicting the condition.

IV. ASSESSMENT OF FETAL WELL-BEING.

The purpose of tests for fetal well-being is to identify fetuses at risk of intrauterine compromise or death, so that timely intervention and delivery can be planned. A sound knowledge of interpretation of the tests is necessary to prevent incorrect decision of premature delivery of healthy fetuses. Despite advances in technology, many of the tests have not significantly reduced fetal mortality or morbidity.

Indications for fetal surveillance. Pregnancies with an increased risk for stillbirth (chronic hypertension, pregestational diabetes, poorly controlled gestational diabetes, growth restriction, advanced maternal age, increased maternal body mass, or vascular disease) or new risk (decreased fetal movement, abdominal trauma, and vaginal bleeding) are candidates for fetal surveillance. Most fetal surveillance begins at 32 weeks, although in the setting of FGR, assessment prior to 32 weeks is often undertaken. The frequency of monitoring is typically weekly; in high-risk conditions or those in which the mother's condition is changing, monitoring may be required more frequently.

A. Antepartum tests mostly rely on fetal behavior and responses, which require a certain degree of fetal neurologic maturity. The following tests *are not used until the third trimester* as fetuses may not respond due to immaturity:

1. **Fetal movement monitoring** is the simplest method of fetal assessment. Mothers generally perceive fetal movements between 16 and 22 weeks of gestation. Fetuses have a sleep–wake cycle, active periods average 30 to 40 minutes. and periods of inactivity >1 hour are unusual. Longer periods of not perceiving movements should alert the physician 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 the day is chosen; fetal movements are noted with the expectation of 10 fetal movements to be felt within 2 hours. The average time to 10 movements is only 20 minutes (±18) in normal fetuses. Lack of attaining 10 movements prompts evaluation. A mother's perception of decreased fetal movement should always elicit further surveillance, although the alert has a low predictive value. Fetal movement counting represents a low-technology screening test that is applicable to all pregnancies. Although its effectiveness in improving perinatal outcomes is debatable, it can be used as a cost-effective first-line strategy. A large systematic review on fetal movement count showed no improvement in perinatal outcomes. But the Society of Obstetrics and Gynecology of Canada (SOGC) advises that women who report decreased fetal movements (<6 distinct movements within 2 hours) should have a complete evaluation of maternal and fetal status, including nonstress test (NST) and/or biophysical profile (BPP).

2. **Nonstress Test (NST)** is the most common method of antepartum fetal assessment. It is simple to perform in any setting where an electronic fetal monitor is available. NST is relatively quick, and noninvasive, with neither discomfort nor risk to the mother or fetus. It is based on the principle that fetal activity results in a reflex acceleration in the heart rate (Fig. 1.1). 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 CNS to inactivate the cardiac reflex. Testing reflects the current fetal state and cannot predict

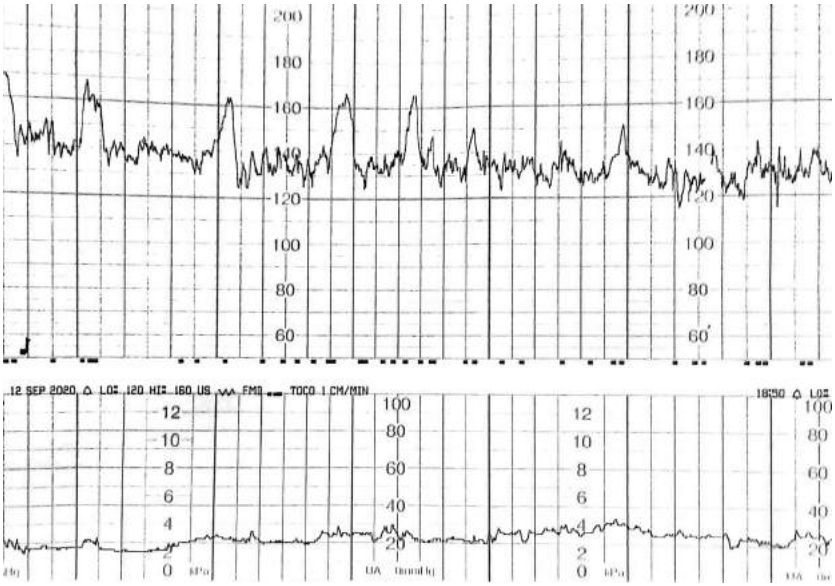


Figure 1.1. Reactive nonstress test showing accelerations occurring with fetal movement.

future events or neonatal outcome precisely. The test is performed by monitoring the fetal heart rate (FHR) either through a Doppler ultrasonographic device or through skin-surface electrodes on the maternal abdomen. The test is performed by placing two transducers on the maternal abdomen, one for recording FHR and another for recording uterine contractions. The test result may be normal, atypical, or abnormal (Table 1.5). An atypical NST requires further assessment.

Table 1.5. Normal, Atypical, and Abnormal NST

Parameter	Normal NST	Atypical NST	Abnormal NST
Baseline	110–160 bpm	■ 100–110 bpm ■ >160 bpm for <30 minutes ■ Rising baseline	■ Bradycardia <100 bpm ■ Tachycardia >160 bpm for >80 minutes ■ Erratic baseline
Variability	■ 6–25 (moderate) ■ ≤5 bpm (absent or minimal) for <40 minutes	≤5 bpm (absent or minimal) for 40–80 minutes	■ ≤5 bpm for ≥80 minutes ■ ≥25 bpm for >10 minutes ■ Sinusoidal
Accelerations			
Term fetus	≥2 accelerations with acme of ≥15 bpm lasting 15 seconds in <40 minutes of testing	≤2 accelerations with acme of ≥15 bpm lasting 15 seconds in 40–80 minutes	≤2 accelerations with acme of ≥15 bpm lasting 15 seconds in >80 minutes
Preterm fetus (<32 weeks)	≥2 accelerations with acme of ≥10 bpm lasting 10 seconds in <40 minutes of testing	≤2 accelerations of ≥10 bpm lasting 10 seconds in 40–80 minutes	≤2 accelerations of ≥10 bpm lasting 10 seconds in >80 minutes
Decelerations	None or occasional variable <30 seconds	Variable decelerations, 30- to 60-second duration	■ Variable decelerations, >60-second duration ■ Late deceleration(s)
Action	Further assessment optional, based on total clinical picture	Further assessment required	URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with ultrasound or BPP is required. Some situations will require delivery

BPP, biophysical profile; NST, nonstress test.
Adapted from Liston R, Sawchuck D, Young DJ. No. 197a—fetal health surveillance: antepartum consensus guideline. *Obstet Gynaecol Can* 2018;40(4):e251–e271.

a. A normal NST result is reassuring, with the risk of fetal demise within the week following the test at approximately 3 in 1,000.

b. An atypical test is generally repeated later the same day or is followed by another test of fetal well-being.

c. An abnormal NST (Table 1.5) requires urgent action including an overall assessment of the situation and further investigation with ultrasound or BPP or may require urgent delivery. The difficulty with interpretation of NST lies in its lack of specificity for fetal death or compromise, the false-positive rate being as high as 50%.

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)** was used in the past as a confirmatory test when the NST was nonreactive, although with the availability of other modalities for fetal surveillance, CST is obsolete now.

4. The **Biophyscial profile test (BPP)** combines an NST with other parameters determined by real-time ultrasonographic examination. A score of 0 or 2 is assigned for the absence or presence of each of the following: a normal NST, adequate amniotic fluid volume (single deepest vertical fluid pocket >2 cm), fetal breathing movements, fetal activity, and normal fetal tone. BPP can assess both acute (NST) and chronic (amniotic fluid volumes) stress. 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 0.6 to 0.7 per 1,000.

5. Doppler ultrasonography of the fetal umbilical artery (flow velocity waveform pattern) is a noninvasive technique to assess placental resistance. A Cochrane systematic review showed that the use of Doppler is associated with a decrease in perinatal mortality, decrease in cesarean sections, and induction of labor.

A healthy placenta shows good diastolic flow in the fetal umbilical artery (Fig. 1.2A). A poorly functioning placenta with extensive vasospasm or infarction results in an increased resistance to flow in the umbilical artery during diastole (Fig. 1.2B). The ACOG practice guidelines support the use of umbilical artery Doppler assessments in the management of suspected FGR. The PORTO study recently established the association of increased morbidity/mortality as occurring primarily among FGR newborns with abnormal umbilical Doppler studies (pulsatility index >95th percentile or absent/reversed end-diastolic flow). Analysis of placental histology with abnormal umbilical artery Doppler flow has suggested loss of 50% to 70% of function associated with absent or reversed umbilical artery blood flow (Fig. 1.2C). The use of umbilical artery Doppler velocimetry measurements, in conjunction with other tests of fetal well-being, can reduce the perinatal mortality in FGR.

Doppler measurements of the **middle cerebral artery (MCA)** can also be used in the assessment of a fetus that is at risk for either FGR or anemia such as that affected by RhD alloimmunization or parvovirus infection. Increased flow in cerebral vessels shows early evidence of placental compromise especially in

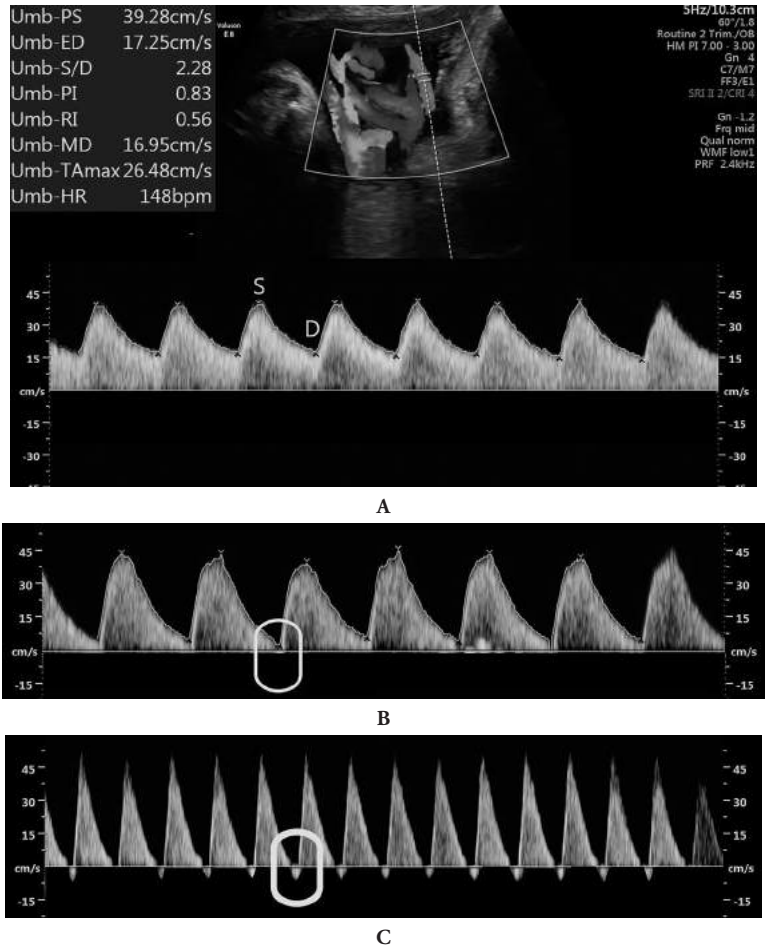
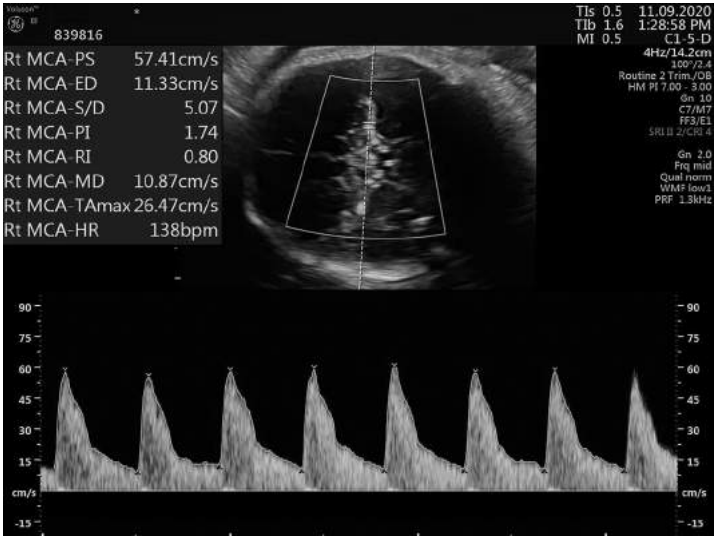


Figure 1.2. **A:** Doppler of fetal umbilical artery (good forward flow in systole and diastole)—low resistance (normal placenta). **B:** Doppler of fetal umbilical artery (decreased forward flow in diastole, increase in S/D ratio, pulsatility index [PI])—placental insufficiency. **C:** Doppler of fetal umbilical artery (reversal of flow in diastole)—severe placental insufficiency.

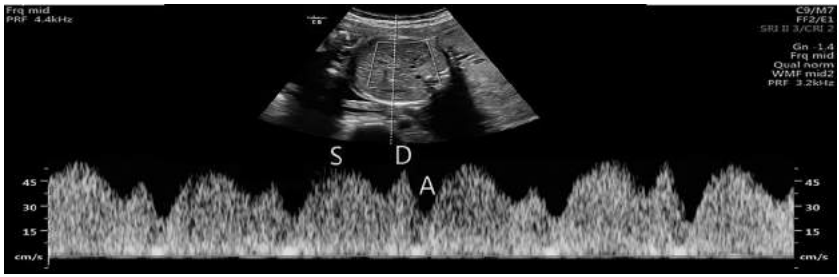
late-onset FGR. The peak velocity of systolic blood flow in MCA (Fig. 1.3A) is a useful parameter for the detection of fetal anemia in RhD alloimmunization; the need for invasive testing to evaluate fetal anemia is greatly reduced. In FGR, the cerebral circulation is preferentially perfused by reducing resistance to blood flow (brain-sparing effect). On the Doppler waveform of MCA, an increase in flow during diastole points to a pathologic FGR.

The clinical utility of venous Doppler velocimetry is greatest in fetal conditions with cardiac manifestations and/or marked placental insufficiency.

Progression of uteroplacental insufficiency can be revealed by ultrasound Doppler assessment of fetal Venosus (DV) flow (Fig. 1.3B). In the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE), the timing of



A



B

Figure 1.3. **A:** Ultrasound image of the fetal cerebral vasculature, with Doppler visualization of the middle cerebral artery and measurement of the peak systolic velocity. **B:** Doppler of fetal ductus venosus showing normal flow pattern. (S wave-ventricular systole, D wave-ventricular diastole, A wave-atrial contraction).

delivery was randomized and based on reduced short term variability (STV) in fetal heart rate on computerized cardiotocography (cCTG), and pulsatility changes in the DV; favorable outcome of early FGR fetuses was observed even on waiting till late DV changes.

A number of studies have explored the role of **uterine artery Doppler** for third trimester fetal assessment among women with high-risk pregnancies, but its role in these settings is not clearly defined. Impedance to flow in the uterine arteries decreases as pregnancy advances. Failure of adequate trophoblast invasion and remodeling of maternal spiral arteries is characterized by a persistent high-pressure uterine circulation and increased impedance to uterine artery blood flow. Elevated uterine artery resistance indices at 22 to 24 weeks of gestation indicate reduced blood flow in the maternal compartment of the placenta and have been associated with PE, FGR, and perinatal death. For classification, follow-up, and management of FGR fetuses, the staging system proposed by Gratacos et al. (Barcelona staging system) is used.

B. Intrapartum assessment of fetus. Intrapartum monitoring is mostly based on fetal heart rate monitoring; if decision making is difficult despite clinical and FHR inputs, invasive methods of intrapartum fetal may be employed - Fetal blood sampling (FBS).

1. Fetal heart rate (FHR) monitoring. FHR can be monitored by auscultation, Doppler, or electronic fetal monitoring (EFM). Doppler is superior to auscultation in picking up an abnormal FHR. EFM is performed using cardiotocograph, which is a paper record of ***FHR pattern plotted simultaneously in relation to uterine activity***. There is no evidence that EFM when compared with intermittent auscultation decreases poor perinatal outcomes. In preterm labor, there seems to be an association between intrapartum cardiotocographic changes and cerebral palsy. NICE guidelines recommend ***intermittent auscultation alone for low-risk pregnancies*** and ***continuous EFM for pregnancies with higher risk***. Continuous EFM monitors FHR and uterine activity simultaneously.

The **FHR** can be done by surface transducers on 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. It is done when external monitoring is not feasible as in morbid obesity. Placement requires dilatation of the cervix and rupture of the fetal membranes. When the electrode is properly placed, it is associated with a low risk of fetal injury. Approximately 4% of monitored babies develop a mild infection at the electrode site, and most respond to local cleansing. Uterine activity is also recorded simultaneously. A tocodynamometer can be strapped to the maternal abdomen to record the timing and duration of contractions. When a more precise evaluation is needed, an intrauterine pressure catheter can be inserted following rupture of the fetal membranes; this allows quantitative record of contraction pressure. Invasive monitoring is associated with an increased incidence of chorioamnionitis and postparmaternal infection.

Uterine activity is also recorded simultaneously. A tocodynamometer can be strapped to the maternal abdomen to record the timing and duration of contractions. When a more precise evaluation is needed, an intrauterine pressure catheter can be inserted following rupture of the fetal membranes; this allows quantitative record of contraction pressure. Invasive monitoring is associated with an increased incidence of chorioamnionitis and postpartum maternal infection.

The uterine contractions can compromise an unhealthy fetus. The pressure generated during contractions can briefly reduce or eliminate perfusion of the intervillous space. A healthy fetoplacental unit has sufficient reserve to tolerate this short reduction in oxygen supply. Under pathologic conditions, however, respiratory reserve may be so compromised that the reduction in oxygen results in fetal hypoxia. Oxygenation, acidemia, and other vital functions are monitored by peripheral chemoreceptors and baroreceptors, which provide input on fetal status through afferent neurologic networks to the CNS.

Parameters of the FHR include the following:

a. Baseline heart rate is normally between 110 and 160 bpm.

i. Baseline fetal bradycardia, defined as an FHR <110 bpm, may result from congenital heart block associated with congenital heart

malformation, maternal systemic lupus erythematosus, maternal medications (β-antagonists—labetalol), or fetal acidosis.

ii. Baseline tachycardia, defined as an FHR >160 bpm, may result from a maternal fever, infection, stimulant medications (atropine) or drugs (β_2-agonists), 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 baseline variability or recurrent decelerations.

b. Baseline variability The autonomic nervous system of a healthy, awake term fetus constantly varies the heart rate from beat to beat by approximately 5 to 25 bpm. Reduced baseline variability may result from depression of the fetal CNS, due to fetal immaturity, hypoxia, fetal sleep, or specific maternal medications such as narcotics, sedatives, β-blockers, corticosteroids, and intravenous magnesium sulfate.

c. Accelerations of the FHR in response to movements are reassuring.

FHR accelerations in response to mechanical stimulation of the fetal scalp (gently nudging the presenting vertex with the examiner's finger) or to vibroacoustic stimulation are also reassuring.

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

i. Early decelerations are symmetric in shape and closely mirror uterine contractions in time of onset, nadir, duration, and termination. They are benign and maintain good baseline variability. These decelerations are more commonly seen in active labor when the fetal head is compressed in the pelvis, resulting in a parasympathetic effect.

ii. Late decelerations are decreases in the FHR that occur "late" in relation to uterine contractions. The onset, nadir, and recovery of the deceleration occur after the beginning, peak, and end of the contraction, respectively. A fall in the heart rate of 15 bpm below baseline (even if still within the range of 110 to 160 bpm) and lasting for >15 seconds is significant. Late decelerations are the result of uteroplacental insufficiency and possible fetal hypoxia. As the uteroplacental insufficiency/hypoxia worsens, (i) baseline variability will be reduced and then lost, (ii) decelerations will last longer, (iii) they will begin sooner following the onset of a contraction, (iv) they will take longer to return to baseline, and (v) the rate to which the fetal heart slows will be lower. Repetitive late decelerations demand action.

iii. *Variable decelerations* vary in their shape and have no specific relationship with contractions. Usually, they result from fetal umbilical cord compression.

"Concerning characteristics" of variable decelerations include deceleration lasting more than 60 seconds, reduced baseline variability within the deceleration, failure to return to the baseline, biphasic (W) shape, and absence of shouldering (transient increase in the heart rate before the start of deceleration).

The labor room team must categorize and interpret intrapartum cardiotocograph and plan management accordingly. It emphasizes that when reviewing the cardiotocograph trace, assessment and documentation of contractions and all four features of FHR should be made, i.e., baseline rate, baseline variability, presence or absence of decelerations (concerning characteristics of variable decelerations if present), and presence of accelerations (Tables 1.6 and 1.7).

Digital fetal scalp stimulation should be offered and if this leads to an acceleration in FHR, cardiotocograph monitoring can be continued.

Table 1.6. Classification and Interpretation of Intrapartum Monitoring

	Baseline (bpm)	Baseline Variability (bpm)	Decelerations
Reassuring	110–160	5–25	■ None or early ■ Variable decelerations with no concerning characteristics* for less than 90 minutes
Non-reassuring	100–109† OR 161–180	Less than 5 for 30–50 minutes OR More than 25 for 15–25 minutes	Variable decelerations with no concerning characteristics* for 90 minutes or more OR Variable decelerations with any concerning characteristics* in up to 50% of contractions for 30 minutes or more OR Variable decelerations with any concerning characteristics* in over 50% of contractions for less than 30 minutes OR Late decelerations in over 50% of contractions for less than 30 minutes, with no maternal or fetal clinical risk factors such as vaginal bleeding or significant meconium
Abnormal	Below 100 OR Above 180	Less than 5 for more than 50 minutes OR More than 25 for more than 25 minutes OR Sinusoidal	Variable decelerations with any concerning characteristics* in over 50% of contractions for 30 minutes (or less if any maternal or fetal clinical risk factors [see above]) OR Late decelerations for 30 minutes (or less if any maternal or fetal clinical risk factors) OR Acute bradycardia, or a single prolonged deceleration lasting 3 minutes or more

Adapted from NICE. *Intrapartum Care for Healthy Women and Babies; Clinical Guideline*; 2014.
*Regard the following as concerning characteristics of variable decelerations: lasting more than 60 seconds, reduced baseline variability within the deceleration, failure to return to the baseline, biphasic (W) shape, and no shouldering.
†Although a baseline fetal heart rate between 100 and 109 beats/minute is a non-reassuring feature, continue usual care if there is normal baseline variability and no variable or late decelerations.

Table 1.7. Classification and Interpretation of Intrapartum Monitoring

Category	Definition	Management
Normal	All features are reassuring	■ Continue cardiotocograph (unless it was started because of concerns arising from intermittent auscultation and there are no ongoing risk factors) and usual care ■ Talk to the woman and her birth companion(s) about what is happening
Suspicious	One non-reassuring feature AND Two reassuring features	■ Correct any underlying causes, such as hypotension or uterine hyperstimulation ■ Perform a full set of maternal observations ■ Start one or more conservative measures* ■ Inform an obstetrician or a senior midwife ■ Document a plan for reviewing the whole clinical picture and the CTG findings ■ Talk to the woman and her birth companion(s) about what is happening and take her preferences into account
Pathologic	One abnormal feature OR Two non-reassuring features	■ Obtain a review by an obstetrician and a senior midwife ■ Exclude acute events (e.g., cord prolapse, suspected placental abruption, or suspected uterine rupture) ■ Correct any underlying causes, such as hypotension or uterine hyperstimulation ■ Start one or more conservative measures* ■ Talk to the woman and her birth companion(s) about what is happening and take her preferences into account ■ If the cardiotocograph trace is still pathologic after implementing conservative measures □ Offer digital fetal scalp stimulation and document the outcome ■ If the cardiotocograph trace is still pathologic after fetal scalp stimulation □ Consider fetal blood sampling □ Consider expediting the birth □ Take the woman's preferences into account

Adapted from NICE. *Intrapartum Care for Healthy Women and Babies; Clinical Guideline*; 2014.
*Conservative measures: Encourage the woman to mobilize or adopt an alternative position (and to avoid being supine); offer intravenous fluids if the woman is hypotensive; reduce contraction frequency by reducing or stopping oxytocin if it is being used and/or offering a tocolytic drug (a suggested regimen is subcutaneous terbutaline 0.25 mg).

Consider fetal blood sampling (FBS) if the cardiotocograph trace is still pathologic.

2. **Fetal blood sampling (FBS).** FBS is recommended for women in labor in whom expedited delivery by cesarean section is being planned for fetal distress (abnormal FHR pattern). The acidosis or rise in lactate is considered as a marker of fetal hypoxia. Decisions may be made without FBS, if the whole clinical picture indicates that the birth should be expedited—for example, there is an acute event (e.g., cord prolapse, suspected placental abruption,

or suspected uterine rupture). Contraindications for FBS include risk of maternal-to-fetal transmission of infection or risk of fetal bleeding disorders. Interpretation of FBS:

- pH
  - Normal: ≥7.25
  - Borderline: 7.21 to 7.24
  - Abnormal: ≤7.20
- Lactate
  - Normal: ≤4.1 mmol/L
  - Borderline: 4.2 to 4.8 mmol/L
  - Abnormal: 4.9 ≥mmol/L

If the fetal blood sample result is normal and there are no accelerations in response to fetal scalp stimulation, a second fetal blood sample no more than 1 hour later is considered (if this is still indicated by the cardiotocograph trace).

If the fetal blood sample result is borderline and there are no accelerations in response to fetal scalp stimulation, a repeat fetal blood sample no more than 30 minutes later is considered (if this is still indicated by the cardiotocograph trace).

If the fetal blood sample result is still abnormal, a senior obstetrician must be informed; the woman and her birth companion(s) must be explained about the situation. Birth should be expedited by instrumental delivery if the cervix is fully dilated or otherwise an emergency caesarean section should be planned.*

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2 Maternal Diabetes Mellitus

Aviva Lee-Parritz

KEY POINTS

- Due to increasing obesity, the incidence of gestational diabetes mellitus (GDM) and type 2 diabetes in pregnancy is increasing in women of all races.
- Women with GDM or pregestational diabetes (i.e., type 1 or type 2 diabetes) have higher rates of maternal and perinatal complications compared to the general population.
- Women with type 1 or type 2 diabetes are at significantly increased risk for hypertensive disorders, such as preeclampsia, which is potentially deleterious to both maternal and fetal well-being.
- Preconception care is paramount in women with pregestational diabetes to appropriately counsel women about risks, optimize glycemic control, advise regarding folic acid supplementation, assess complications, and discontinue any teratogenic medications.
- Appropriate management of pregnant women with GDM or pregestational diabetes lowers the risk of maternal and perinatal adverse outcomes.
- 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.
- Strict glycemic control can reduce fetal macrosomia in both GDM and pregestational diabetes. Target both postmeal and premeal glucose.
- Tight intrapartum glucose control is important to reduce fetal oxidative stress and neonatal hypoglycemia.
- Women with pregestational diabetes may have reduced glycemic profiles and insulin requirements postpartum, especially in breastfeeding women.

I. DIABETES AND PREGNANCY OUTCOME. Diabetes in pregnancy refers to pregestational diabetes (type 1 or type 2 diabetes) and gestational diabetes mellitus (GDM) or glucose intolerance first recognized in pregnancy (Table 2.1). Women with all forms of diabetes in pregnancy have higher rates of maternal and perinatal complications, particularly women with pregestational diabetes, compared to the general population. Women with advanced microvascular disease, such as hypertension, nephropathy, and retinopathy, have a 25% risk of preterm delivery or preeclampsia. Improved management of diabetes mellitus and advances in obstetrics have reduced the incidence of adverse maternal and perinatal outcomes in pregnancies complicated by diabetes mellitus.

Table 2.1. Nomenclature of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

Class	Description
Type 1 diabetes	Autoimmune disorder with absolute insulin deficiency due to β-cell destruction (idiopathic or immune)
Type 2 diabetes	Due to insulin resistance with relative insulin deficiency (secretory defect with insulin resistance) Fasting plasma glucose ≥126 mg/dL* Or 2-Hour postglucose ≥200 mg/dL during a 75-g OGTT* Or Hemoglobin A_{1c} ≥6.5%* Or Classic symptoms of hyperglycemia with random plasma glucose ≥200 mg/dL*
GDM	Two-step approach ■ 2 step approach: Perform a standardized nonfasting 50-g glucose challenge screening test with plasma glucose measured 1 hour later □ If the value is <140 mg/dL, no further testing is required □ If the value of the glucose challenge screening test is 140 to 200 mg/dL, a 100-g, 3 hour GTT should be performed ■ 1 step approach: Perform a 75-g GTT with plasma glucose measurement when patient is fasting and at 1 and 2 hours, at 24 to 28 weeks. gestation in women not previously diagnosed with overt diabetes □ The diagnosis of GDM is made when any of the following plasma glucose values is met or exceeded: □ Fasting: 92 mg/dL □ 1 hour: 180 mg/dL □ 2 hours: 153 mg/dL □ Several other approaches to diagnose GDM are available
Other specific types	Genetic defects of β-cell function or insulin action, disease of exocrine pancreas, abnormal endocrine functions, infections, chemical or drug-induced and rare immune-mediated diabetes, some genetic syndromes associated with diabetes

GDM, gestational diabetes mellitus; GTT, glucose tolerance test; OGTT, oral glucose tolerance test.
*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

II. DIABETES IN PREGNANCY

A. General principles

1. Pregestational diabetes is associated with adverse perinatal and maternal outcomes. The most important complication is diabetic embryopathy resulting in congenital anomalies. Congenital anomalies are associated with 50% of perinatal deaths among women with diabetes compared to 25% among women

without diabetes. The risk of congenital anomalies is associated with glycemic control at the time of conception. The most common types of anomalies include cardiac malformations and neural tube defects. Folic acid supplementation is recommended to reduce the risk of congenital malformations in women with pregestational diabetes. Women with type 1 and type 2 diabetes are at significantly increased risk for hypertensive disorders, such as preeclampsia, which is potentially deleterious to both maternal and fetal well-being.

2. **Epidemiology of gestational diabetes.** GDM affects 5% to 25% of pregnancies. Approximately 3% to 5% of the patients with GDM actually have underlying type 1 or type 2 diabetes, but pregnancy is the first opportunity for testing. Risk factors for GDM include advanced maternal age, multifetal gestation, increased body mass index, and strong family history of diabetes. Certain ethnic groups, such as Native Americans, Southeast Asians, and African Americans, have an increased risk of developing GDM.

3. **Physiology unique to women with diabetes antedating pregnancy.** In 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. Maternal hyperglycemia leads to fetal hyperglycemia and fetal hyperinsulinemia, which results in fetal overgrowth. 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.

B. Complications of type 1 and/or type 2 diabetes during pregnancy

1. **Diabetic ketoacidosis** is a serious complication in women with type 1 diabetes during pregnancy. It carries a 50% risk of fetal death, especially if it occurs before the third trimester. Ketoacidosis 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 presents with hyperglycemia and symptoms such as nausea, vomiting, or abdominal pain.

2. **Stillbirth** occurs in women with diabetes in pregnancy more frequently than in the general population. It is most often associated with poor glycemic control, fetal anomalies, severe vasculopathy, and intrauterine growth restriction (IUGR) as well as severe preeclampsia. Shoulder dystocia that cannot be resolved can also result in fetal death.

3. **Polyhydramnios** 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. **Severe maternal vasculopathy**, especially nephropathy and hypertension, is associated with uteroplacental insufficiency, which can result in IUGR, fetal intolerance of labor, and neonatal complications.

III. MANAGEMENT OF DIABETES DURING PREGNANCY

A. General principles for type 1 or type 2 diabetes. For those with pregestational diabetes, preconception care is paramount to appropriately counsel women about risks, optimize glycemic control, advise regarding folic acid supplementation, assess and manage any diabetes-related (e.g., microvascular and macrovascular) complications and comorbidities, and discontinue any teratogenic medications (e.g., angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]). Folic acid supplementation of 1 mg/day 3 months prior to conception and continuing to at least 12 weeks into gestation is recommended to reduce the risk of congenital malformations in women with pregestational diabetes. Although higher doses of 5 mg/day are advised by academic bodies, such high doses can aggravate vitamin B12 deficiency. Tight glucose control is important 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, <30% of pregnancies are planned. Physicians should discuss pregnancy planning or recommend reliable contraception for all women with diabetes of childbearing age until glycemic control is optimized.

B. General principles for GDM. Several approaches to diagnose GDM are used with no consensus regarding the use of one-step versus two-step approach. Commonly, most women are screened for GDM between 24 and 28 weeks' gestation by a nonfasting 50-g, 1-hour glucose challenge. A positive screen is followed by a diagnostic fasting 75-g, 2-hour oral glucose tolerance test (GTT). A positive test is defined as one or more elevated values on the GTT (Table 2.1). Uncontrolled GDM, as well as pregestational diabetes, can lead to fetal macrosomia and concomitant risk of fetal injury at delivery. GDM shares many features with type 2 diabetes. Women diagnosed with GDM have 2.6% risk of type 2 diabetes at 6 weeks postpartum, this increases to 70% when followed up 28 years postpartum! Hence, GDM mothers must be advised lifestyle modification for type 2 diabetes.

1. **Testing (first trimester) for type 1 and type 2 diabetes**

   a. **Measurement of glycosylated hemoglobin** in the first trimester can give a risk assessment for congenital anomalies by reflecting ambient glucose concentrations during the period of organogenesis.

   b. **Accurate dating of the pregnancy** is obtained by ultrasonography.

   c. **Ophthalmologic examination** is mandatory because retinopathy may progress because of the rapid normalization of glucose concentration in the first trimester. Women with retinopathy need periodic examinations throughout pregnancy, and they are candidates for laser photocoagulation as indicated.

   d. **Renal function** is assessed by an albumin:creatinine ratio or a 24-hour urine collection for protein excretion and creatinine clearance if the former is not available. Because the incidence of preeclampsia is significantly

elevated in women with pregestational diabetes, identification of baseline proteinuria can impact the diagnosis of preeclampsia later in pregnancy. Serum creatinine should also be assessed in patients with pregestational diabetes.

e. **Thyroid function** should be evaluated.

f. **Nuchal translucency and serum screening for aneuploidy.** Although diabetes in and of itself is not a risk factor for aneuploidy, this is part of routine pregnancy care. Nuchal translucency assessment is particularly important because an abnormal measurement is also associated with structural abnormalities, the risk of which is increased in this group of patients.

2. **Testing (second trimester) for type 1 and type 2 diabetes**

a. **Maternal serum screening** for neural tube defects is performed between 15 and 19 weeks' gestation. Women with diabetes have a 10-fold increased risk of neural tube defects compared to the general population.

b. All patients undergo a thorough **ultrasonographic survey**, including fetal echocardiography for structural anomalies.

c. Women older than 35 years or with other risk factors for fetal aneuploidy are offered **noninvasive prenatal testing or karyotyping via chorionic villus sampling or amniocentesis**.

3. **Testing (third trimester) for type 1 and type 2 diabetes**

a. **Ultrasonographic examinations** are performed monthly through the third trimester for fetal growth measurement.

b. **Weekly or twice-weekly fetal surveillance** using nonstress testing or biophysical profiles is implemented between 28 and 32 weeks' gestation, depending on glycemic control and other complications.

C. Treatment for all types of glucose intolerance. Strict **glucose control** is achieved with nutritional modification, exercise, and medications, with the traditional goals of fasting glucose concentration <95 mg/dL and postprandial values <140 mg/dL for 1 hour and 120 mg/dL for 2 hours. Recent data have suggested that in pregnant women, euglycemia may be even lower, with fasting glucose levels in the 60-mg/dL range and postmeal glucose levels <105 mg/dL. Insulin therapy has the longest record of accomplishment of perinatal safety. It has been demonstrated that human insulin analogs do not cross the placenta. More recently, oral hypoglycemic agents for the management of GDM, such as glyburide and metformin which do have placental crossover, have been shown to be safe and effective when compared to insulin, or in combination with insulin, but as long-term follow up data are still pending, they should not be used as first line.

IV. MANAGEMENT OF LABOR AND DELIVERY FOR WOMEN WITH DIABETES

A. General principles. The risks of spontaneous preterm labor (adjusted odds ratio [aOR] 11.2; 95% confidence interval [CI] 10.5 to 11.95), having an offspring large for gestational age (LGA) (aOR 43.8; 95% CI 40.9 to 46.9) and birth trauma are markedly increased in patients with diabetes; additionally, the risk of iatrogenic preterm delivery has been increased for patients with microvascular

disease as a result of IUGR, nonreassuring fetal testing, maternal obesity, and maternal hypertension. Among spontaneous deliveries, the risk of moderately preterm births was high; in insulin-treated diabetes the risk for extremely preterm births was also increased. The recent meta-analysis also suggests that maternal diabetes mellitus including GDM and pre-GDM is associated with an increased risk of neonatal respiratory distress syndrome (OR 1.47; 95% CI 1.2 to 1.7). Antenatal corticosteroids for induction of fetal lung maturity (FLM) should be employed for the usual obstetric indications. Corticosteroids can cause temporary hyperglycemia; therefore, patients may need to be managed with continuous intravenous (IV) insulin infusions until the effect of the steroids wears off. **Delivery is planned** for 39 to 40 weeks, unless other pregnancy complications dictate earlier delivery. Elective delivery after 39 weeks does not require FLM testing. Indicated delivery before 39 weeks' gestation should be carried out without FLM testing. **Route of delivery** is determined by ultrasonography-estimated fetal weight, maternal and fetal conditions, and previous obstetric history. The ultrasonography-estimated weight at which an elective cesarean delivery is recommended is a controversial issue, with the American College of Obstetricians and Gynecologists recommending discussion of cesarean delivery at an estimated fetal weight of >4,500 g due to the increased risk of shoulder dystocia.

B. Treatment. **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. Centers vary in intrapartum management, but often an infusion of IV short-acting insulin is preferred. 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. Cesarean delivery is performed for obstetric indications. The risk of a cesarean section for obstetric complications is approximately 50%. Patients with **advanced microvascular disease** are at an increased risk for a cesarean delivery because of the increased incidence of IUGR, preeclampsia, and nonreassuring fetal status. A history of retinopathy that has been treated in the past is not necessarily an indication for a cesarean delivery. Patients with active proliferative retinopathy that is unstable or active hemorrhage may benefit from an elective cesarean delivery. **Postpartum**, patients with pre-existing diabetes (type 1 or type 2 diabetes) are at an increased risk for hypoglycemia, especially in the postoperative setting with minimal oral intake. Insulin doses should be decreased immediately after delivery below prepregnant doses and titrated as needed to achieve optimal glycemic control. Women with pre-existing diabetes are prone to have hypoglycemia; therefore, they should have frequent blood glucose monitoring in the initial days after delivery. Women with type 1 diabetes should be screened for postpartum thyroiditis with a thyroid-stimulating hormone (TSH) test at 2 to 4 months postpartum. 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 especially in the immediate postpartum period. For women with type 2 diabetes, the use of metformin and glyburide is compatible

with breastfeeding. Patients with GDM should receive counseling regarding healthy behavior interventions to reduce the recurrence rate in subsequent pregnancies and reduce their increased risk of type 2 diabetes. In GDM patients, metformin can be used in conjunction with behavior interventions to prevent/delay the onset of diabetes.

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3 Preeclampsia and Related Conditions

Bahaeddine Sibai and Cristina Wallace

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 severity of disease, dilatation/effacement of the maternal cervix, gestational age at diagnosis, and pulmonary maturity of the fetus all influence obstetric management.
- 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.
- Elevated blood pressure during pregnancy is associated with an increased risk of developing cardiovascular disease, chronic kidney disease, and diabetes mellitus later in life.
- Hypertension in pregnancy adds significantly to neonatal morbidity and mortality by increasing the risk of intrauterine growth restriction, preterm delivery, and perinatal asphyxia.

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 proteinuria, in addition to possible concurrent thrombocytopenia, or transaminase derangements 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.

D. Preeclampsia. Blood pressures ≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least two occasions 4 hours apart with proteinuria after 20 weeks' gestation in a previously normotensive women. In 2013, the American College of Obstetricians and Gynecologists (ACOG) removed proteinuria as an essential criterion for the diagnosis of preeclampsia.

Thereafter, hypertension plus any one sign of significant end-organ dysfunction is also sufficient for making a diagnosis of preeclampsia in the absence of proteinuria and these signs are as follows:

1. Platelet count <100,000/μL

2. Serum creatinine >1.1 mg/dL or doubling of the creatinine concentration in the absence of other renal disease
3. Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
4. Pulmonary edema
5. New-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics
6. Visual symptoms (e.g., blurred vision, flashing lights or sparks, scotomata)

Preeclampsia can be further subdivided into with ("preeclampsia with severe features") or without severe features (see section III).

E. Eclampsia. Generalized tonic–clonic seizure activity in a pregnant woman with no prior history of a seizure disorder

F. Hemolysis, elevated liver enzymes, and low platelet syndrome. Clinical findings consistent with hemolysis, elevated liver function tests, and thrombocytopenia

II. INCIDENCE AND EPIDEMIOLOGY. Gestational hypertension complicates 6% to 17% of healthy nulliparous and 2% to 4% of multiparous women. Overall, hypertensive disorders in pregnancy are a major cause of maternal morbidity and mortality, accounting for 15% to 20% of maternal deaths worldwide. In the United States, hypertensive disorders are the second leading cause of maternal mortality after thrombotic/hemorrhagic complications. 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. Several risk factors have been identified, as outlined in Table 3.1.

Preeclampsia has been called the "disease of theories," and many **etiologies** have been proposed. What is clear, however, is that it is a condition of dysfunction within the maternal endothelium. Increased levels of the soluble receptors soluble fms-like tyrosine kinase-1 *(sFLT1)* and *endoglin* within the maternal circulation for vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), respectively, may be associated with preeclamptic pathology. Higher circulating levels of these soluble receptors reduce the bioavailable levels of VEGF, placental growth factor (PlGF), and TGF-β, resulting in endothelial dysfunction within the maternal circulatory system. This dysfunction can manifest as both increased arterial tone (hypertension) and increased capillary leak (edema/proteinuria/pulmonary congestion). It is unclear what insult prompts the initial increase in sFLT1 and endoglin in some women versus in others. One suggestion has been that abnormal trophoblastic invasion of both the maternal decidual arteries with an accompanying abnormal maternal immune response is at the root of this condition. This abnormal placentation is believed to lead to a reduction in placental perfusion and relative placental ischemia. However, the exact cause of excess production of these antiangiogenic proteins still remains unclear. Interestingly, the levels of sFLT1 and endoglin begin to rise in the second trimester months before preeclampsia is clinically evident, thus providing an opportunity to predict the risk of developing preeclampsia in the near future. The National Institute of Clinical Excellence (NICE) guidelines recommend PIGF-based testing in patients with chronic hypertension to predict the development of preeclampsia.

Table 3.1. Risk Factors for Hypertensive Disorders

Nulliparity
Age >40 years
Obesity
Preeclampsia in previous pregnancy
Family history of preeclampsia
Preexisting chronic hypertension
Chronic renal disease
History of thrombophilia
Diabetes (type 1 or type 2)
Multifetal pregnancy
Systemic lupus erythematosus
In vitro fertilization
Molar pregnancy
Fetal hydrops

Source: From the American College of Obstetricians and Gynecologists. *Hypertension in pregnancy*. http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy. Accessed May 28, 2016; and Moussa H, Arian S, Sibai B. Management of hypertensive disorders in pregnancy. *Womens Health (Lond)* 2014;10(4):385–404.

III. DIAGNOSIS. The classic presentation which defines preeclampsia is hypertension and proteinuria after 20 weeks' gestation. Some patients will also have nondependent edema, but this is no longer a part of the diagnostic criteria for preeclampsia. 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.

A. Criteria for the diagnosis of preeclampsia without severe features

1. **Hypertension** 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 or protein to creatinine ratio ≥0.3 mg/mg or urine dipstick reading ≥1+ (used only if other quantitative methods are not available).

B. Criteria for the diagnosis of preeclampsia with severe features. *Of note, you do not need every criteria listed here 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 or severe hypertension can be verified within minutes to aid in administering 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 preeclampsia with severe features.

3. **Pulmonary edema**
4. **Renal insufficiency** is defined as serum creatinine >1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease.
5. **Thrombocytopenia** is defined as a platelet count of <100,000/μL.
6. **Hepatocellular dysfunction.** Elevated transaminases (to twice the upper limit of normal concentration)

C. HELLP syndrome stands for hemolysis, elevated liver enzymes, and low platelets. It represents an alternative presentation of preeclampsia and reflects systemic end-organ damage. HELLP syndrome may appear without either hypertension or proteinuria.

IV. COMPLICATIONS.

Complications of preeclampsia result in a maternal mortality rate of 3 per 100,000 live births in the United States. 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 with increase in the severity of preeclampsia. Fetal morbidity may include 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 the disease, gestational age, and expected pulmonary maturity of the fetus influence the obstetric management. Delivery is usually indicated if there is fetal indication (category 3 fetal heart tracing) in a viable fetus or if the maternal status becomes unstable regardless of the gestational age.

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 until 37 weeks' gestation or some other ominous development such as the progression to preeclampsia with severe features, fetal distress, 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. If the patient is >34 weeks, the recommendation by the ACOG is delivery. Prior to 34 weeks, three management options include delivery immediately, betamethasone and then delivery, and expectant management. The timing of delivery is discussed in further detail in section VII.

E. Expectant management. Monitoring includes daily maternal–fetal testing, routine vital signs, and monitoring for symptoms of preeclampsia. Patients may even be given oral antihypertensive drugs to bring their blood pressure down. Women with uncontrolled hypertension despite maximum doses of antihypertensive

medications, thrombocytopenia, hepatocellular dysfunction, pulmonary edema, compromised renal function, or persistent headache or visual changes and with previable fetus or fetal compromise are not candidates for expectant management.

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, 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.

VI. CLINICAL MANAGEMENT OF PREECLAMPSIA WITHOUT SEVERE FEATURES

A. Antepartum management. Conservative management of preeclampsia without severe features generally consists of daily assessment of the maternal symptoms and fetal movement by the women, biweekly blood pressure checks, and weekly assessment of platelet counts and liver enzymes. It is recommended that strict bed rest and salt restriction not be prescribed in these women.

1. 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 to 4 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 the 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.

2. 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; 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. However, whenever used, the aim should be to target blood pressure 135/85 mm Hg or less. Use of antihypertensive agents is reserved for severe hypertension, so as to reduce maternal cerebrovascular

accidents. We should not aim to reduce BP drastically as it will reduce uterine blood flow.

f. When early delivery is indicated, it is our practice that vaginal delivery is preferred. 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).

g. Antenatal steroid (<34 weeks) and intravenous (IV) magnesium sulfate for neuroprotection (<32 weeks) should be offered, if indicated, in case of preterm delivery to improve the neonatal outcome.

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 are noted such as systolic blood pressure >160 mm Hg, diastolic blood pressure >110 mm Hg, or maternal symptoms noted.
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 variable or late decelerations not responsive to standard resuscitative measures.
4. Patients may be safely administered **epidural anesthesia** if the platelet count is >70,000 and there is no evidence of DIC. Consideration should be given for early epidural catheter placement when the platelet count is reasonable and there is concern that it is decreasing. 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 hypotension.
5. **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, they usually resolve within 1 or 2 weeks. Promote breastfeeding and reassure that antihypertensive medications do not prevent them from breastfeeding.

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

A. Timing of delivery.

If <23 weeks' or >**34 weeks' gestation**, delivery is indicated.

1. Prior to 34 weeks, **expectant management** can be attempted unless there is evidence of eclampsia, pulmonary edema, DIC, uncontrollable severe hypertension, nonviable fetus, abnormal fetal test results, placental abruption, or

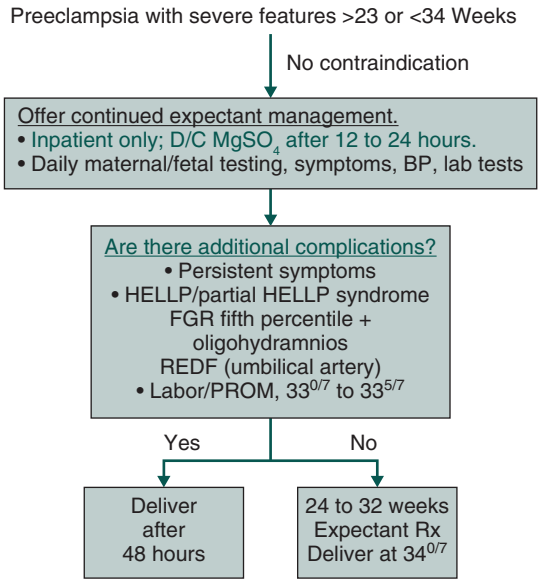

Figure 3.1. Management of preterm preeclampsia with severe features. BP, blood pressure; D/C, discontinue; FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, and low platelets; $MgSO_4$, magnesium sulfate; PROM, premature rupture of membrane; REDF, reversed end-diastolic flow; Rx, reaction.

intrapartum fetal demise. In those situations, the goal is to stabilize the mother and then deliver. If the patient has evidence of persistent symptoms, HELLP, partial HELLP, fetal growth restriction with severe oligohydramnios (largest vertical pocket <1 cm) or reversed end-diastolic flow on umbilical artery Doppler studies, labor, 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, expectant management is recommended until 34 weeks or delivery can be performed sooner if the patient develops evidence of worsening disease. Two randomized trials performed in the United States compared immediate delivery with 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.

2. 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.

B. Intrapartum management. Magnesium sulfate (4 to 6 g loading dose followed by 1 to 2 g/h infusion for 24 to 48 hours after postpartum) is used as seizure

prophylaxis. It is started when the decision to proceed with delivery is made and is continued for at least 24 hours postpartum. 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. Because magnesium sulfate is excreted from the kidneys, urine output should be carefully monitored. Signs and symptoms of maternal toxicity include loss of deep tendon reflexes, somnolence, respiratory depression, cardiac arrhythmia, and, in extreme cases, cardiovascular collapse.

1. **Careful monitoring of fluid balance** is critical because preeclampsia is associated with endothelial dysfunction leading to decreased intravascular volume, pulmonary edema, and oliguria. A serum magnesium level should be considered if reduced renal function is suspected while magnesium sulfate is being administered. In addition, if the patient has evidence of reduced kidney function, that is, 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.
2. **Continuous fetal heart rate monitoring is recommended.** Reduced fetal heart rate variability may also result from maternal administration of magnesium sulfate.
3. **Severe hypertension** may be controlled with agents including IV hydralazine, IV labetalol, or oral nifedipine. 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.
4. **Blood pressure** needs to be monitored every 15 to 30 minutes during labor until it is less than 160/110 mm Hg.

C. Postpartum management. 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, urine output, lung evaluation, and deep tendon reflexes are monitored closely for evidence of magnesium sulfate toxicity.

1. Hypertension >150 mm Hg systolic or 100 mm Hg diastolic on at least two occasions 4 to 6 hours apart needs to be treated in the postpartum period with antihypertensive therapy. Some patients, though sufficiently stable for discharge, may require antihypertensive medications for up to 8 weeks after delivery.
2. 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 the patient's blood pressure closely for 72 hours after delivery, preferably in the hospital, and then to have the patient return to clinic 7 to 10 days after delivery again to reassess blood pressure. If the patient develops symptoms of preeclampsia in the interim, he or she should be assessed again sooner.

3. Nonsteroidal anti-inflammatory agents generally should be avoided in the postpartum period in patients with severe hypertension and in those with superimposed preeclampsia. These medications can increase blood pressure and increase sodium retention.

VIII. MANAGEMENT OF ECLAMPSIA

A. Approximately half of eclamptic seizures occur before delivery, 20% occur during delivery, and another 30% occur in the postpartum period. 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, but most preeclamptic women with headaches do not develop seizures.

B. Basic principles of maternal resuscitation should be followed in the initial management of an eclamptic seizure: airway protection, oxygen supplementation, left lateral displacement to prevent uterine compression of the vena cava, IV access, and blood pressure control.

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

D. A transient fetal bradycardia is usually seen during the seizure followed by a transient fetal tachycardia with loss of variability. Ideally, the fetus should be resuscitated (stabilized before delivery) *in utero*.

E. 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. Because of the risk of DIC, coagulation parameters should be assessed, and appropriate blood products should be available if necessary.

F. A neurologic exam should be performed once the patient recovers from the seizure. If the seizure is atypical or any neurologic deficit persists, brain imaging is indicated.

G. If a patient has recurrent seizures while on magnesium sulfate, a reloading dose of 2 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.

IX. RECURRENCE RISK.

Patients who have a history of preeclampsia are at an increased risk for hypertensive disease in a subsequent pregnancy. 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. Severe disease and eclampsia are also associated with recurrence. The recurrence rate for HELLP syndrome is approximately 5%.

X. RISK OF CHRONIC HYPERTENSION.

Elevated blood pressure during pregnancy, regardless of type and even without known risk factors, can be indicative of a high risk of cardiovascular disease, chronic kidney disease, and diabetes mellitus later in

life. 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. 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 body mass index.

XI. INNOVATIONS AND PROPOSED TREATMENTS

A. Several analytic assays based on sFLT1 and PIGF protein levels and soluble endoglin early in the second trimester are currently under evaluation. The ultimate clinical utility of these analytes has yet to be determined. Some newer studies show that these biomarkers in combination with uterine artery Dopplers may be predictive of early onset preeclampsia. In addition, randomized trials are ongoing to evaluate several modalities to decrease the need for preterm birth for maternal/fetal indications.

B. Low-dose aspirin is recommended for women at risk of developing preeclampsia later during the third trimester. The ACOG recommends a dose of 81 mg/day of aspirin (the NICE recommends 75–150 mg/day) for patients with single "high-risk" factor or two or more "moderate-risk" factors (Table 3.2). It should be started after 12 weeks of gestation, preferably before 16 weeks, and needs to be continued throughout the pregnancy till delivery.

C. Antenatal calcium supplementation did not show any benefit when given to healthy nulliparous women.

D. Antioxidant therapy (vitamin E) supplementation during pregnancy was found to be associated with an increased risk of adverse outcome compared with placebo.

XII. EFFECTS OF MEDICATIONS USED ANTEPARTUM OR INTRAPARTUM ON THE FETUS

A. Short-term sequelae of hypermagnesemia, such as hypotonia and respiratory depression, are sometimes seen.

B. Antihypertensive medications are safe for the fetus and are not contraindications to breastfeeding.

C. Low-dose aspirin therapy does not increase the incidence coagulation problems or persistent pulmonary hypertension.

XIII. EFFECTS OF PREECLAMPSIA ON THE NEWBORN. Infants born to mothers with preeclampsia may show evidence of intrauterine growth restriction (**IUGR**) (hypoglycemia, polycythemia) and are frequently delivered prematurely. They may tolerate labor poorly and therefore require resuscitation. Some infants born to mothers with early onset preeclampsia 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 an increased risk for neonatal infection.

Table 3.2. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	■ History of preeclampsia, especially when accompanied by an adverse outcome ■ Multifetal gestation ■ Chronic hypertension ■ Type 1 or 2 diabetes ■ Renal disease ■ Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	■ Nulliparity ■ Obesity (body mass index greater than 30) ■ Family history of preeclampsia (mother or sister) ■ Sociodemographic characteristics (African American race, low socioeconomic status) ■ Age 35 years or older ■ Personal history factors (e.g., low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	■ Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.
†Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.
‡A combination of multiple moderate-risk factors may be used by clinicians to identify women at a high risk of preeclampsia. These risk factors are independently associated with a moderate risk of preeclampsia, some more consistently than the others.
§Moderate-risk factors vary in their association with an increased risk of preeclampsia.
Adopted from American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol* 2020;135:e237–e260.

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4 Resuscitation in the Delivery Room

Steven A. Ringer

KEY POINTS

- Most (85%) term born babies will need no help at birth; 10% will breath after stimulation and drying, 5% may need positive-pressure ventilation, 2% may get intubated, 0.1% may need cardiac compressions, and 0.05% need epinephrine.
- Preparing for resuscitation includes anticipation, team briefing, and equipment checking.
- Delay cord clamping for 30 to 60 seconds, if the baby needs no resuscitation.
- Babies who make a normal transition at birth must not be separated from the mother: Keep warm with skin-to-skin contact and allow breastfeeding.
- Babies in primary apnea respond to initial steps: Provide warmth, open the airway (position and suction if necessary), dry, and stimulate.
- Babies with good tone and breathing effort may be started on oxygen if saturations persist below target; persistent cyanosis/respiratory distress may be treated with continuous positive airway pressure (CPAP).
- Positive-pressure ventilation (PPV) is the key to neonatal resuscitation.
- PPV may be required by 4% to 10% of term/late preterm babies.
- Improvement in heart rate is the best measure of effective PPV.
- If chest rise is poor, adjust mask and suction, increase pressure, and consider alternate airway.
- If the heart rate is <60 bpm despite effective PPV, start chest compression (CC). If the heart rate is <60 bpm despite effective PPV and CC for 60 seconds, give epinephrine IV.
- Preterm babies <32 weeks may be received in a plastic sheet/bag.
- No routine suction of airway is required in meconium-stained liquor; intubation for suction is not necessary for even nonvigorous babies.
- Resuscitation may not be initiated in babies unlikely to survive: Accurate regional information must guide the parents; if not sure, initiate full standard resuscitation.
- If no spontaneous circulation (heartbeat) is present at 10 to 20 minutes after effective resuscitation and excluding reversible factors, resuscitation may be stopped.

I. GENERAL PRINCIPLES. Among babies born at term:

- 85% will initiate breathing within 10 to 30 seconds of birth.
- 10% will breathe in response to stimulation and drying.
- 5% will require positive-pressure ventilation (PPV).

- 2% will require intubation.
- 0.1% will require cardiac compressions.
- 0.05% will require epinephrine.

A person skilled in basic neonatal resuscitation, whose primary responsibility is the newly born baby, should be present at every birth.

Some babies with no recognized perinatal risk factors may need resuscitation at birth. Delivery of all high-risk infants should be attended by a team which possesses the skills required to perform a complete resuscitation.

The highest standard of care requires the following: (i) knowledge of resuscitation protocol, (ii) mastery of the technical skills required, and (iii) a clear understanding of the roles of other team members and coordination among team members.

Completion of the Newborn Resuscitation Program (NRP) by every caregiver (pediatrician, obstetrician, resident doctors, nurses, and paramedics) helps ensure a consistent approach to resuscitations and team-based training.

The guidelines on resuscitation at birth are guiding principles for teaching and effective teamwork. They may be *adapted according to resources*, for example, Indian guidelines, NRP India, by National Neonatology forum of India. The Navjaat Shishu Suraksha Karyakram (NSSK) for health care workers is further simplified and asks only one question for assessment at birth and thereafter - assess breathing. Self-inflating bag is preferred as it is not dependent on oxygen availability; high-cost and complex technology such as signal extraction technology (SET) pulse oximeters, ECG, blender, and CO_2 detector are not recommended.

II. RESUSCITATION PHYSIOLOGY—TRANSITION FROM FETUS TO NEONATE. *In utero* (before birth), the lungs have no role in gas exchange (breathing) and are fluid filled; oxygen and carbon dioxide of the fetus are managed by the placenta. At birth, the placenta is separated from the baby (the umbilical cord is clamped/cut) and the responsibility of gas exchange must be immediately transferred to the baby's lungs. The *baby must start and sustain effective breathing* immediately after the umbilical cord is clamped.

The *placenta may have been failing* in function and ineffective respiration may be associated with fetal hypoxia, hypercarbia, and acidosis. The longer the compromise, the more likely the breathing efforts at birth would be poor, cardiac function of the fetus may be compromised, and tone may be affected in late stages.

Resuscitation efforts, when needed, must help the newborn to successfully make the physiologic respiratory and circulatory transitions at birth:

- The *lungs expand* (fluid is replaced by air), effective breathing (gas exchange) is established, and hypoxia and hypercarbia do not happen.
- *Pulmonary vascular resistance falls* and perfusion of alveoli is established, allowing gases to be exchanged with alveolar air.
- The right-to-left circulatory shunts terminate.

The partial pressure of oxygen (PO_2) in both the alveoli and the accompanying pulmonary circulation rapidly increases from the fetal level of approximately 25 mm Hg to values of 50 to 70 mm Hg. This 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. Adequate systemic arterial oxygenation and carbon dioxide elimination result from perfusion of well-expanded, well-ventilated lungs and adequate systemic circulation.

Fetuses initially respond to brief hypoxia by irregular respirations and apnea—*primary apnea*. Rapid recovery from this state is generally accomplished with gentle stimulation and PPV (breathing), if necessary. If the period of hypoxia continues, the fetus will irregularly gasp and lapse into *secondary apnea*. Infants born during this period progress to hypotension and bradycardia; they require extensive resuscitation with assisted ventilation and often chest compressions and medications.

Why is resuscitation in babies different from that in children or adults? Newborn babies who need resuscitation often have problems related to ineffective ventilation, unlike adults who most often have cardiac arrest as the primary life-threatening condition. Therefore, the focus of neonatal resuscitation differs totally, *with establishing ventilation being central to resuscitation.* In adults, the focus is on chest compression, defibrillation, and cardiac medications.

III. RESUSCITATION ALGORITHM. See Figure 4.1.

A. Before birth of baby

1. Identifying high-risk pregnancies
2. Antenatal counseling, team briefing, and equipment check

B. After birth of baby

1. Delayed cord clamping
2. Rapid assessment at birth—term/preterm, tone, and breathing/crying
3. Routine care—stay with the mother
4. Initial steps—temperature, airway, and breathing
5. Oxygen/continuous positive airway pressure (CPAP)
6. Breathing—PPV
7. Alternative airway—intubation/laryngeal mask airway (LMA)
8. Chest compressions
9. Medications
10. Documentation of resuscitation and post-resuscitation care
11. Debriefing

A. Before birth of baby

1. **Identifying high-risk pregnancies.** Anticipation is the key to adequate preparations for a neonate likely to require resuscitation at birth. It is estimated that 10% of neonates require some assistance at birth, whereas <1% require extensive resuscitation. The delivery of high-risk pregnancies requires at least two skilled persons to be available for assessment and triage. One of the members should be skillful in chest compressions, umbilical catheterization, and medications, if necessary (*there should be one person for all deliveries exclusively for the baby, even for those deliveries with no identified risk, who can assess the baby and complete initial steps and PPV; he or she should call for additional help as soon as the baby needs any help at birth*).

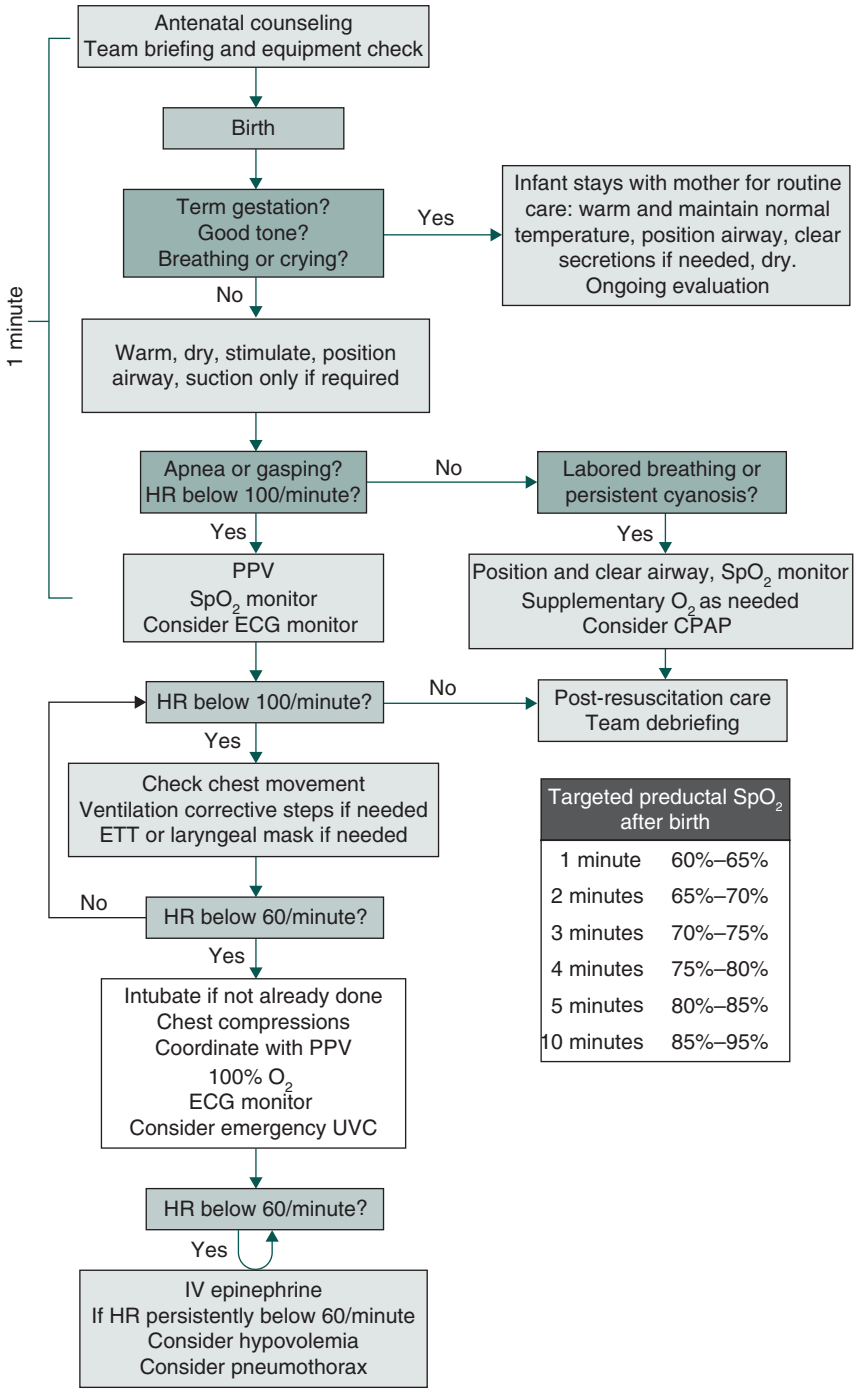

Figure 4.1. Neonatal resuscitation algorithm—2020 update.

The *obstetrician should notify* the pediatrician about any medical, obstetric, and fetal concerns; the *pediatrician should then prepare* for the specific anticipated problems.

The problems should be discussed with the parent(s), if time permits. The following antepartum and intrapartum events warrant the presence of an experienced resuscitation team at delivery:

a. Antepartum risk factors (see Chapter 1)

- **i.** Prematurity (<37 weeks) and postmaturity (>41 weeks)
- **ii.** Fetal growth restriction, anticipated low birth weight (<2.5 kg), or high birth weight (>3.5 kg)
- **iii.** Oligohydramnios/polyhydramnios
- **iv.** Major congenital anomalies diagnosed prenatally
- **v.** Hydrops fetalis
- **vi.** Multiple gestation (see Chapter 11)

b. Evidence of non-reassuring fetal status

- **i.** Decreased fetal movement or abnormalities of umbilical vessel Doppler flow studies
- **ii.** Meconium staining of the amniotic fluid (see Chapter 35)
- **iii.** Category II or III fetal heart rate tracing (Chapter 1)
- **iv.** Acute perinatal event (e.g., placental abruption, cord prolapse)

c. Labor and delivery conditions

- **i.** Cord prolapse
- **ii.** Abruptio placentae/significant vaginal bleeding
- **iii.** Abnormal presentations—breech extraction
- **iv.** Forceps/vacuum-assisted delivery
- **v.** Prolonged or unusual labor
- **vi.** Concern about possible shoulder dystocia
- **vii.** General anesthesia
- **viii.** Chorioamnionitis
- **ix.** Maternal illness
  - **a)** Diabetes mellitus
  - **b)** Rh or other isoimmunization
  - **c)** Chronic hypertension or pregnancy-induced hypertension
  - **d)** Narcotic analgesics given to the mother within 4 hours of birth

2. Antenatal counseling, equipment check, and team briefing

a. Antenatal counseling of parents. Introduce the resuscitation team and potential risk factors, and plan in case of anticipated risk. Preparing for resuscitation includes gathering important information.

Following questions need to be asked. They include the following:

- Is the baby term or preterm?
- Is it a singleton or multiple pregnancy?

- Is the liquor clear or meconium stained?
- Are there any other risk factors?
- What is the cord management plan?

b. Equipment check. Necessary equipment must be present, clean and functioning. Each delivery room should be equipped with the following:

- **Routine care.** Sterile blade and umbilical cord tie/cord clamp
- **Warmth.** Radiant warmer
- **Caps.** Plastic wrap for covering the baby/exothermic mattress
- **Transport incubator**
- **Airway**
  - Bulb suction
  - Suction catheter 10 and 12 F and wall suction <100 mm Hg
  - Shoulder roll
- **Assessment.** Stethoscope/ECG leads (optional)
- **Breathing**
- **PPV device**
  - T-piece/self-inflating/flow inflating
  - Term and preterm face mask
  - Flow meter set at 10 L/minute
  - Oxygen source
  - Blender with adjustable flowmeter and adequate length of tubing
  - Warm and humidified oxygen is desirable
  - **Monitoring equipment.** Pulse oximeter and disposable probes. Signal extraction technology (SET) enhanced pulse oximeters allow faster assessment of saturation
  - Signal extraction technology–enhanced pulse oximeters allow better and faster detection of saturation.
- **Alternate airway**
  - Laryngoscope with 0, 1, and 00 blades; extra batteries
  - Endotracheal (ET) tubes 2.5, 3, 3.5, and 4; tapes and scissors
  - LMA number 1
  - Orogastric tube and syringe
  - End tidal carbon dioxide ($ETCO_2$) monitor (optional)
- **Medications**
  - Epinephrine
  - Normal saline
  - Syringes (1.0, 10.0 mL)
  - Umbilical venous catheter and procedure tray
- **Universal precautions.**
  - Personal protective equipment (PPE)

- Caps
- Goggles or glasses
- Gloves
- Impervious gowns (*these have become particularly relevant in view of the ongoing COVID epidemic*)

Preparation of equipment. On arrival in the delivery room, check that the transport incubator is plugged in and warm and has a full oxygen tank. While the history or an update is obtained, the following should be done:

- Ensure that the radiant warmer is switched on and that three clean towels are prewarmed.
- Check oxygen source and set blender to room air for a term infant and up to 30% for a preterm infant; flow is set as per manufacturer's recommendation for the T-piece resuscitator (10 L/minute).
- Test the T-piece resuscitator and set to positive end-expiratory pressure (PEEP) of 5 to 6 and peak inspiratory pressure (PIP) of 20 to 25 mm Hg; check the self-inflating bag by feeling the pressure against your palm. Be sure that the proper-sized mask is present (term/preterm).
- Make sure that the laryngoscope light is bright and has an appropriate blade for the anticipated baby (no. 1 for full-term neonates, no. 0 for premature neonates, no. 00 for extremely low-birth-weight neonates).
- Set out an appropriate ET tube for the expected birth weight (3.5 mm for full-term infants, 3.0 mm for premature infants >1,250 g, and 2.5 mm for extreme preterm infants).
- If the clinical situation suggests that extensive resuscitation may be needed, the following actions may be required:
  - Set up an umbilical catheterization tray for venous catheterization (3.5- and 5-French catheters).
  - Draw up 1:10,000 epinephrine and isotonic saline for catheter flush solution and volume replacement.

c. Team briefing. A team prebriefing is needed to assign roles to team members to ensure smooth performance during the resuscitation. Such briefing before and debriefing after resuscitation have been shown to improve short-term clinical outcomes of infants and performance of the staff (2020 guidelines). One person is assigned as the team leader who takes responsibility and oversees the entire procedure. The pediatrician should introduce himself or herself to the obstetrician and anesthetist, the mother (if she is awake), and the father (if he is present).

B. After birth of baby

1. Delayed cord clamping. 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. The infant should be placed on the maternal chest or abdomen, dried, and kept warm. In a sick neonate, placental transfusion is known to stabilize the blood pressure and hematocrit, but current guidelines recommend

immediate cutting of the cord and shifting the sick neonate to the radiant warmer for assessment and resuscitation.

In infants who require resuscitation for inadequate or absent respiratory effort, the cord should be clamped and divided shortly after birth. Ongoing studies continue to evaluate the feasibility and effectiveness of providing resuscitation with the umbilical circulation still intact. Cord milking is currently not recommended, higher rates of IVH were found in babies born before 28 weeks gestation.

2. **Rapid assessment at birth.** Immediately following delivery, begin a process of evaluation, decision, and action (resuscitation).

   Three questions need to be asked after the baby is born:

   - Is the baby term?
   - Is the tone good?
   - Is the baby breathing or crying?

3. **Routine care: Infant breathes spontaneously and has good tone.** If the answer to the above-mentioned questions is YES, the baby is placed on the mother's abdomen (for warmth). Cord clamping is delayed for 1 minute. The infant is dried with warm linen. Early skin-to-skin contact is initiated and continued for a duration of 1 hour. Breastfeeding is initiated as soon as possible. This situation is found in >90% of all term newborns, with a median time to first breath of approximately 10 seconds. Following (or during) warming, drying, and positioning, the infant should be assessed.

4. **Initial steps: warmth, airway, and breathing.** In case the infant has poor tone or breathing efforts, the newborn is taken to the radiant warmer for resuscitation. Dry the infant completely and discard the wet linen. Ensure that the infant remains warm.

   Place the infant with the head in the midline position, with slight neck extension (a shoulder roll of 1-inch height will ensure neck deflexion). 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. If meconium-stained amniotic fluid is present, be vigilant for the increased possibility of upper airway obstruction and have equipment for suctioning available (Chapter 35). Routine suction is not recommended, even in nonvigorous babies.

   Some newborns do not immediately establish spontaneous respiration but will rapidly respond to tactile stimulation that includes rubbing the back (e.g., cases of **primary apnea**). More vigorous or other techniques of stimulation have no therapeutic value and are potentially harmful. If breathing does not start after **two** attempts at tactile stimulation, 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.

   Tactile stimulation by tapping the sole or rubbing the back gently may help initiate breathing, if effective breathing is not established despite warmth and clearing airway.

5. **Oxygen/CPAP**

   a. **Do rapid assessment after initial steps.** Assess breathing, heart rate, and color (saturation).

   b. **If the infant breathes spontaneously and has good tone, but the overall color appears cyanotic** (this situation is not uncommon), a pulse oximeter should be placed on the right upper extremity (usually the hand) as soon as possible after birth. Often the measured saturation levels improve rapidly without the use of oxygen. If the saturation does not improve, oxygen may be started to maintain saturation levels in the reference range.

   c. **Supplemental oxygen.** In the fetal life, oxygen saturation levels are well below those 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 truly normal for several minutes. Excessive oxygen is proven to be harmful to the newborn. One must not provide oxygen with intentions to see the magic saturation number of 90 or more immediately after birth. 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 pulse oximeter should be attached to a "preductal" site (i.e., the right upper extremity). It is recommended that pulse oximeter be used to measure saturations to avoid overtreatment, if supplemental oxygen is administered.

      The concentration of oxygen used to begin resuscitation remains an area of debate. Several trials have shown that survival is improved when resuscitation is initiated with room air compared with 100% oxygen in full-term infants. Studies of preterm infants have shown that the use of air or a minimally increased concentration of a blended air–oxygen mixture as the initial gas resulted in an appropriate rise in oxygen saturation levels after birth. Once assisted ventilation or supplemental oxygen use is begun, the oxygen concentration should be adjusted so that the measured preductal oxygen saturation value lies within a specified minute-specific reference range (Table 4.1) as advocated by the NRP.

      Room air is recommended as the initial concentration for term babies and 21% to 30% oxygen for premature babies.

      - Air should be used if blended oxygen is not available.

Table 4.1. Target Preductal 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%

- Oxygen concentration should be increased to 100% if bradycardia (heart rate <60 bpm) does not improve after 90 seconds of resuscitation.

The early initiation of CPAP in a preterm infant who is spontaneously breathing but exhibiting respiratory distress in the delivery room is strongly advocated. CPAP may also be considered if the baby is breathing and heart rate is >100 bpm, but the baby cannot maintain saturation in the target range despite free-flow oxygen. In infants born at 29 weeks of gestation or earlier, CPAP at birth was as effective as 'intubation and surfactant' in eventual outcomes (death or BPD). Early CPAP use reduced the need for intubation, mechanical ventilation, and exogenous surfactant administration. In spontaneously breathing preterm infants with respiratory distress, use of CPAP in the delivery room is clearly a preferred choice over intubation and mechanical ventilation. A T-piece resuscitator is preferred over self-inflating bag, if PPV has to be given.

6. **PPV.** In the newly born infant, essentially all resuscitation problems within the initial postnatal period occur because of inadequate respiratory effort or some obstruction to the airway. Therefore, the initial focus must be on ensuring an adequate airway and adequate breathing.

Indications for PPV are as follows:

- The infant is apneic/gasping despite tactile stimulation.
- The infant has a heart rate of <100 bpm despite apparent respiratory effort.

Apnea with bradycardia represents **secondary apnea** and requires treatment with PPV. When starting this intervention, call for assistance if your team is not already present. When indicated, PPV must be started within 1 minute of birth. A T-piece resuscitator is connected to an air–oxygen blender (initial concentration depending on gestational age, 21% for >35 weeks and 21% to 30% for <35 weeks) at a rate of 10 L/minute and to a mask of appropriate size. The mask should cover the chin and nose but leave the eyes uncovered. After positioning the newborn's head in the midline with slight extension, the initial breath should be delivered at a peak pressure that is adequate to produce appropriate chest rise; often, 20 cm H_2O is effective (30 to 40 cm H_2O may be required in the first few breaths). This will establish functional residual capacity, and subsequent inflations will be effective at lower inspiratory pressures.

The inspiratory pressures for subsequent breaths should be adjusted to ensure that there is just adequate but not excessive chest rise. In infants with normal lungs, this inspiratory pressure is usually no more than 15 to 20 cm H_2O. In infants with known or suspected disease causing decreased pulmonary compliance, continued inspiratory pressures in excess of 20 cm H_2O may be required.

If no chest rise can be achieved despite apparently adequate pressure and there is no evidence of a mechanical obstruction/leak, intubation should be considered. Especially in premature infants, every effort should be made to use the minimal pressures necessary for chest rise and the maintenance of normal oxygen saturation levels. A rate of 40 to 60 breaths per minute should be used, and the infant should be reassessed in 15 to 30 seconds. It is usually preferable to aim for a rate closer to 40 bpm, as many resuscitators deliver less adequate breaths at higher rates. Support should be continued until respirations are

spontaneous, and the heart rate is >100 bpm; effectiveness is best gauged by improvements in the heart rate.

The use of a T-piece resuscitator enhances the ability to provide consistent pressure-regulated breaths. It offers greater control over manual ventilation by delivering breaths of reproducible size (peak and end-expiratory pressures) and a simplified method to control the delivered breath rate. A self-inflating or flow-inflating bag may be used for PPV.

a. Adequacy of ventilation. *The most important indicator of adequate ventilation is a rise in the heart rate.* The first assessment after initiation of PPV should be at 15 seconds; if there is insufficient improvement in the heart rate, check for chest movement. If there is a rise in the heart rate and adequate chest rise, then PPV is continued for a period of 30 seconds. In case of poor chest rise at 15 seconds, the acronym MRSOPA is used to optimize ventilation:

- M—mask adjustment
- R—reposition infant
- S—suction airway
- O—open airway
- P—pressure to be increased
- A—alternate airway (intubation)

If the baby's heart rate is >100/minute and he/she has good tone and respiratory efforts, one may decrease rates and pressure of PPV, provide oxygen or CPAP for a while, and observe.

7. **Alternative airway** *is absolutely indicated* only when a diaphragmatic hernia or airway anomaly is suspected or known to exist. The use of an alternate airway 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. Intubation may be necessary for the suction of airway or surfactant administration (both meconium and prematurity are not indications for intubation *per se*). 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, an LMA 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 the heart rate to >100 bpm and a rapid improvement in oxygen saturation. Detection of expiratory carbon dioxide 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 all lined up 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 an approximately 60° 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). Appropriate-sized ET tubes need to be used as per the birth weight or gestational age. The depth of insertion of an ET tube is given by the formula NTL + 1, where NTL denotes the nasotragal length. The nasotragal length is measured from the columella to the tragus. One must complete the intubation in 30 seconds. If repeated efforts at intubation fail, one must consider a LMA. Laryngeal masks are easy to insert and are effective for ventilating newborns weighing >2,000 g. They should be considered when bag-and-mask ventilation is not effective and intubation is unsuccessful or no skilled intubator is immediately available. LMA can be life saving, and units must target availability, education, and skill development.

8. **Chest compression.** If the heart rate remains below 60 bpm, despite 30 seconds of effective PPV, chest compression needs to be initiated. Prior to initiation of chest compression, the resuscitator needs to call for additional help, preferably intubate the infant, and switch to 100% oxygen. 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. Compress the sternum about one-third of the antero-posterior diameter of the chest at a rate of 90 times per minute in a ratio of three compressions for each breath. PPV should be continued at a rate of 30 breaths per minute, interspersed in the period following every third compression. After 60 seconds of chest compression and PPV, briefly stop chest compression and check the heart rate. ECG is more accurate than auscultation but is not feasible in most neonatal units in Asia. ECG must be considered in a baby, when alternative airway is required. If the baby's heart rate is >60 bpm, chest compression should be discontinued, and ventilation continued until respiration is spontaneous. If no improvement is noted and the heart rate remains below 60 bpm, compression and ventilation should be continued. Epinephrine should be considered.

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

9. **Medications.**

   a. **Epinephrine.** If the heart rate of the baby remains <60 bpm despite adequate ventilation with 100% oxygen (for 30 seconds) and chest compressions (60 seconds), epinephrine (1:10,000, 0.1 mg/mL) should be given. The most accessible intravenous (IV) route for neonatal administration of medications is catheterization of the umbilical vein (see Chapter 69) (or intraosseous route), which should be done rapidly and aseptically. The umbilical catheter should be advanced only 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.

The recommended dose of IV epinephrine 0.1 to 0.3 mL/kg (up to 1.0 mL) of a 1:10,000 epinephrine solution should ideally be given through the umbilical venous catheter and flushed with 3 mL normal saline into the central circulation. This dose may be repeated every 3 to 5 minutes if necessary, and there is no apparent benefit to higher doses.

When access to central circulation is difficult or delayed, epinephrine may be delivered through an ET tube for transpulmonary absorption, although a positive effect of this therapy has been shown only in animals at doses much higher than those currently recommended. In case there is difficulty in accessing the IV route, epinephrine can be administered through the intratracheal route/intraosseous route. The intratracheal route of administration may be considered while IV access is being established, using doses of 0.5 to 1.0 mL/kg of 1:10,000 dilution (0.05 to 0.10 mg/kg). These larger doses need not be diluted to increase the total volume. If two doses of epinephrine do not produce improvement, additional doses may be given, but one should consider other causes for continuing depression.

b. Volume expansion. Indications for volume expansion include evidence of acute bleeding or poor response to resuscitative efforts and newborns who have pallor and shock in the delivery room (see Chapters 40 and 43). 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. These newborns will be pale, tachycardic (>180 bpm), and tachypneic, with poor capillary filling and weak pulses.

After starting respiratory support, immediate transfusion of normal saline boluses may be necessary if acute blood loss is the underlying cause. A volume of 10 mL/kg can be given through an umbilical venous catheter, over 5 to 10 minutes. If clinical improvement is not seen, causes of further blood loss should be sought, and blood replacement should be considered. 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.

Sodium bicarbonate and naloxone are not used in acute care, and need not be available in the labor room.

10. Documentation of resuscitation and post-resuscitation care. The whole sequence of resuscitation must be documented with time in detail. Ideally an independent person should document in real time. In resource-limited settings, where there are not enough people to attend all births, the same person documents after the resuscitation is complete. Use of a stop clock (Apgar timer) allows reasonable orientation to time, even in stressful situations.

a. Apgar scores. 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.

i. One-minute Apgar score. *It does not correlate with the outcome* and hence Apgar should not guide resuscitation.

This score generally correlates with the umbilical cord blood pH and is an index of intrapartum depression. Babies with a score of 0 to 4 have been shown to have a significantly lower pH, higher partial pressure of carbon dioxide ($PaCO_2$), and lower buffer base than those with Apgar scores >7.

In the very low-birth-weight (VLBW) infant, a low Apgar score may not indicate severe depression. As many as 50% of infants with gestational ages of 25 to 26 weeks and Apgar scores of 0 to 3 have a cord pH of >7.25. Therefore, a VLBW infant with a low Apgar score cannot be assumed to be severely depressed.

The more prolonged the period of severe depression (i.e., Apgar score 3), the more likely is an abnormal long-term neurologic outcome. Nevertheless, many newborns with prolonged depression (>15 minutes) are normal on follow-up. The American Academy of Pediatrics is currently recommending an expanded Apgar score reporting form, which details both the numeric score and the concurrent resuscitative interventions (see Table 4.2).

ii. Combined Apgar. It consists of the following parameters: **C**PAP, **O**xygen, **M**ask and **B**ag, **I**ntubation, **N**eonatal chest compressions, **E**xogenous surfactant, and **D**rugs. Each intervention is scored 0 (if performed) and 1 (if not performed). This is taken in combination with the above-specified Apgar score, and a score <10/17 is an indicator for high morbidity/mortality.

b. Post-resuscitation care. A severely compromised fetus and newborn may have multiorgan dysfunction as a result of hypoxia-ischemia. Every organ system (Table 4.3) must be monitored clinically and supported with lab tests. Early intervention will limit the morbidities associated with severe hypoxia- ischemia.

IV. SPECIAL SITUATIONS

A. Meconium aspiration (see Chapter 35). There are significant changes in resuscitation practices in the setting of meconium-stained amniotic fluid.

1. Routine suctioning of all meconium-stained infants, at birth, is not recommended.

2. 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.

a. Infants who are vigorous should be treated as normal, despite the presence of meconium-stained fluid.

Table 4.2. Expanded Apgar Reporting Form

SIGN	0	1	2	1 minute	5 minute	10 minute	15 minute	20 minute
Color	Blue or pale	Acrocyanotic	Completely Pink					
Heart rate	Absent	<100 minute	>100 minute					
Reflex irritability	No response	Grimace	Cry or active withdrawal					
Muscle tone	Limp	Some flexion	Active motion					
Respiration	Absent	Weak Cry: hypoventilation	Good, crying					
			Total					

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

b. If the infant is not vigorous, appropriate resuscitative measures should be given. 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. In these infants, oral suctioning needs to be done.

3. For infants at risk for meconium aspiration syndrome who show initial respiratory distress, oxygen saturation levels should be monitored and babies should be monitored for a few hours.

B. Prematurity. Premature infants require additional special care in the delivery room; they are more likely to need resuscitation. There should be a team of experienced people to receive a preterm baby at birth.

Preterm babies are more vulnerable to heat loss, oxygen injury, hypoglycemia, and brain injury; they may have immature lung and infection. Extra care is necessary to minimize the heat loss: Set room temperature to 23°C to 25°C (Neonatal Life Support 2020), and use plastic wraps or bags (<32 weeks' gestation), caps, and/or exothermic mattresses to prevent heat loss. Use blended oxygen–air mixtures and pulse oximetry to guide oxygen therapy (start with 21% to 30% FiO_2).

Table 4.3. Clinical Signs, Laboratory Findings, and Management

Organ System	Clinical Signs and Laboratory Findings	Management Considerations
Neurologic	Apnea, seizures, irritability, poor tone, altered neurologic examination, poor feeding coordination	Monitor for apnea. Support ventilation as needed. Monitor glucose and electrolytes. Avoid hyperthermia. Consider anticonvulsant therapy. Consider therapeutic hypothermia. Consider delayed initiation of feedings and use of intravenous fluids.
Respiratory	Tachypnea, grunting, retractions, nasal flaring, low oxygen saturation, pneumothorax	Maintain adequate oxygenation and ventilation. Avoid unnecessary suctioning. Cluster care to allow periods of rest. Consider antibiotics. Consider x-ray and blood gas. Consider surfactant therapy. Consider delayed initiation of feedings and use of intravenous fluids.
Cardiovascular	Hypotension, tachycardia, metabolic acidosis	Monitor blood pressure and heart rate. Consider volume replacement or inotrope administration if baby is hypotensive.
Renal	Decreased urine output, edema, electrolyte abnormalities	Monitor urine output. Monitor serum electrolytes as indicated. Monitor weight. Restrict fluids if baby has decreased urine output and vascular volume is adequate.
Gastrointestinal	Feeding intolerance, vomiting, abdominal distention, abnormal liver function tests, gastrointestinal bleeding	Consider abdominal x-ray. Consider delayed initiation of feedings and use of intravenous fluids. Consider parenteral nutrition.
Endocrine–metabolic	Metabolic acidosis, hypoglycemia (low glucose), hypocalcemia (low calcium), hyponatremia (low sodium), hyperkalemia (high potassium)	Monitor blood glucose. Monitor serum electrolytes as indicated. Consider intravenous fluids. Replace electrolytes as indicated.
Hematologic	Anemia, thrombocytopenia, delayed clothing, pallor, bruising, petechiae	Monitor hematocrit, platelets, and coagulation studies as indicated.
Constitutional	Hypothermia	Delay bathing.

Therapeutic hypothermia must be considered.

Surfactant-deficient lungs are poorly compliant, and higher ventilatory pressures may be needed for the first and subsequent breaths. CPAP is the preferred respiratory support, if the preterm baby has respiratory distress or cyanosis. If respiratory efforts are poor, or the baby has significant apnea, PPV is required; restrict PIP to a minimum. If the baby requires intubation for resuscitation, consider surfactant therapy (ideally in the neonatal intensive care unit [NICU], rather than in the labor room). Avoid large/rapid saline boluses. Post-resuscitation care with close attention to temperature, glucose monitoring, and apnea monitoring is important. Depending on the reason for premature birth, perinatal infection is more likely in premature infants, which increases their risk of perinatal depression.

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. Pneumothorax (unilateral or bilateral) and pneumopericardium should be suspected by decreased breath sounds, ruled out by transillumination or diagnostic thoracentesis (see Chapter 38) and treated if present.

D. Hydrops fetalis. The resuscitation requires at least four members with an experienced member leading the resuscitation. The infant may be depressed and hypovolemic, and with effusions. In addition to initial steps and intubation, the infant may require pleural drainage, ascitic tap, and fluid boluses. Suspect pleural effusion if there is decreased breath sound in the setting of hydrops. The baby will need most often umbilical catheterization for volume replacement and medications.

E. Airway obstruction by thick secretions may be considered in the setting of meconium-stained amniotic fluid. If ventilation is ineffective despite intubation, suction using a 3- to 5-French suction catheter must be done, before proceeding with further steps. The combination of retrognathia, cleft palate, and glossoptosis constitutes Pierre Robin sequence that presents with a difficult airway. Pierre Robin anatomy is managed by keeping the baby prone, passing a 2.5 size ET tube through the nose, and LMA if necessary. Intubation can be exceedingly difficult.

Choanal atresia can be managed by an oropharyngeal airway or a modified pacifier.

F. Abnormalities of fetal lung. Congenital diaphragmatic hernia (CDH) is known antenatally in most cases; one may suspect CDH in a baby if there is asymmetry in breath sounds, shift in heart sounds and scaphoid abdomen. Avoid mask ventilation and intubate the baby early. A feeding tube must be inserted to prevent bowel distension by excess air being swallowed; bowels distended by air will make breathing more difficult.

G. Poor respiratory efforts and tone. Baby's saturation and heart rate improve on PPV, but respiratory effort and tone remain poor.

If the baby has poor respiratory efforts due to maternal narcotics, establish breathing by PPV. Naloxone is not an emergency care medication; it may be administered later if indicated.

Neuromuscular disorders, brain disorders, magnesium sulfate, and general anesthesia given to the mother produce a similar picture.

H. Out-of-hospital resuscitation. One may have to adapt to the situation, keeping the principles of resuscitation in mind. Skin-to-skin contact/plastic bags may protect from hypothermia; mouth-to-mouth PPV may be necessary. In emergency

wards, an intraosseous needle may be necessary for medications, if umbilical cannulation is not possible.

I. **Bradycardia despite adequate ventilation with good perfusion.** In case the infant has good tone, good respiratory efforts, and good saturation and still has bradycardia, congenital heart block needs to be suspected. Extensive resuscitation with chest compression and epinephrine should not be started as a reflex. With good antenatal sonography, most of these cases are antenatally confirmed.

V. EVOLVING RESUSCITATION SCIENCE. Recent NRP has focused on evidence-driven changes in the practice of resuscitation; also many new devices have become available to monitor and manage babies who need resuscitation at birth.

A. **End-tidal or expiratory CO_2 detectors/flow sensors.** They help in confirming ET tube placement in the trachea. These devices may also have utility during bag-and-mask ventilation in helping to identify airway obstruction. They are not available in most delivery rooms in India and Asia. Also, there is not sufficient evidence to support the routine use of CO_2 detectors. In fact, in one study flow sensors were more sensitive and quicker in detecting ET intubation than CO_2 detectors.

B. **Passive cooling in labor room.** Therapeutic hypothermia is the standard therapy for infants born at ≥36 weeks' gestation who manifest moderate to severe hypoxic-ischemic encephalopathy. It is likely that earlier initiation may be necessary for maximum effectiveness. Passive cooling in the labor room and during transfer to the NICU has been suggested and may be feasible at all levels of health care. Yet there are concerns on the safety and effectiveness of passive cooling. Servo-controlled cooling was found to be faster and safer; out-of-range temperatures were far fewer. Hyperthermia must always be avoided.

VI. WITHHOLDING OR WITHDRAWING RESUSCITATION. Resuscitation at birth aims at improving survival and decreasing neuromorbidity.

In those situations where survival is unlikely or associated morbidity is very high, *extensive and prolonged resuscitation must be avoided* (see Chapter 19).

If there are no signs of life in an infant after 10 to 20 minutes (2020 guidelines) of aggressive resuscitative efforts, with no evidence of correctible factors, discontinuation of resuscitation efforts may be considered. It is appropriate to assess the availability of advanced intensive care, including therapeutic hypothermia, the baby's gestational age, and any specific circumstances known prior to birth. There are case series of reasonable intact survival in babies resuscitated with Apgar 0 after 10 minutes.

Resuscitation must be initiated and continued, if indicated, *except* in genetically established conditions such as trisomy 13 and 18, and major malformations such as anencephaly and extreme preterm birth. If the physician is sure, from the available information, that survival is unlikely, then initiating resuscitation is not ethical. Within Europe, neonatologists from different countries considered different thresholds of viability between 22 and 24 weeks. A consensus guideline from the Philippines recommends resuscitation/non-resuscitation between 24 and 28 weeks as optional, given the limitations of resources at most levels of care. Each country/region/hospital must have a guiding process, to avoid conflict between physicians and between physicians and parents. Regional laws and hospital ethics committee

must guide in difficult situations. The Indian Academy of Pediatrics formulated an end-of-life care consensus statement for sick children in 2014; in 2020, ICMR has published Do Not Attempt Resuscitation (DNAR) guidelines. Although they do not mention neonates specifically, the guiding principles are clearly outlined.

Humane and culturally sensitive palliative care should be followed in cases of noninitiation or stopping of resuscitation. If possible, an opportunity to understand parental wishes under these circumstances may be extremely helpful. The parents must be presented with accurate, unbiased information. If the parents' opinion is unknown or uncertain, resuscitation should be initiated and continued as standard and full care.

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5 Nonimmune Hydrops Fetalis

Kenneth J. Moise Jr. and Suzanne Lopez

KEY POINTS

- Hydrops fetalis has classically been defined as the presence of edema or excess of extracellular fluid in at least two fetal body compartments.
- With routine use of Rhesus (Rh) immune globulin for the prevention of Rh alloimmunization, 95% of hydrops cases are due to nonimmune causes.
- Plans for neonatal resuscitation should account for the location and severity of fluid collections and assess the need for immediate drainage as part of the initial resuscitation; *ex utero* intrapartum treatment (EXIT) procedure may be helpful. Three or more trained persons may be required to be present at the time of delivery.
- Definitive treatment would depend on the underlying cause; in a few cases, the cause may not be found.

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, 5.2, 5.3, 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 3,700 pregnancies.

III. ETIOLOGY (Table 5.1). The advent of the widespread use of Rhesus (Rh) immune globulin for the prevention of RhD alloimmunization has resulted in a shift in favor of 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 review of literature by Bellini et al. between 1997 and 2007, involving 5,437 patients, found cardiovascular malformations the most common etiology followed by idiopathic causes, chromosomal abnormalities, and hematologic etiologies. A subsequent review by the same authors between 2007 and 2013 revealed. A decreasing trend in chromosomal abnormalities, thoracic problems, urinary tract malformations, and twin–twin transfusion was noted between

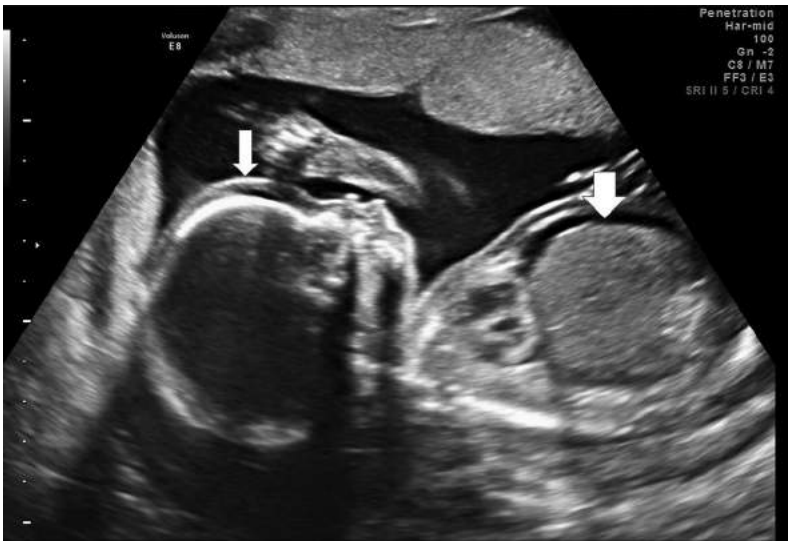

Figure 5.1. Scalp edema (*small arrow*) and ascites (*larger arrow*) in a case of nonimmune hydrops fetalis secondary to parvovirus at 22 weeks' gestation.

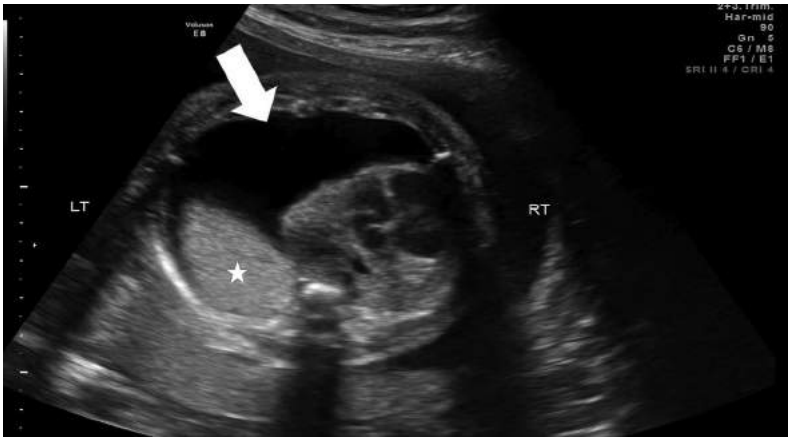

Figure 5.2. Large left-sided pleural effusion (*arrow*) in a fetus at 28 weeks' gestation with bronchopulmonary sequestration (lesion indicated by *star*).

the two consecutive time periods while etiologies of lymphatic dysplasia and gastrointestinal causes appear to have increased. The overall contributions of the various etiologies from the two series are noted in Table 5.1.

A recent systematic review addressed the issue of evaluation for lysosomal storage disease in cases of NIHF. In the 676 cases that were specifically evaluated for these conditions, the incidence was 5.2% of all cases tested and 17.5% of cases initially

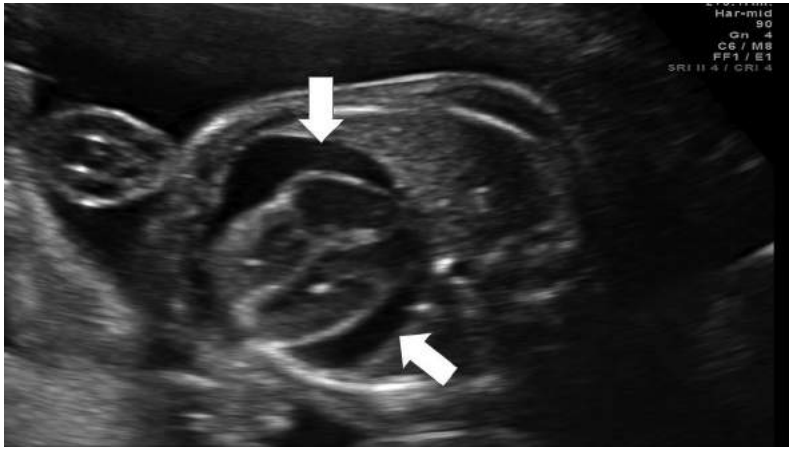

Figure 5.3. Pericardial effusion (between the *arrows*) in a recipient twin with severe twin–twin transfusion at 24 weeks' gestation.

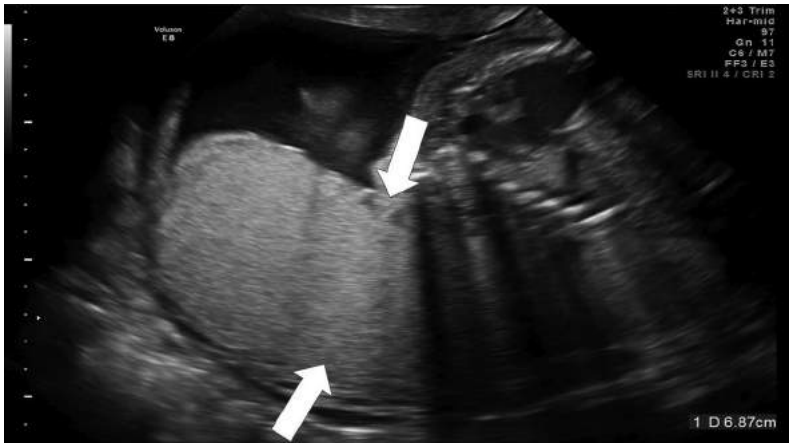

Figure 5.4. Placentomegaly (between the *arrows*) at 25 4/7 weeks' gestation associated with nonimmune hydrops fetalis in a fetus with an unbalanced atrioventricular canal and heterotaxy syndrome.

thought to be idiopathic. The three most common disorders were mucopolysaccharidosis type VII, Gaucher's disease, and GM1 gangliosidosis.

IV. PATHOPHYSIOLOGY. Because the etiology of NIHF is so diverse, few studies have addressed the pathophysiology of this condition. Lymphatic return of interstitial fluid to the vascular space is either inadequate or compromised. Anatomical obstruction is present in cases of Turner's syndrome or lymphatic dysplasia, whereas a functional obstruction can occur due to elevated right atrial pressures noted in cases of severe fetal anemia (parvovirus) or tachyarrhythmias. Certain cardiac malformations (Ebstein anomaly) or intrathoracic tumors (congenital pulmonary airway

Table 5.1. Etiologies of Nonimmune Hydrops

Category	Percentage	Typical Causes
Cardiovascular	21.4	Hypoplastic left heart, Ebstein anomaly, endocardial cushion defect, bradyarrhythmias/tachyarrhythmias (congenital heart block, SVT, atrial flutter)
Idiopathic	18.2	—
Chromosomal	12.5	45 XO, trisomy 21, trisomy 18
Hematologic	10.1	α-Thalassemia, fetomaternal hemorrhage and severe anemia
Lymphatic dysplasia	7.5	Congenital lymphatic dysplasia
Infections	6.8	Parvovirus, CMV, adenovirus, enterovirus
Thoracic	5.3	CPAM, diaphragmatic hernia, extrapulmonary sequestration, hydrothorax, chylothorax
Twin–twin transfusion	5.3	Donor/recipient fetus (more common)
Syndromic	4.6	Noonan's syndrome
Miscellaneous	3.7	—
Urinary tract malformations	2.0	Urethral obstruction, prune belly syndrome
Inborn errors of metabolism	1.1	Lysosomal storage diseases
Extrathoracic tumors	0.7	Vascular tumors, teratomas, leukemia, hepatic tumors, neuroblastoma
Gastrointestinal	0.7	Meconium peritonitis, GI obstruction

CMV, cytomegalovirus; CPAM, congenital pulmonary airway malformation; GI, gastrointestinal.
Source: Modified from Bellini C, Domarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: an update. *Am J Med Genet* 2015;167A:1082–1088.

malformation [CPAM]) are associated with increased venous pressure and a resultant increase in the production of interstitial fluid. Alternatively, vasculitis from infection (cytomegalovirus) can result in intravascular protein loss and enhanced interstitial fluid production. Severe tissue hypoxia can lead to endothelial cell damage and capillary leak of fluid and protein. Severe anemia and hepatic extramedullary hematopoiesis may result in decreased production of plasma proteins leading to decreased plasma oncotic pressure and hypoalbuminemia.

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. These authors 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 should be undertaken. Special emphasis should be placed on the evaluation of cardiac structures and rhythm. If necessary, a fetal echocardiogram should be undertaken. The peak systolic velocity of the middle cerebral artery (MCA) >1.5 multiples of the median corrected for the gestational age has been associated with fetal anemia in cases of NIHF.

A careful maternal and reproductive 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

Table 5.2. Evaluation of Hydrops Fetalis

Prenatal Evaluation (Alive Fetus)	Prenatal Evaluation (Intrauterine Demise)
■ Maternal history* ■ Maternal blood type* ■ 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 ■ 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—liver, skin, heart, brain

*Evaluations performed in immune hydrops fetalis.
CMA, chromosomal microarray; FISH, fluorescent *in situ* hybridization; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.
Source: Modified from Bellini C, Domarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: an update. *Am J Med Genet* 2015;167A:1082–1088.

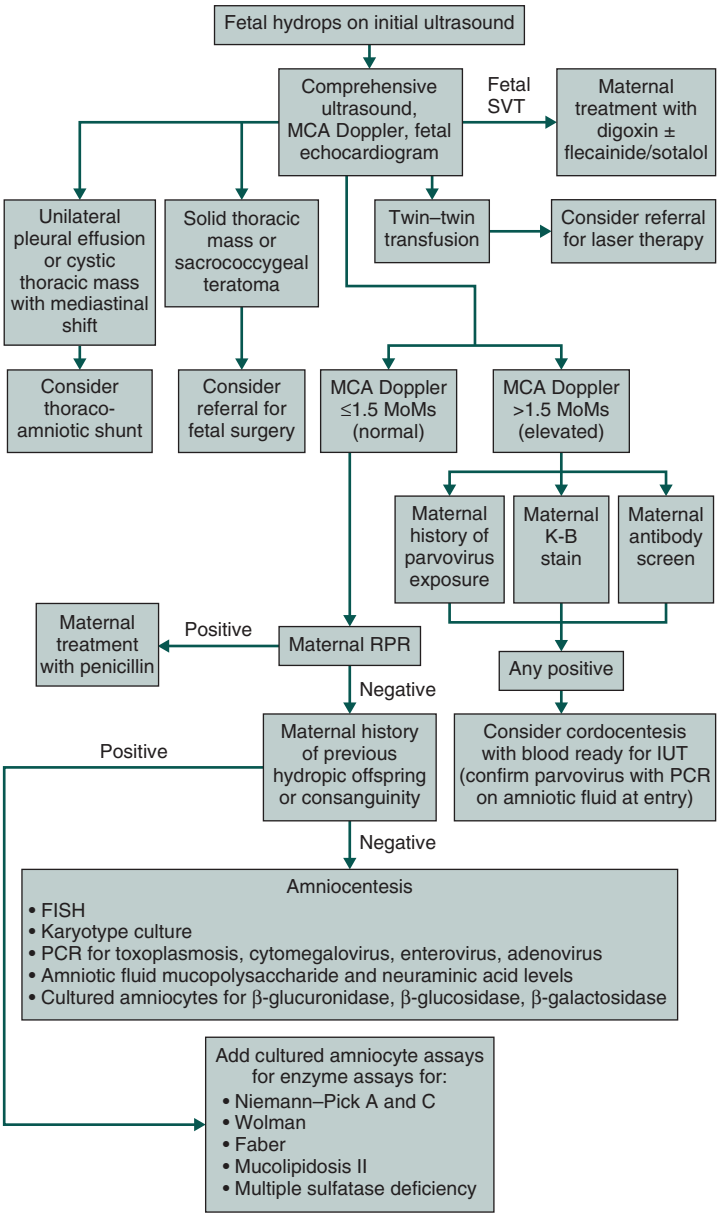

Figure 5.5. Algorithm for the management and treatment of nonimmune hydrops fetalis. FISH, fluorescent *in situ* hybridization; IUT, intrauterine transfusion; K-B, Kleihauer–Betke; MCA, middle cerebral artery; MoM, multiples of median; PCR, polymerase chain reaction; RPR, rapid plasma reagin; SVT, supraventricular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

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 contemplate lysosomal storage diseases. Similarly, a consanguineous relationship would also lead one to consider autosomal recessive diseases as the etiology. If the couple is of far Eastern descent, review of the maternal red cell mean corpuscular volume (MCV) (<82, abnormal) should lead to an evaluation for α-thalassemia.

The next step in the diagnostic evaluation usually entails maternal venipuncture. 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. Maternal serologies 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 panel of investigation. Amniotic fluid samples should be sent for fluorescent *in situ* hybridization (FISH), computerized 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 lysosomal storage disease panels.

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 (see Chapter 48). In one series of 1,019 pregnant women with seroconversion, the risk for fetal hydrops was 3.9%. The MCA Doppler can be used in an analogous fashion to confirm the anemia when there is an elevated peak systolic velocity of >1.5 multiples of the median. Although maternal serology (positive immunoglobulin M [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. In one series, intrauterine transfusion (IUT) of packed red cells was associated with survival in approximately 85% of cases, whereas those cases with hydrops that were observed with no intervention universally had a fatal outcome. 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 Bart's hemoglobin 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.

B. 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.

C. 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 betamimetics 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 usually successful in converting these to a sinus rhythm with subsequent resolution of NIHF.

D. Fetal lung lesions. Unilateral pleural effusions (typically a chylothorax) or a large, predominantly CPAM of the fetal lung represents 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 CCAM lesions 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.

E. Twin–twin transfusion. The recipient twin can exhibit NIHF in cases of twin–twin transfusion in up to 7% of cases. Laser photocoagulation of the putative placental anastomoses can result in complete resolution of the NIHF with an 80% perinatal survival. Most cases of donor NIHF occur after successful laser therapy. These cases are thought to be the result of the acute anemia that can occur during the laser procedure; they are transient and resolve spontaneously.

VII. MATERNAL COMPLICATIONS OF FETAL HYDROPS.

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's syndrome (also known as mirror syndrome, triple edema, and pseudotoxemia). First described in association with hydrops secondary to maternal Rh alloimmunization in 1892, many subsequent case descriptions have appeared in the literature secondary to NIHF due to a variety of etiologies. In a recent review of 56 cases published between 1956 and 2009, Braun et al. noted clinical and laboratory findings similar to those of preeclampsia. 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 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 should be undertaken.

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 that can be treated with *in utero* therapy. 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.

IX. NEONATAL MANAGEMENT OF FETAL HYDROPS

A. Predelivery consultation. Predelivery outpatient prenatal consultation with neonatology, pediatric subspecialty services, and perinatal palliative care team should be considered at tertiary care centers with a fetal medicine service. Prenatal consultations include discussion of postdelivery care of the fetal condition with and without premature delivery, tour of neonatal intensive care unit, and addressing specific neonatal questions (resuscitation, hospitalization course, outcomes, and possible birth plan). Consultation discussions can 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. 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 5.3). EXIT procedure (ex-utero intrapartum treatment procedure or placental circulation resuscitation) gives more time to stabilize the neonate at birth. 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, hypothyroidism, and pulmonary hypertension. Hemodynamic instability is

Table 5.3. 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 emergency umbilical venous catheterization)	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	

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 spaces. 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 the 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 is necessary for fluid management. Free water and salt intake 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 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 not to 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 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, and forces can lead to injury in the newborn.
- Other risk factors for birth injury include prematurity, instrumental birth, and certain maternal factors
- Shoulder dystocia is a major risk factor for brachial plexus injury
- Planned cesarean delivery for breech presentation decreases mortality and morbidity
- Posterior fossa subdural hematoma can cause brain stem compression leading to respiratory compromise and needs close monitoring
- Not all birth injuries are avoidable.
- A newborn at risk for birth injury should have a thorough examination, including a detailed neurologic evaluation.
- 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. Injuries caused by amniocentesis and intrauterine transfusions before birth are not considered birth injuries unlike those from fetal scalp electrodes and intrapartum heart rate monitoring.

A. Incidence. The birth trauma and injury rate fell from 2.6 per 1,000 live births in 2004 to 1.9 per 1,000 live births in 2012. The reported incidence of birth injuries is approximately 2% among singleton vaginal deliveries in a cephalic position versus approximately 1.1% for cesarean deliveries.

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. Obstetric instrumentation may increase the mechanical forces, amplifying or inducing a birth injury. 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 midforceps or 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 an 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.

Table 6.1 lists the birth injuries associated with various risk factors.

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.

Table 6.1. Risk Factors for Birth Trauma and Associated Injury

Risk Factors	Related Injuries
Forceps delivery	Facial nerve injuries
Vacuum extraction	Depressed skull fracture, subgaleal hemorrhage
Forceps/vacuum	Cephalohematoma, intracranial hemorrhage, shoulder dystocia, retinal hemorrhages
Breech presentation	Brachial plexus palsy, intracranial hemorrhage, gluteal lacerations, long bone fractures
Macrosomia	Shoulder dystocia, clavicle and rib fractures, cephalohematoma, caput succedaneum
Abnormal presentation (face, brow, transverse, compound)	Excessive bruising, retinal hemorrhage, lacerations
Precipitous delivery	Bruising, intracranial and extracranial hemorrhage, retinal hemorrhage

Adapted from: Akangire G, Carter B. Birth injuries in neonates. Pediatr Rev 2016;37(11):451–462.

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 the periosteum. The lesion is always confined by suture lines and does not cross the midline although can be bilateral over occipital or parietal region. It may occur in as many as 2.0% of all live births. It is more commonly seen in instrumented deliveries.

ii. An extensive cephalohematoma can result in significant hyperbilirubinemia. Hemorrhage is rarely serious enough to necessitate blood transfusion. Infection is also a rare complication and usually occurs in association with septicemia and meningitis. It may even cause erosion of the underlying bone with osteomyelitis and accompanying extradural empyema. Skull fractures have been associated with 5% 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. Anemia, hyperbilirubinemia, or secondary infection 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 without anatomic tamponade. A 1-cm increase in the depth of subgaleal space may hold up to 260 mL of blood.

iii. The clinical picture may be progressive and hence demands frequent reassessments (Table 6.2). The initial presentation ranges from no signs at birth, just a fluctuant swelling on the scalp, to a slow insidious onset or sometimes a rapidly progressive pallor and shock. The time to

Table 6.2. Management of Subgaleal Hemorrhage

1.	Anticipate a 40-mL blood loss for every 1-cm increase in occipitofrontal circumference
2.	Monitor urinary output and signs of shock
3.	Monitor serial hematocrit and evaluate for coagulopathy
4.	Transfuse packed red cells if the baby is in shock or has severe anemia, fresh frozen plasma (or cryoprecipitate) or platelets may be required in specific coagulation disorders.

Adapted from: Akangire G, Carter B. Birth injuries in neonates. Pediatr Rev 2016;37(11)451–462.

diagnosis is usually 1 to 6 hours after birth. With progressive spread, there is anterior displacement of the ears, periorbital swelling, and ecchymosis of the scalp. Rising lactate, low hemoglobin, and prolonged international normalized ratio (INR) are the indicators of progressing shock and impending circulatory collapse. The blood is resorbed slowly, and swelling gradually resolves. The mortality rate can range from 12% 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. Hourly monitoring of head circumference is required to identify infants with progression of bleed. Phototherapy should be provided for hyperbilirubinemia. An investigation for a bleeding disorder should be considered, especially if it occurs in noninstrumental deliveries. 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.

v. Presence of encephalopathy is an indicator of poor outcome.

vi. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) in 2009 issued a position statement with recommendations for appropriate vacuum extraction techniques to minimize the risk of subgaleal hemorrhage with regards to patient selection, appropriate techniques for vacuum extraction, and stratification of at-risk neonates for further observations.

3. **Intracranial hemorrhage** as a consequence of birth injury include subdural, subarachnoid, epidural, intraventricular hemorrhages, and less frequently, intracerebral and intracerebellar hemorrhages. 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 is 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 the 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 crepitus or respiratory distress with poor feeding. Untreated fractures can lead to facial deformities with subsequent malocclusion and mastication difficulties. Treatment should begin promptly because maxillary and lacrimal fractures begin to heal within 7 to 10 days, and mandibular fractures start to repair within 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 exerted on 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's membrane of the cornea (which can lead to astigmatism and amblyopia). Significant ocular trauma occurs in <0.5% of all deliveries. There is a high risk of visual impairment if there is an associated optic nerve injury.

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.

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 the development of a hematoma and subsequent fibrosis and shortening, hence also called fibromatosis colli (sternocleidomastoid tumour of infancy).

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. Ultrasound shows fusiform enlargement and heterogeneous echogenicity ("masslike") of the affected SCM muscle. Fine needle aspiration cytology is recommended if other differential diagnoses are considered, demonstrating bland-appearing fibroblasts, degenerative, atrophic skeletal muscle, and muscle giant cells without inflammatory cells.

e. Treatment is initially conservative. Stretching of the involved muscle should begin promptly and be performed several times per day. Recovery typically occurs within 3 to 4 months in approximately 80% of cases. Surgery is needed if torticollis persists after 6 months of physiotherapy. Botulinum toxin injection is also rarely considered.

f. In up to 10% of patients with congenital torticollis, congenital hip dysplasia may be present. A careful hip examination is warranted with further evaluation as indicated.

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 is obtained if the leak persists or the perforation is large.

11. Tracheal injuries

a. Tracheal rupture can be anterior subglottic or distal tracheal.

b. This rare and potentially fatal entity can occur in a difficult delivery.

c. It should be suspected in neonates who develop subcutaneous emphysema, pneumothorax, and pneumomediastinum shortly after birth.

d. Bronchoscopy should be performed to confirm the diagnosis.

e. Management is mostly conservative; open surgical repair is undertaken if necessary, especially in cases of distal tracheal rupture.

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 cranial 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 mid-forceps), pressure on the nerve secondary to the fetal face lying against the maternal sacral promontory, or, rarely, 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 facial nerve injury involves the entire side of the 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. Occasionally, chest tube insertion or surgery injures this nerve. Injury to the nerve is thought to occur where it crosses the brachial plexus. Therefore, approximately 75% of patients also have brachial plexus injury.

ii. Respiratory distress and cyanosis are often seen. Some infants present with persistent tachypnea. 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 3 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 1.5 per 1,000 live births in the United States. The cause is excessive traction on the head, neck, and arm during birth. Risk factors include macrosomia, shoulder dystocia, malpresentation, and instrumental 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.

iii. **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.

iv. **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's syndrome may be seen.

v. **Klumpke palsy** is 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's syndrome.

a) **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. Generally, infants "self-splint," holding the affected arm in a comfortable position.

b) The diagnosis of brachial plexus injury is clinical. 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. These should be started at 7 to 10 days when the postinjury neuritis has resolved. "Statue of Liberty" splinting should be avoided, as contractures in the shoulder girdle may develop. Wrist and digit splints may be useful.

c) The severity of BPI ranges from least (neuropraxia: permitting complete prompt recovery) to intermediate (axonotmesis: allowing gradual recovery) to severe, with avulsion of the roots from the spinal cord causing permanent injury (neurotmesis). The Gilbert and Tassin/Narakas classification scheme (Table 6.3) can be used to grade the severity and prognosticate recovery, which varies with the extent of injury. If the nerve roots are intact and not avulsed, the prognosis for full recovery is excellent (>90%). Other predictors of outcome (at birth) include induction of labor, birth weight, clavicle fracture, Horner's syndrome, and pseudo meningocele on imaging. Notable clinical improvement in the first 2 weeks after birth indicates that normal or near-normal function will return. Most infants recover fully by 3 months of age. In those with slow recovery, electromyography and nerve conduction studies may distinguish an avulsion from a stretch injury. Surgery has most commonly been

Table 6.3. Narakas Classification of Obstetric Brachial Plexus Injury

Name	Weakness/Paralysis	Likely Outcome	Roots Impaired
Upper Erb's	Shoulder abduction External rotation Elbow flexion	Good 80% spontaneous recovery	C5, C6
Extended Erb's	As above + drop wrist	Good 60% spontaneous recovery	C5, C6, C7
Total palsy with no Horner's syndrome	Complete flaccid paralysis	Good spontaneous recovery of the shoulder and elbow in 30%-50% of cases. A functional hand may be seen in many patients	C5, C6, C7, C8, T1
Total palsy with Horner's syndrome	Complete flaccid paralysis + Horner's syndrome	The worst outcome. Without surgery, severe defects throughout the limb are expected	C5, C6, C7, C8, T1

recommended when there is a *lack of biceps function at 3 months of age*. Nerve reconstruction, (nerve graft repair and nerve transfer), is generally undertaken beyond age 6 months. Botulinum toxin has been used in older infants with contractures. Initial pain management is important for affected neonates.

d) Management: There is a significant change in management of Brachial plexus injuries of newborn in favor of early mobilization and referral by 1 month age in absence of recovery. Passive range of movements, promoting functional use, and strengthening of affected muscles must start early. Therapeutic methods include stretching, splinting, and targeted strengthening. There is insufficient evidence for therapeutic taping, electric stimulation, and desensitization. Comorbidities include torticollis, speech delay and chronic pain manifesting as self-mutilation and biting of affected extremity.

If the recovery is not complete by 1 month, the infant should be referred to a specialist team. At 3 months age, elbow flexion and extension; wrist, thumb extension are evaluated by movement against gravity and with gravity eliminated (in a horizontal plane, across a table top). An objective score (University of Toronto score) has good predictive ability in selecting babies for surgery at 3 months age. The infants with milder injury not requiring surgery are evaluated again at 9 moths age ("cookies test").

C. Bone injuries

1. **Clavicle fracture.** Clavicle is the most injured bone during delivery, occurring in up to 2% of newborns. 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 clavicle 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. Humerus fractures have a prevalence of 0.05 per 1,000 live births.

      i. Humerus 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 2 weeks. Displaced fractures 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 for 10 to 14 days.

b. Femur fractures have a prevalence of 0.17 per 1,000 live births.

i. Femoral fractures usually follow a breech delivery. Infants with congenital hypotonia are at an increased risk. It can happen with cesarean births due to the limited space available for maneuvering.

ii. Most common is spiral fracture involving the femoral shaft; rarely transphyseal fracture through the distal femur is also reported.

iii. 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.

iv. Complete healing without limb shortening is expected.

a) Fractures, even if unilateral, should be treated with splinting and immobilization using a spica cast or Pavlik harness.

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 probable 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 those of 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 compromise to immunity in future.

3. Adrenal hemorrhage

a. The relatively large size of the adrenal gland in the newborn predisposes it to injury. Risk factors are breech presentation and macrosomia. Ninety percent of adrenal hemorrhages are unilateral; 75% occur on the right. Incidence is 0.2% of neonates.

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. Petechiae are seen when there is a tight nuchal cord, precipitous delivery, or breech presentation causing a sudden increase in venous pressure that can lead to pinpoint capillary rupture in the affected areas. 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 is caused by panniculitis secondary to focal pressure and ischemia to the adipose tissue within the subcutaneous space during the birth process. 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. Affected infant needs to be followed up for hypercalcemia, which may manifest even up to 6 months from the onset of the initial lesion. No treatment is necessary. Lesions typically resolve completely over several weeks to months.

Suggested Readings

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

Vincent C. Smith

KEY POINTS

- Certain maternal, placental, or fetal conditions are associated with a high risk to newborns; hence, providers must be prepared to stabilize and manage these infants.
- Providers must ascertain the gestational age (GA) to properly contextualize the risk.
- Providers should be aware of the risk factors such as pre- and post-term birth, small for gestational age (SGA), and large for gestational age (LGA), all of which have associated clinical management challenges.
- The placenta should be saved in all cases of high-risk delivery.

I. HIGH-RISK NEWBORNS are often associated with certain maternal, placental, or fetal conditions; when one or more are present, nursery staff should be aware and prepared for possible difficulties. The placenta should be saved in all cases of high-risk delivery, including cases that involve transfer from the birth hospital because an elusive diagnosis such as toxoplasmosis may be made on the basis of placental pathology. The following factors are associated with a high risk to newborns:

A. Maternal characteristics and associated risk for fetus or neonate

1. **Age at delivery**
   - a. **Over 40 years.** Chromosomal abnormalities, macrosomia, intrauterine growth restriction (IUGR), blood loss (abruption or previa)
   - b. **Under 16 years.** IUGR, preterm birth, child abuse/neglect (mother herself may be abused)
2. **Personal factors**
   - a. **Poverty.** Preterm birth, IUGR, infection
   - b. **Smoking.** Increased perinatal mortality, IUGR
   - c. **Drug/alcohol use.** IUGR, fetal alcohol syndrome, withdrawal syndrome, sudden infant death syndrome, child abuse/neglect
   - d. **Poor diet.** Mild IUGR to fetal demise in severe malnutrition
   - e. **Trauma (acute, chronic).** Fetal demise, abruptio placentae, preterm birth
3. **Medical conditions and risk to fetus**
   - a. **Diabetes mellitus.** Stillbirth, macrosomia/birth injury/IUGR in advanced stages with vascular insufficiency, respiratory distress syndrome (RDS), hypoglycemia, congenital anomalies

b. **Thyroid disease.** Goiter, hypothyroidism, hyperthyroidism (see Chapter 61)

c. **Renal disease.** Stillbirth, IUGR, preterm birth

d. **Urinary tract infection.** Preterm birth, sepsis

e. **Heart and/or lung disease.** Stillbirth, IUGR, preterm birth

f. **Hypertension (chronic or pregnancy-related).** Stillbirth, IUGR, preterm birth, asphyxia, polycythemia, thrombocytopenia, leukopenia

g. **Anemia.** Stillbirth, IUGR, hydrops, preterm birth, asphyxia

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

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

4. **Obstetric history**

a. **Past history of infant with preterm birth, jaundice, RDS, or anomalies.** Same with current pregnancy

b. **Maternal medications** (see Appendices A and B)

c. **Bleeding.** Stillbirth, preterm birth, anemia

d. **Hyperthermia.** Fetal demise, fetal anomalies

e. **Premature rupture of membranes.** Infection/sepsis

f. **Toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex (TORCH) infections** (see Chapter 48)

B. Fetal characteristics and associated risk to neonate

1. **Multiple gestation.** IUGR, twin–twin transfusion syndrome, preterm birth, asphyxia, birth trauma
2. **IUGR.** Fetal demise, genetic abnormalities, congenital anomalies, asphyxia, hypoglycemia, polycythemia
3. **LGA and/or macrosomia.** Congenital anomalies, birth trauma, hypoglycemia
4. **Abnormal fetal position/presentation.** Congenital anomalies, birth trauma, hemorrhage
5. **Abnormality of fetal heart rate or rhythm.** Congestive heart failure, heart block, hydrops, asphyxia
6. **Decreased activity.** Fetal demise, neurologic abnormalities, asphyxia
7. **Polyhydramnios.** Anencephaly, other central nervous system (CNS) disorders, neuromuscular disorders, problems with swallowing (e.g., esophageal atresia, agnathia, any mass in the mouth), chylothorax, diaphragmatic hernia, omphalocele, gastroschisis, trisomy, tumors, hydrops, isoimmunization, anemia, cardiac failure, intrauterine infection, maternal diabetes or other etiologies of inability to concentrate urine, large for gestational age (LGA), preterm delivery
8. **Oligohydramnios.** Fetal demise, placental insufficiency, IUGR, renal agenesis, pulmonary hypoplasia, deformations, intrapartum distress, post-term delivery

C. Labor and delivery characteristics and associated risk

1. **Preterm delivery.** RDS, other complications of preterm birth (see Chapter 13)

2. **Post-term delivery (occurring >2 weeks after term).** Stillbirth, asphyxia, meconium aspiration (see section IV)
3. **Maternal fever.** Infection/sepsis
4. **Maternal hypotension.** Stillbirth, asphyxia
5. **Rapid labor.** Birth trauma, ICH, retained fetal lung fluid/transient tachypnea
6. **Prolonged labor.** Stillbirth, asphyxia, birth trauma
7. **Abnormal presentation.** Birth trauma, asphyxia
8. **Uterine tetany.** Asphyxia
9. **Meconium-stained amniotic fluid.** Stillbirth, asphyxia, meconium aspiration syndrome, persistent pulmonary hypertension
10. **Prolapsed cord.** Stillbirth, asphyxia
11. **Cesarean section.** RDS, retained fetal lung fluid/transient tachypnea, blood loss
12. **Obstetric analgesia and general anesthesia.** Respiratory depression, hypotension
13. **Placental anomalies**
    a. **Small placenta.** IUGR
    b. **Large placenta.** Hydrops, maternal diabetes, large infant, congenital nephrotic syndrome
    c. **Torn placenta and/or umbilical vessels.** Blood loss, anemia, hypovolemic shock
    d. **Abnormal attachment of vessels to placenta.** Blood loss, anemia

D. Newly born characteristics (immediately after birth) and associated risk

1. **Preterm birth.** RDS, other complications of preterm birth
2. **Low 5-minute Apgar score.** Prolonged transition, birth asphyxia
3. **Low 10-minute Apgar score.** Neurologic damage
4. **Pallor or shock.** Blood loss
5. **Foul smell of amniotic fluid or membranes.** Infection
6. **SGA** (see section V)
7. **LGA** (see section VI). Hypoglycemia, birth trauma, congenital anomalies
8. **Postmaturity syndrome** (see section IV)

II. GA AND BIRTH WEIGHT CLASSIFICATION.

Neonates should be classified by gestational age (GA), as this generally correlates more closely with outcomes than a birth weight–based classification does. Birth weight becomes significant if neonate is either small for gestational age (SGA) or LGA.

A. GA classification

1. Assessment based on **obstetric information** is covered in Chapter 1. GA estimates in the first trimester by ultrasonography are accurate within 7 days. Second- and third-trimester ultrasounds are accurate within approximately 11 to 14 and 21 days, respectively.

2. To **confirm or supplement** obstetric dating, the modified Dubowitz (Ballard) examination for newborns (Fig. 7.1) may be used for GA estimation. However, there are limitations to this method, especially with the use of the neuromuscular component in sick newborns.
3. **Infant classification by GA**
   a. **Preterm** infants are born at <37 completed weeks of gestation (258 days). Subgroups of preterm infant include the following:
      i. **Extremely preterm** infants are born <28 weeks (195 days).

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 –1	0	1	2	3	4	5	RECORD SCORE HERE
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	

PHYSICAL MATURITY

PHYSICAL MATURITY SIGN	SCORE –1	0	1	2	3	4	5	RECORD SCORE HERE
SKIN	Sticky Friable Transparent	Gelatinous Red Translucent	Smooth pink Visible veins	Superficial Peeling and /or rash, few veins	Cracking Pale areas Rare veins	Parchment Deep cracking No vessels	Leathery Cracked Wrinkled	
LANUGO	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald		
PLANTAR SURFACE	Heel–toe 40–50 mm: –1 <40 mm: –2	>50 mm no crease	Faint red marks	Anterior transverse crease only	Creases ant. 2/3	Creases over entire sole		
BREAST	Imperceptible	Barely perceptible	Flat areola no bud	Stippled areola 1 to 2 mm bud	Raised areola 3 to 4 mm bud	Full areola 5 to 10 mm bud		
EYE/EAR	Lids fused Loosely: –1 Tightly: –2	Lids open Pinna flat Stays folded	Sl. curved pinna; soft; slow recoil	Well-curved pinna; soft but ready recoil	Formed and firm instant recoil	Thick cartilage ear 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 and labia flat	Prominent clitoris and small labia minora	Prominent clitoris and enlarging minora	Majora and minora equally prominent	Majora large minora small	Majora cover clitoris and minora		
							TOTAL PHYSICAL 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

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

Figure 7.1. New Ballard score. (From Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr* 1991;119:417–423.)

ii. **Early preterm** infants are born <34 weeks (237 days).

iii. **Moderate and very preterm** comes under early preterm. May be changed to extreme, very, moderate, late.

iv. **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 a subgroup of term infants born between 37 0/7 and 38 6/7 weeks of gestation (259 to 272 days).

ii. **Full term** between 39 0/7 to 40 6/7 weeks and post (late) term 41 0/7 to 41 6/7 weeks.

B. Birth weight classification. Although there is no universal agreement, the commonly accepted definitions are as follows:

1. **Normal birth weight (NBW).** From 2,500 to 4,000 g
2. **Low birth weight (LBW).** <2,500 g (till 2,499 g)

Note that many LBW infants are preterm; in resource-limited countries, a larger proportion of LBW infants are term but SGA. LBW infants can be further subclassified as follows:

a. **Very low birth weight (VLBW).** <1,500 g (till 1,499 g)

b. **Extremely low birth weight (ELBW).** <1,000 g (till 999 g)

III. PRETERM BIRTH. A preterm neonate is one who is born at <37 weeks of gestation.

A. Incidence. In 2014, the National Center for Health Statistics completed the transition to a new method of quantifying GA, shifting from the previous practice of counting from the last menstrual period (LMP) to using the best obstetric estimate (OE) of gestation at delivery. Approximately 10% of all births in the United States are preterm. The incidence is higher in developing countries (13% in India).

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

1. **Low socioeconomic status** (SES), whether measured by family income, educational level, geographic area, social class, and/or occupation
2. **Women younger than 16 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.
3. **Maternal activity** requiring long periods of standing or substantial amounts of physical stress may be associated with IUGR and preterm birth.
4. **Acute or chronic maternal illness** is associated with early delivery, whether onset of labor is spontaneous or not.
5. **Multiple-gestation pregnancies** frequently lead to preterm births (57% of twins and 93% of triplets in the United States).

6. **Prior poor birth outcome** is the single strongest predictor of poor birth outcome. History of a preterm delivery is a strong predictor of a second preterm birth. One preterm birth increases the risk for a second by a factor of 4.
7. **Obstetric factors** such as uterine malformations, uterine trauma, placenta previa, abruptio placentae, hypertensive disorders, preterm cervical shortening, previous cervical surgery, premature rupture of membranes, and chorioamnionitis
8. **Fetal physiologic monitoring parameters** such as a nonreassuring test of fetal well-being (see Chapter 1), IUGR, or severe hydrops often lead to a preterm delivery.
9. **Inadvertent early delivery** because of incorrect estimation of GA may be an infrequent cause.

C. Problems associated with preterm birth are related to difficulty in extrauterine function due to immaturity of organ system.

1. **Respiratory.** Preterm infants may experience the following:
   a. **Perinatal depression** in the delivery room due to hypoxic-ischemic perinatal conditions (see Chapter 55)
   b. **RDS** due to surfactant deficiency and pulmonary immaturity (see Chapter 33)
   c. **Apnea** due to immaturity in mechanisms controlling breathing (see Chapter 31)
   d. **Chronic lung disease (CLD)** of prematurity, also referred to as bronchopulmonary dysplasia (BPD) (see Chapter 34)
2. **Neurologic.** Preterm infants have a higher risk of neurologic problems including the following:
   a. **Perinatal depression** (see Chapter 55)
   b. **ICH** (see Chapter 54)
   c. **Periventricular leukomalacia** (PVL) (see Chapter 54)
3. **Cardiovascular.** Preterm infants may present with cardiovascular problems including the following:
   a. **Hypotension**
      i. Hypovolemia
      ii. Cardiac dysfunction
      iii. Sepsis-induced vasodilation
   b. **Patent ductus arteriosus** (PDA) is common and may lead to pulmonary overcirculation and steal phenomenon leading to systemic hypoperfusion (see Chapter 41).
4. **Hematologic.** Preterm infants are at a higher risk of the following:
   a. Anemia (see Chapter 45)
   b. Hyperbilirubinemia (see Chapter 26)
5. **Nutritional.** Preterm infants require specific attention to the content, caloric density, volume, and route of feeding, including parenteral nutrition when indicated (see Chapter 21).

6. **Gastrointestinal.** Premature infants are at an increased risk for necrotizing enterocolitis; formula feeding is an additional risk factor; a mother's own breast milk appears to be protective (see Chapter 27).
7. **Metabolic.** Dysregulation of glucose and calcium metabolism is 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. Therefore, fluid and electrolyte management requires close attention (see Chapters 23 and 28).
9. **Temperature regulation.** Preterm infants are especially susceptible to hypothermia; iatrogenic hyperthermia can also be a problem (see Chapter 15).
10. **Immunologic.** Because of deficiencies in both humoral and cellular response, preterm infants are at a greater risk for infection as compared to term infants.
11. **Ophthalmologic.** Retinopathy of prematurity may develop in the immature retina. Infants <32 weeks or with birth weight <1,500 g are at a higher risk. In Asian population, babies less than 34 weeks and 1,800 g are screened. These "bigger babies" are genetically at higher risk and may have greater exposure to postnatal risk factors such as sepsis, blood products, and hyperoxia (see Chapter 67).

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

1. **Immediate postnatal management**
   a. **Delivery** in an appropriately equipped and staffed hospital is preferable. Risks to the very premature or sick preterm infant are greatly increased by delays in starting the necessary specialized care.
   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 Neonatal Resuscitation Program (NRP). Anticipation and prevention are always preferred over reaction to problems already present. Temperature, airway, breathing, and circulation are assessed and supported (see Chapter 4). Initiation of care around birth strategies (delayed cord clamping, early initiation of breast feeding if indicated, skin-to-skin contact) should be an important component of any resuscitation and stabilization process.
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 energy expenditure. For preterm infants, this will require either an overhead radiant warmer (with the advantages of infant accessibility and rapid temperature response) or, for extreme preterm, an 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. When enteral feedings are tolerated, ineffective suck and swallow usually necessitate gavage feeding (see Chapter 21).

e. Hyperbilirubinemia, which is inevitable in less mature infants, can usually be managed effectively by careful monitoring of bilirubin levels and early use of phototherapy. In the most severe cases, exchange transfusion may be necessary (see Chapter 26).

f. Infection may be the reason for preterm delivery. If an infant displays signs or symptoms that could be attributed to infection, the infant should be carefully evaluated for sepsis (e.g., physical exam, blood culture, and sepsis screens). There should be a low threshold for starting broad-spectrum antibiotics (e.g., ampicillin and gentamicin) until sepsis can be ruled out. Consider empiric antibiotics based on regional microbes and antibiotic sensitivity (see Chapters 48 and 49).

g. PDA may present as symptomatic (tachycardia, poor perfusion, murmur, precordial pulsations, and wide pulse pressure) or may be detected by screening echocardiography (ECHO) in ELBW babies. There are variations in practice in management; some units prefer medical ligation (with ibuprofen, paracetamol, or indomethacin) for babies with ECHO findings alone, and some treat only severely symptomatic babies. Extreme preterm babies with significant PDA have a higher association with bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL) and pulmonary hemorrhage. Management includes fluid restriction, if there are signs of heart failure. In PDA that is not responding to medications and is hemodynamically significant or likely cause for ventilator dependence, surgical ligation is an option (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. 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 after the neonate achieves a weight of 2,000 g. Respiratory syncytial virus (RSV) (not a practice in Asian countries) and influenza prophylaxis should be given as indicated. Special consideration should be given to the rotavirus vaccine (RV) because it is a live oral vaccine and is not given until neonatal intensive care unit (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. For many reasons, survival statistics vary by institution as well as geographic region and country. Figures 7.2 and 7.3 show survival rates of VLBW preterm infants from nearly 1,000 centers around the

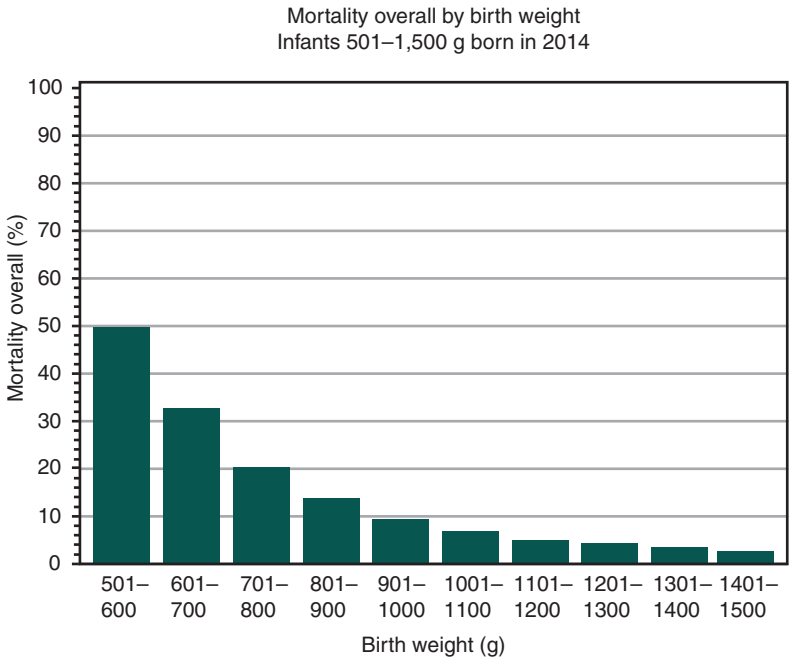

Figure 7.2. Mortality by birth weight. (From Vermont Oxford Network 2014 with permission of Erika M. Edwards, PhD, MPH, editor of *2014 Very Low Birth Weight Database Summary*. Vermont Oxford Network, 33 Kilburn Street, Burlington, VT 05401. E-mail: nightingale@vtoxford.org. Website: www.vtoxford.org.)

globe that voluntarily submitted data about the care and outcomes of high-risk newborn infants enrolled in the Vermont Oxford Network (VON) in 2014. The VON databases hold critical information on >2 million infants representing >63 million patient days.

F. Long-term problems 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**
   - **a.** Major handicaps (cerebral palsy, developmental delay)
   - **b.** Cognitive dysfunction (language disorders, learning disability, hyperactivity, attention deficits, behavior disorders)
   - **c.** Sensory impairments (hearing loss, visual impairment) (see Chapters 67 and 68), retinopathy of prematurity (see Chapter 67)
2. **CLD** (see Chapter 34)
3. **Poor growth.** Preterm infants are at risk for a wide range of growth problems (see Chapter 21). Although clinicians can visually assess the size and growth of infants and most use growth charts routinely, there is considerable controversy on which growth charts to use for preterm. Extrauterine growth of preterm infants is different from that of their intrauterine fetal counterparts; there are growth charts derived from both expected intrauterine growth and postnatal

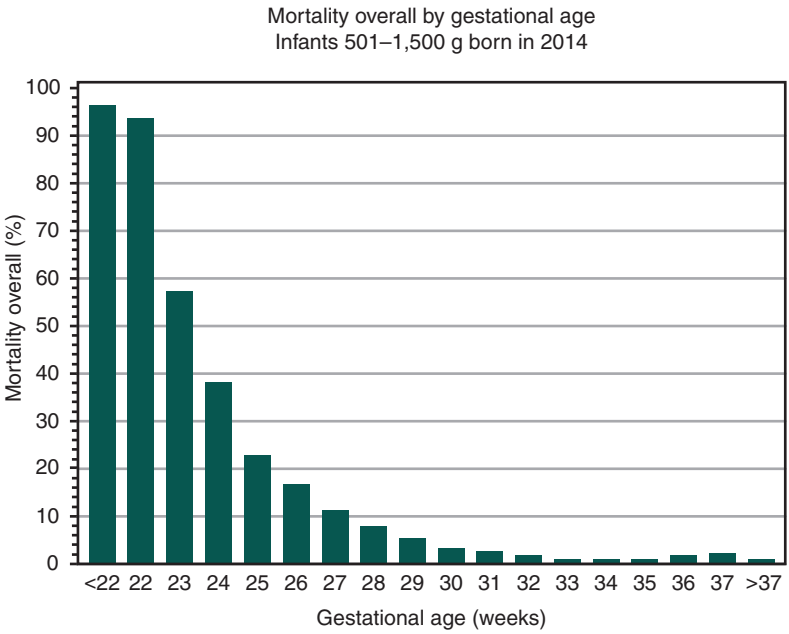

Figure 7.3. Mortality by gestational age. (From Vermont Oxford Network 2014 with permission of Erika M. Edwards, PhD, MPH, editor of *2014 Very Low Birth Weight Database Summary*. Vermont Oxford Network, 33 Kilburn Street, Burlington, VT 05401. E-mail: nightingale@vtoxford.org. Website: www.vtoxford.org.)

growth observed from preterm babies of same gestation. A simpler approach is to use the same growth curve to assess the fetal growth (size at birth) and preterm infant longitudinal growth (Fig. 7.4). For example, the Fenton growth charts use a relatively recent and diverse cohort of infants who had accurate GA assessments, but they rely on data that are statistically smoothed between 36 and 46 weeks (see Fig. 7.4). This growth chart may not be proper for monitoring postnatal growth in infants >36 weeks of gestation. It is suggested that the WHO growth charts may be used for preterm neonates after 40 weeks of postmenstrual age. Prior to that, the Fenton's charts can be used. Intergrowth 21 growth charts are well designed growth charts. It is preferable to use the postnatal growth charts as compared to the intrauterine growth charts for evaluating growth. Infants are not likely to achieve the same growth rates as the fetuses of the same postmenstrual age (*in utero*).

4. Increased rates of childhood illness and readmission to the hospital

IV. POST-TERM INFANTS

A. Definition. Approximately 6% (3% to 14%) of pregnancies extend beyond 42 weeks of gestation and are considered post-term. The rate of post-term pregnancies is heavily influenced by local obstetrical practices.

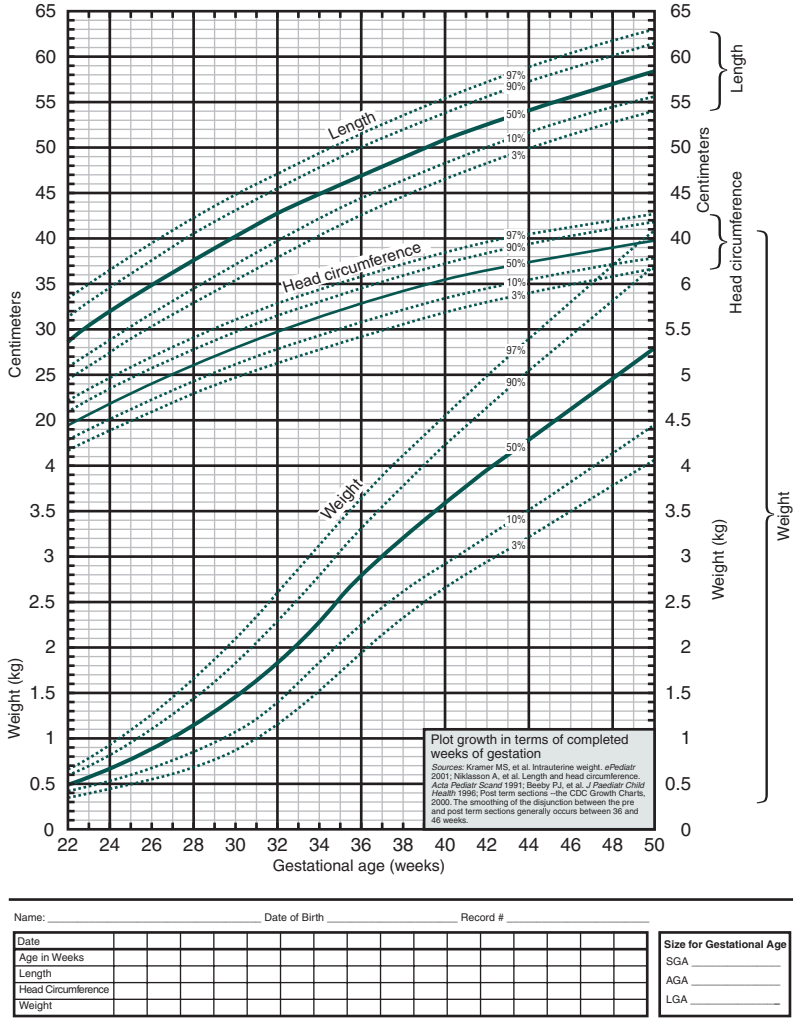

Figure 7.4. Fetal–infant growth chart for preterm infants (weight, head circumference, and length). AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age. (Reproduced with permission from Fenton TR, licensee BioMed Central Ltd. This is an open-access article: Verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article's original URL. http://www.biomedcentral.com/1471-2431/3/13.)

B. Etiology. Some cases of post-term pregnancy are the result of inaccurate dating of the pregnancy. In most cases, the cause of prolonged pregnancy is unknown. There is no association between maternal age or race and the incidence of post-term pregnancy. Risk factors for post-term pregnancies include the following:

1. Nulliparity

2. Previous post-term pregnancy

3. Obesity
4. Anencephaly. An intact fetal pituitary–adrenal axis appears to be necessary for the initiation of labor.
5. Trisomies 13 and 18
6. Seckel's syndrome (bird-headed dwarfism)

C. Morbidities associated with post-term pregnancy include

1. Postmaturity syndrome. Post-term infants who have begun to lose weight but have normal length and head circumference. They may have the following symptoms: dry, cracked, peeling, loose, and wrinkled skin; malnourished appearance; and decreased subcutaneous tissue.
2. Meconium staining of amniotic fluid (MSAF), perinatal depression (in some cases), and a higher risk of fetal, intrapartum, or neonatal death

D. Management

1. **Antepartum management**
   a. Careful estimation of true GA, including ultrasonographic data
   b. **Antepartum assessments** by cervical examination and monitoring of fetal well-being (see Chapter 1) should be initiated between 41 and 42 weeks on at least a weekly basis. If fetal testing is not reassuring, delivery is usually initiated. In most instances, a patient is a candidate for induction of labor if the pregnancy is at >41 weeks of gestation and the condition of the cervix is favorable.
2. **Intrapartum management** involves the use of fetal monitoring and preparation for possible perinatal depression and meconium aspiration.
3. **Postpartum management**
   a. **Evaluation for other conditions.** Infant conditions more frequently associated with post-term delivery include the following:
      i. Congenital anomalies
      ii. Perinatal depression
      iii. Persistent pulmonary hypertension
      iv. Meconium aspiration syndrome
      v. Hypoglycemia
      vi. Hypocalcemia
      vii. Polycythemia
   b. **Attention to proper nutritional support**

V. INFANTS WHO ARE SMALL FOR GESTATIONAL AGE OR HAVE INTRAUTERINE GROWTH RESTRICTION (SEE CHAPTER 1)

A. Definition. Although many use the terms "SGA" and "IUGR" interchangeably, they refer to two different concepts. 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. 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). After birth, IUGR babies appear malnourished, with poor subcutaneous fat, whereas SGA babies will look like small but normal babies. Babies who are constitutionally SGA are at an overall lower risk compared to those who are IUGR due to some pathologic process. Numerous "normal birth curves" have been published from different populations. The etiology and management of SGA and IUGR fetuses overlap considerably.

B. Etiology. Approximately one-third of LBW infants are SGA/IUGR. There is an association between the following factors and SGA/IUGR:

1. **Maternal factors** include genetic size; demographics (age at the extremes of reproductive life, race/ethnicity, socioeconomic status [SES]); nulliparity and grand multiparity status; underweight before pregnancy (e.g., malnutrition); uterine anomalies; chronic disease; factors interfering with placental flow and oxygenation (cardiovascular disease, renal disease, hypertension [chronic or pregnancy-induced]); sickle cell anemia; pulmonary disease; collagen-vascular disease; diabetes (classes D, E, F, and R); autoimmune diseases; thrombotic disease (see Chapter 2); post-term delivery; high-altitude environment; exposure to teratogens including radiation; and alcohol, tobacco, or cocaine use.
2. **Placental and umbilical anatomical factors** include malformations (e.g., chorioangioma, infarction, circumvallate placenta, placental mosaicism, obliterative vasculopathy of the placental bed, vascular malformations, or velamentous umbilical cord insertion), infarction or focal lesions, abruption, suboptimal implantation site (e.g., **low-lying placenta**), previa, insufficient uteroplacental perfusion, and single umbilical artery.
3. **Fetal factors** include constitutional (normal, "genetically small"), malformations (e.g., abnormalities of the CNS and skeletal system), chromosomal abnormality (<5% of SGA infants; more likely in the presence of malformation), congenital infection (i.e., rubella and cytomegalovirus [CMV]) (see Chapter 48), and multiple gestation.

C. Management of Small for Gestational Age/Intrauterine Growth Restriction

1. **Pregnancy** (see Chapter 1)
   a. Attempt to **determine the cause** of SGA/IUGR by searching for relevant factors (listed earlier) by history, laboratory, and ultrasonic examination. Treat any underlying cause when possible. Chronic fetal hypoxemia is encountered in about 30% of SGA/IUGR fetuses. Once the diagnosis is made, changes in obstetrical management may improve the outcome.
   b. **Monitor fetal well-being**, including nonstress test, a biophysical profile, fetal movement counts, amniotic fluid volume evaluation, and serial ultrasonic examinations (see Chapter 1). Doppler evaluation of placental flow may be used to evaluate uteroplacental insufficiency.
   c. Consider the effects of prematurity if early delivery is contemplated (see Chapter 1).
2. **Delivery.** Early delivery is necessary if the risk of intrauterine fetal demise still is considered greater than the risks of preterm birth.
   a. Generally, **indications for delivery** are an arrest of fetal growth and/or fetal distress, especially closer to term.

b. Acceleration of pulmonary maturity with glucocorticoids administered to the mother should be considered at 24 to 34 weeks pregnancy.

c. If there is **poor placental blood flow**, the fetus may not tolerate labor and may require a cesarean delivery.

d. Infants with extreme SGA/IUGR are at a **risk for perinatal** complications and often require specialized care in the first few days of life. Therefore, if possible, delivery should occur at a center with a NICU or special care nursery. The delivery team should be prepared to manage perinatal depression, meconium aspiration, hypoxia, hypoglycemia, and heat loss.

3. Postpartum

a. Attempt should be made to establish the etiology of SGA/IUGR.

i. Newborn examination. The infant should be evaluated for signs of any of the previously listed causes of poor fetal growth, especially chromosomal abnormalities, malformations, and congenital infection.

a) Infants with growth restriction during the later part of pregnancy will have a relatively normal head circumference and mild/no reduction in length, but 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 × 100]/[length in centimeters]) or the weight-to-length ratio may be used to categorize growth-retarded infants. Those with asymmetric growth retardation have low Ponderal index. These infants generally have little subcutaneous tissue, peeling loose skin, a wasted appearance, and meconium staining.

b) Infants whose growth restriction begins early in pregnancy will have a proportionally small head circumference, length, and weight in contrast to IUGR that begins later in pregnancy. These infants are sometimes referred to as *symmetric IUGR* and their Ponderal index may be normal. 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).

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

iii. Because of potential for hearing loss associated with infection, it is advisable to screen SGA/IUGR infants for CMV. Screening for other congenital infections is equally important. **Serologic screening** for congenital infections has low yield and is generally not indicated unless history or examination is suggestive of infection. However, it should be borne in mind that most of the intrauterine infections have a nonspecific course in pregnancy and an apparent asymptomatic course in the early infancy; hence, the examiner should actively assess for their presence in a SGA/IUGR neonate.

b. SGA infants generally require **more calories per kilogram** than appropriate for gestational age (AGA) infants for "catch-up" growth; term SGA infants will often regulate their intake accordingly.

c. Potential complications related to SGA/IUGR

i. Congenital anomalies

ii. Perinatal depression

iii. Meconium aspiration, persistent pulmonary hypertension

iv. Hypoglycemia from depletion of glycogen stores

v. Hypothermia from depletion of subcutaneous fat

vi. Polycythemia

vii. Neutropenia

viii. Thrombocytopenia

ix. Hypocalcemia

D. Outcomes of SGA/IUGR infants. Compared to AGA infants of the same GA, SGA/IUGR infants have a higher incidence of neonatal morbidity and mortality. At the same birth weight, more mature SGA/IUGR infants have a lower risk of neonatal death when compared to preterm infants. In general, SGA/IUGR infants and children (especially those from disadvantaged socioeconomic environments) are at a higher risk for poor postnatal growth, neurologic impairment, delayed cognitive development, and poor academic achievement. Finally, some adults who were SGA/IUGR at birth appear to have a higher risk of coronary heart disease, hypertension, non–insulin-dependent diabetes, stroke, obstructive pulmonary disease, renal impairment, decreased reproductive function, as well as other health risks and growth-related psychosocial issues (fetal origin of adult onset diseases).

E. Management of subsequent pregnancies is important because in some, SGA and IUGR will recur. The mother should be cared for by personnel experienced in handling high-risk pregnancies. The health of the mother and fetus should be assessed throughout pregnancy with ultrasonography and nonstress tests (see Chapter 1). Early delivery should be considered if fetal growth is compromised.

VI. INFANTS WHO ARE LARGE FOR GESTATIONAL AGE

A. Definition. Birth weight above the mean for GA by 2 SD or >90th percentile for the corresponding GA

B. Etiology

1. Constitutionally large infants (large parents)

2. Infants of diabetic mothers

3. Beckwith–Wiedemann and other overgrowth syndromes

4. Some post-term infants

C. Management

1. Look for evidence of birth trauma, including brachial plexus injury and perinatal depression (see Chapters 6 and 55).

2. Allow the infant to feed early and monitor the blood sugar level. Some LGA infants may develop hypoglycemia secondary to hyperinsulinism (especially infants of diabetic mothers, infants with Beckwith–Wiedemann syndrome, or infants with erythroblastosis) (see Chapters 2 and 24).
3. Asses for polycythemia (see Chapter 46).

Suggested Readings

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

Lise 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.
- The fact that most babies are normal on examination can result in oversight of abnormalities. A systematic (checklist based) head-to-toe examination will ensure that important physical examination findings are not missed.

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

Table 8.1. Important Aspects of Maternal and Perinatal History

Family history
Inherited diseases (e.g., metabolic disorders, bleeding disorders, hemoglobinopathies, cystic fibrosis, polycystic kidneys, sensorineural hearing loss, 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
Overweight or obesity
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, postmaturity, malformations)
Blood type, blood group sensitizations, and getting anti-Rh (anti-D) treatment

(*Continued*)

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

Chronic maternal illness (e.g., diabetes mellitus, hypertension, renal disease, cardiac disease, thyroid disease, systemic lupus erythematosus, myasthenia gravis)
Infectious disease screening in pregnancy (rubella immunity status; syphilis, gonorrhea, chlamydia, and HIV screening; hepatitis B surface antigen screening; group *B Streptococcus* [GBS] culture; varicella, cytomegalovirus, and toxoplasmosis testing, if performed; purified protein derivative [PPD] status and any past treatments; any recent infections or exposures)
Inherited disorder screening (e.g., hemoglobin electrophoresis, glucose-6-phosphate dehydrogenase [G6PD] deficiency screening, "Jewish panel" screening, cystic fibrosis mutation testing, fragile X testing)
Medications
Tobacco, alcohol, and recreational or illegal substance use
Pregnancy complications (e.g., gestational diabetes mellitus, preeclampsia, infections, bleeding, anemia, trauma, surgery, acute illnesses, cholestasis, preterm labor with or without use of tocolytics or glucocorticoids)
Fetal testing
First- and/or second-trimester screens for aneuploidy (serum markers and ultrasonographic examination) and presence of more than one fetus
Second-trimester (approximately 18 weeks) fetal survey by ultrasound
Genetic testing, including preimplantation, chorionic villus sampling, amniocentesis genetic testing and cell-free fetal DNA testing
Ultrasound monitoring of fetal well-being
Tests of fetal lung maturity (rarely done these days)
Fetal medical or surgical therapy
Intrapartum history
Gestational age at parturition and method of calculation (e.g., ultrasound, artificial insemination or *in vitro* fertilization, last menstrual period)
Presentation
Onset and duration of labor
Timing of rupture of membranes and appearance of amniotic fluid (volume, presence of meconium, blood)
Results of fetal monitoring
Fever
Medications, especially antibiotics, analgesics, anesthetics, glucocorticoids, tocolytics, and magnesium sulfate
Complications (e.g., excessive blood loss, chorioamnionitis, shoulder dystocia)

(*Continued*)

Table 8.1. Important Aspects of Maternal and Perinatal History *(Continued)*
Method of delivery
Use of vacuum or forceps
Infant delivery room assessment including Apgar scores, cord pH, deferred cord clamping or milking, any resuscitation measures, vitamin K, and prophylactic eye antibiotics received
Placental examination
Social history
Cultural background of family
Marital status of mother
Nature of involvement of father of baby
Household members
Custody of prior children
Maternal and paternal occupations
Identified social supports
Maternal/parental wishes and preferences for newborn care, e.g., skin-to-skin contact, breast feeding, cord blood banking
Current social support service involvement
Past or current history of involvement of child protective agencies
Current or past history of domestic violence

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. All newborns need a:

(i) Brief physical examination **within the first few minutes after birth** while being flexible to allow skin-to-skin care and bonding

(ii) A comprehensive head-to-toe and front-to-back assessment **within the first 48 hours**

(iii) **An examination before discharge** to assess readiness and ensure that all relevant newborn screenings have been completed (see Chapter 18)

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. The examination needs to be a pleasant experience for the baby, parents, and clinician.

A. General examination.

- At the **initial examination immediately after birth**, attention should be directed to (i) determine whether any major congenital anomalies are present; (ii) determine whether the infant has made a successful transition from fetal life to air breathing; (iii) determine the extent to which gestation, labor, delivery,

analgesics, or anesthetics have affected the neonate; (iv) determine whether the infant has any signs of infection or metabolic disease (v) confirm or exclude the presence of any finding related to antenatal problems (from the mother's history, examination, or investigations). Ensure the following anomalies are not missed in the initial examination.

- Anal opening
- Cleft palate
- Meningomyelocele
- Abdominal wall defects

- **A comprehensive examination** must be done by a pediatrician, as early as possible, surely within few hours of life. The infant should be examined, ideally in a well-lit room under warming lights to avoid hypothermia which occurs easily in the neonatal period.

1. 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. A *standard checklist or a template* can ensure that examination and documentation is complete. Each neonatal unit should have a checklist of its own.

B. Rapid assessment. It is best taken when the infant is quiet, if possible.

1. **Sensorium.** Assess the baby's response to touch, uncovering the baby and consoling. Healthy babies often cry lustily when disturbed and are consoled by patting, gentle rocking, or cuddling. A hungry baby may settle only with breast feeding. A sleeping baby may be confused to be dull/lethargic. Reassess in 1 to 2 hours if the baby is otherwise well. In the first few days of life, a "sleep" of more than 3 to 4 hours should be evaluated.
2. **Temperature.** Babies' thermal status should be assessed by touch with the dorsum of the hand (more sensitive). Touch the abdomen first, and the hands and feet after that. The peripheries must feel warm as well. If not, this may indicate that the baby is nursed in an environment that is too cold for the baby. Wrap the baby and reassess after 30 minutes. A baby still cold to touch may be unwell (sepsis, shock, or heart failure). Temperature in the neonate is usually measured in the axilla. Rectal temperature is not recommended routinely. Normal axillary temperature is between 36.5°C and 37.4°C (97.7°F and 99.3°F). Mercury thermometers have been replaced due to safety to environment.
3. **Oxygenation**
   a. **Saturation.** Babies may not have a saturation of 90% immediately after birth. (Routine measurement is not indicated.)
   b. **Respiratory pattern.** The normal respiratory rate in a newborn is between 30 and 40 breaths per minute; more than 60 must be evaluated. Periodic breathing is common in newborns; short pauses (usually 5 to 10 seconds) are considered normal. Apneic spells associated with cyanosis, bradycardia, or loss of tone are not normal and deserve further evaluation (see Chapter 31).

4. **Perfusion**

   a. **Heart rate.** Normal heart rate in a newborn ranges between 95 and 160 beats per minute (bpm), although the heart rate in well babies in a wakeful alert state is very close to 140 bpm. Some infants may have resting heart rates as low as 80 bpm, especially in sleep. Good acceleration with waking up or stimulation is reassuring in these infants. A normal blood pressure and perfusion in these babies are reassuring that this is likely to be sinus bradycardia.

   b. **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. Blood pressure increases with gestation and postnatal day (normogram), but it may help a new pediatric resident or nurse to have in mind that the numbers are almost half of adult values—around 60 mm Hg systolic and 40 mm Hg diastolic. The mean arterial pressure (MAP) is calculated by the machine; it is most often more than the gestation age of the baby in weeks (e.g., MAP of 35 mm Hg or more in a 35-week-old preterm baby). 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. **Sugars.** Healthy babies do not require monitoring of blood sugar. Babies at risk of hypoglycemia (preterm, low birth weight, infant born to mother with diabetes, and any sick baby) must have periodic check of blood sugar by point-of-care glucometer.

6. **Measurements.** All newborns should have their weight, length, and head circumference measured shortly after birth. Newborns may have extensive molding and/or caput and, hence, a reliable head circumference measurement is the one taken 2 days after birth. Length measurement in the immediate newborn period can be inaccurate due to tight flexion that the babies have. 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 the sequelae of these conditions (see Chapter 7).

7. **Pulse oximetry.** It is recommended to screen for congenital heart disease by pulse oximetry before hospital discharge. 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 which are less sensitive to motion artifact. Criteria for a positive screening test that merits further clinical investigation for critical congenital heart disease (CCHD) include the following: (i) any oxygen saturation measure <90%; (ii) oxygen saturation <95% in the right hand and either foot on three measures, each separated by 1 hour; or (iii) there is a >3% absolute difference in oxygen saturation between the right hand and the foot on three measures, each separated by 1 hour.

C. Cardiorespiratory system

1. **Color.** The healthy newborn should have a reddish pink hue, 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 intercostal retractions. Significant respiratory disease in the absence of tachypnea is rare. Asymmetry of breath sounds or adventitious sounds in a baby with tachypnea or retractions of chest wall should be evaluated by chest x-ray.
3. **Heart.** The examiner should observe precordial activity, rate, and rhythm of heat beats, and check for murmurs.
   - Apex (maximum cardiac impulse) of the heart is on the left or right side.
   - Arrhythmias, most often due to premature atrial contractions, are occasionally heard on the routine newborn examination. An electrocardiogram (EKG) with rhythm strip should be obtained, if persistent or associated with poor perfusion.
   - The heart sounds should be auscultated, for ejection clicks which may indicate pulmonary or aortic valve stenosis or a bicuspid aortic valve.
   - 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), investigations 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 should ideally be obtained before discharge from the hospital. Where echocardiography is not available, a hyperoxia test should be obtained in babies with cyanosis to determine the potential need for institution of prostaglandin E1 (see Chapter 41).
   - Femoral pulses should be palpated; if there is doubt about the femoral pulses by the time of discharge, the blood pressure in the upper and lower extremities should be measured to investigate the concern for coarctation of the aorta.

D. Thorax.

The clavicles should be palpated, especially in large babies or babies born through prolonged labor or difficult delivery. 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.

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. Breast buds due to the influence of maternal hormones can normally be palpated 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.

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.

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 that there may be situs inversus. The hands of the examiner must not be wet or cold.

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 no food and little 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.

The umbilical stump should be inspected. The umbilical vein and one or two umbilical arteries should be identified. Discharge, odor, or periumbilical erythema and swelling should be noted, if present. A mere yellow discharge after the cord falls off is not suggestive of infection; erythema and swelling may need antibiotics. Umbilical hernias are frequently seen in neonates and are generally benign and resolve spontaneously.

F. Genitalia and rectum

1. Male

a. The **penis** almost invariably has marked phimosis. 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, and the baby referred to a urologist/pediatric surgeon whenever hypospadias is identified.

b. The **scrotum** is often quite large because it is an embryonic analogue 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. They 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 cm (length) × 1.0 cm (width) up to 2.9 cm × 1.8 cm. A hard, bigger testis that shows no transillumination should be suspected to be a torsion (there is often no pain/redness); urgent ultrasound and surgery may be indicated. 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.

2. **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. Hymenal 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 ±1 SD is 4.0 ± 1.24 mm. Clitoral enlargement, particularly when there is accompanying hyperpigmentation, should raise suspicion for androgen excess (see Chapter 63).
3. The **anus** should be checked carefully for patency, position, and size. Occasionally, a large fistula is mistaken for a normal anus; on closer examination, it may be noted that the fistula is positioned either anterior or posterior to the usual location of a normal anus.

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. They 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/white 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, and 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 eventually (weeks to months) fade. 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 *Staphylococcus*) 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-sized 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 (wrist) 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. 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, deemed resistant (inability to achieve a foot dorsiflexion of 90° or touch the anterior part of leg) requires orthopedic intervention which should be sought as soon as possible after birth (see Chapter 58).

2. **Joints.** There is a change in the understanding and practice of hip examination in a newborn. The practice of examining for dislocatable hips (Barlow's test) has led to overtreatment of babies. The treatment has been associated with a higher risk of femoral head avascular necrosis. Referral to ortho/ultrasound or treatment may be deferred till the baby is 3 to 4 months old. It is now recommended to look only for dislocated hips (Ortolani's maneuver), which causes reduction of the dislocation.
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, located >2.5 cm from the anal verge, or associated with other cutaneous markers such as hypertrichosis, subcutaneous mass, or a caudal appendage.

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 1 or 2 days. 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. They may initially be obscured by the 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 production, 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. Serial monitoring of the head circumference will allow early detection.

c. **Skull bones.** The skull bones (occipital, parietal, and frontal) should be examined, 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, iris coloring, iris coloboma, 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 sinus, 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. Choanal atresia can be excluded by noting for misting from both nostrils on a cold spatula or even easier on a spare spectacle.

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, absent or bifid uvula, and natal teeth. The lingual frenulum should also be inspected and any degree of ankyloglossia (tongue tie) noted. Significant tongue tie is associated with cracked nipples.

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 range of motion, goiter, and thyroglossal and branchial arch sinus tracts.
7. **Jaw.** The mandible should be inspected from front and lateral side for the presence of micrognathia (small underdeveloped jaw) or retrognathia (posteriorly displaced jaw). The presence raises concerns for facial dysmorphism associated with genetic syndromes and potential airway obstruction. Receding (small) chin is very common and causes noisy breathing due to posteriorly displaced tongue; repositioning the baby from supine to lateral will result in dramatic decrease in "nose block" sounds.

K. Neurologic examination. In approaching the neurologic examination of the neonate, the examiner must be at once humble and nonambitious. On the one hand, severe neurologic anomalies may be inapparent on examination in the newborn. Also, prognosis of abnormal neonatal neurologic examination must be discussed after re-examination for persistence of signs. 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, and 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 (pink color 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. 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, grasping, or dysregulatory motor activities such as arching, flailing, and 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, stepping, and placing 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.

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9 Care of the Well Newborn

Heena K. Lee and Elizabeth Oh

KEY POINTS

- Family-centered care promotes the initiation of breastfeeding and early bonding.
- Evaluate perinatal history and perform a structured examination to detect deviation from "normal."
- Ensure that the mother is prepared to care for the infant at home.
- Routine care of the well newborn includes screening and prevention measures.

Care of a newborn begins with care in pregnancy, care at birth, and continued after the baby is born.

I. PREPARATION BEFORE BIRTH OF BABY. Review maternal records for maternal age, previous pregnancy outcomes, weight gain in pregnancy, consanguinity, history of any medical disease, obstetric complication, medications taken (native medicines, drugs, abortifacients), sociodemographic background including alcohol and drug use, pregnancy screening tests, and ultrasound reports. It is important to ask the mother and her caretakers, and not depend on the medical records alone, important information may be missed. A sensitive enquiry, ensuring privacy must be made regarding previous obstetric adverse outcomes, consanguinity, family history of infant deaths, or development disorders.

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:

- Blood type, Rh, and antibody screen
- Hepatitis B surface antigen (HBsAg)
- Serologic test for syphilis
- Human immunodeficiency virus (HIV)
- Glucose tolerance test
- Antenatal testing results, including serum markers for aneuploidy, and ultrasonography results

II. CARE AT BIRTH. The transition from fetal life to extrauterine life involves dramatic changes in physiology. Fortunately, in most babies, this is seamless and requires no formal evaluation or support. During this period, the infant's pulmonary vascular resistance decreases, blood flow to the lungs is greatly increased, oxygenation improves rapidly, and the ductus arteriosus begins to constrict or close.

Interruption of normal transitioning, usually due to complications occurring in the peripartum period, will necessitate resuscitation at birth and cause signs of distress in the newborn.

Common signs of disordered transitioning are the following:

- Poor cry at birth/poor respiratory efforts
- Poor tone and movements
- Poor color/perfusion/heart rate
- Respiratory distress ± cyanosis

If the neonate requires only initial steps of resuscitation (tactile stimulation or short positive-pressure ventilation), observation near the mother may be considered. The neonate may be observed closely near the mother (in the same room, in an observation area near the birthing bed, or in a neonatal nursery/ICU based on the severity of illness/anticipated morbidities).

Babies who required significant resuscitation (chest compression, medications, prolonged positive-pressure ventilation) or with major malformations, prematurity, low birth weight, maternal diabetes, Rh negative blood group, etc., may have morbidities that may appear or progress in the first few hours; this necessitates shifting away from the mother to a special care area (neonatal intensive care unit [NICU]).

III. AVOID SEPARATION OF NORMAL (WELL) BABY FROM MOTHER. Every effort should be made to avoid separation of the mother and the infant especially during the first hour (even minutes) of life (the "golden hour"), in order to promote immediate initiation of breastfeeding and early bonding through skin-to-skin contact. Delay detailed examination (including taking birth weight), to allow the opportunity to breastfeed, immediately after birth. Healthy newborns must room-in with their mothers. These recommendations follow the global Baby-Friendly Initiative of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to improve exclusive breastfeeding. Family-centered maternity care, in which the nurse cares for the mother and the baby together in the mother's room (couplet care), facilitates mother craft and supports this Baby-Friendly Initiative.

Criteria for couplet care with the mother (no separation from the mother) must be as per the unit protocol, for example, a well-appearing infant with 35 weeks' gestation age or more than 2 kg birth weight may stay with the mother.

Security systems to protect from abduction of newborns are as follows:

- Identification (ID) bands with matching numbers are placed on the newborn and the mother, as soon after birth as possible. Transport of infants between areas should not occur until ID banding has been confirmed. Many nurseries use electronic security systems (bar code, blue tooth, radiofrequency) to track newborns.
- 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.

IV. ROUTINE CARE. Physical assessments, administration of medications, and routine laboratory tests should occur in the mother's room or close to her room (in presence of a family member).

For family-centered maternity care, nursing ratios should not exceed 1:4 mother–baby couplets.

Universal precautions should be used with all patient contact.

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).

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

The infant's temperature is stabilized with skin-to-skin contact with the mother at birth. The baby should be wrapped in cotton wraps, caps, socks, and mittens.

V. FEEDING. Breastfeeding should be started at the earliest given opportunity, preferably during the first golden hour. Details about each feeding session should be recorded in the infant's medical record.

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, American Academy of Pediatrics (AAP), and American College of Obstetricians and Gynecologists.

Mothers should initiate breastfeeding as soon as possible after delivery, preferably in the delivery room, and then the infant should be fed on demand, 8 to 12 times per day during the birth hospitalization (see Chapter 22).

Consultation with a lactation specialist during the postpartum hospitalization is strongly recommended for all breastfeeding mothers.

VI. SKIN CARE. The first bath is given with warm tap water and nonmedicated soap. Avoid the routine dip baths till the baby is in hospital due to the risk of infections. Daily sponging should be done at least once a day with clean water.

There are several acceptable practices for umbilical cord care. Dry cord care is generally sufficient. Routine application of antibiotics and antiseptics should be avoided. Evidence suggests that the use of 7.1% chlorhexidine is justified in community settings with high neonatal mortality rate and unclean cord practices. Keeping the cord dry also promotes earlier detachment of the umbilical stump. The diaper should be folded below the umbilical cord to avoid the risk of infection. Each eye should be cleaned from the inner to the outer canthus using separate sterile swabs (one for each eye) dipped in sterile or distilled water. Routine daily cleaning is not recommended.

VII. MEDICATIONS

A. A single, intramuscular dose of vitamin K_1 (phytonadione; 1 mg IM) should be given to all newborns before 24 hours of age to prevent vitamin K deficiency bleeding (VKDB). Currently available oral vitamin K preparations are not recommended (see Chapter 43).

B. Vaccinations

- Hepatitis B: Administration of the first dose of preservative-free, single-antigen hepatitis B vaccine is recommended for all infants during the newborn hospitalization, even if the mother's HBsAg test is negative (see Chapter 48).

  Hepatitis B vaccine is administered by 12 hours of age when the maternal HBsAg is positive or unknown. Infants of HBsAg-positive mothers require hepatitis B immune globulin in addition to vaccine (see Chapter 48).
- BCG vaccine is administered in most Asian countries. It is known to protect against serious forms of tuberculosis. The vaccine is given intradermal on the arm.

- Oral polio vaccine (OPV)—zero dose—is mandatory in India. It is of great value, as many of the newborns in India may not return for any further vaccination. The risk of vaccine-associated polio due to live strains is not noted.

VIII. ROUTINE ASSESSMENTS

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

B. The physical examination should start with the observation of the newborn's general appearance, posture, and movements followed by head-to-toe examination. Do not forget to palpate the femorals and examine the genitalia, hips, and spine for any deformity or malformation. Always check for vital signs, including respiratory rate, heart rate, and axillary temperature, every 8 to 12 hours and record them.

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

D. Weights are recorded in the infant's chart. Weight loss in excess of 7% to 10% of birth weight should be investigated. Look for attachment and positioning of the neonate. Lactation support is important to help determine further management. If caloric intake is thought to be adequate, organic etiologies should be considered, such as infection, metabolic, or thyroid disorders.

IX. SCREENING

A. Screening for neonatal sepsis risk

All newborns should be screened for the risk of infections from the mother — gestational age <37 weeks, maternal intrapartum temperature ≥100.4°F (38°C), rupture of membranes >18 hours, and signs of chorioamnionitis.

B. Glucose screening

1. Infants should be breastfed early and frequently to prevent hypoglycemia; healthy normal newborns require no glucose screening

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).

C. 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). Indian Academy of Pediatrics (IAP) recommends routine screening for congenital hypothyroidism. In populations in whom glucose-6-phosphate dehydrogenase (G6PD) is common, screening is advised by IAP. Many state governments and private sector hospitals screen for various metabolic disorders. There is no national recommendation.

2. Routine collection of the specimen is between 48 and 72 hours of life.

D. 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 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, G6PD deficiency, ethnicity (especially East Asian), 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 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. Parents should be given verbal and written information about newborn jaundice.

E. 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. The IAP also recommends universal screening for hearing impairment.
2. Verbal and written documentation of the hearing screen results should be provided to the parents with referral information when needed. Parents must be explained that a **'retest' hearing screen** does not mean that the baby is hearing impaired. The need to follow up should be clearly explained and documented.

F. Critical congenital heart disease screening

1. Screening for critical congenital heart disease (CCHD) using pulse oximetry has been endorsed by the AAP, the American Heart Association, and the American College of Cardiology Foundation (see Chapter 41). The pulse oximetry screening should be performed in all neonates after 24 hours of age or prior to discharge, whichever is earlier.
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's 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).

G. Predischarge checklist

- Adequacy of oral intake: This includes a minimum of eight feeds per day, change of meconium to transitional green/yellow stool by the second to third day; and one to two urine voids on the first 2 days and six to eight per day thereafter.
- No significant jaundice; follow-up for jaundice should be scheduled and parents educated on its importance.
- The infant's vital signs are documented to be within the normal ranges (with appropriate physiologic variations) and stable.
- Clinical course and physical examination reveal no abnormalities that require continued hospitalization.
- Maternal and infant laboratory tests have been reviewed.
- Vitamin K, BCG, OPV, and hepatitis B have been given.
- Screening protocol (metabolic, hearing, CCHD) as per institution has been completed.
- Parents should be explained regarding immunization schedule with the date of next immunization visit mentioned on the discharge card.
- Parental competency to care for the newborn has been demonstrated.
- Family, environmental, and social risk factors have been assessed.
- A primary care physician has been identified.
- Danger signs and signs of illness including fever, irritability, lethargy, poor feeding pattern, difficulty in breathing, rapid breathing, or presence of abnormal movements have been explained to the parents.

X. A. Special care - late preterm. Late preterm infants (born between 35 0/7 to 36 6/7 weeks gestation) are often not separated from the mother. Although born preterm, and deserve more care, most of these big looking babies are considered as "near term/near normal" by families and often even by medical teams. However, they are at a 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. In India, there is no structured follow-up by primary care physician or nurse practitioner visiting home. Follow-up is unreliable with a majority of people being from lower income group. Hence, it is unsafe to discharge these babies by 48 hours; discharge may be delayed till feeding is established and jaundice assessment is complete by 4 to 5 days.

X. B. Special care - care of well newborn in the COVID era. Possible risk of vertical transmission of SARS-CoV-2 is very low (less than 3%). All global agencies including the WHO and UNICEF suggest routine care along with direct breastfeeding to continue, while observing respiratory and hygienic precautions.

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 the risk for subsequent hyperbilirubinemia, feeding issues, or other concerns.

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

1. Assess the infant's general state of health including weight, hydration, and degree of jaundice and identify any new problems.
2. Look for danger signs.
3. Review feeding patterns; encourage and support breastfeeding.
4. Review the adequacy of stool and urine patterns.
5. Provide referral for lactation support if feeding and elimination patterns are not reassuring.
6. Assess the 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.

XII. PARENTAL EDUCATION.

Parental education on routine newborn care should be started during antenatal visits, and continued until discharge from birth admission and also on follow-up visits. Written information in addition to verbal instruction may be helpful, and communication by online videos or interaction has been found to be effective, especially as COVID pandemic has necessitated physical distancing.

Suggested Readings

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10 Genetic Issues Presenting in the Nursery

Carlos A. Bacino

KEY POINTS

- Approximately 2% to 3% newborns have a major birth defect.
- Major birth defects have health or social consequences; minor birth defects are mere "markers" to look for major defects.
- The concept of recognized syndromes (multiple system defects that occur together) aids the clinician to look for other defects.
- Underlying basis for birth defects may have its origin in abnormal development (embryology) or may be altered after normal development due to mechanical/vascular or other factors.

I. GENERAL PRINCIPLES. Approximately 2% to 3% of newborns have a ***major birth defect*** and require genetic evaluation. Anomalies may be detected antenatally or after birth and may be consistent with a ***well-known syndrome*** or may be ***sporadic anomalies***. Other neonatal presentations such as ***ambiguous genitalia***, ***inborn errors of metabolism*** (IEM), unexplained seizures, extreme hypotonia necessitating ventilator support, feeding difficulties, or ***growth abnormalities*** (growth restriction, disproportion, overgrowth) may need genetic evaluation. A thorough clinical evaluation requires a detailed prenatal history, a family history, and a comprehensive clinical exam, often including anthropometric measurements.

A. Classification of congenital anomalies based on their severity.

1. **Major malformations** are structural abnormalities that have medical or social 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 direct health or social significance. They are common; 15% of children are born with a minor malformation. Presence of these may point to (be a marker for) a major malformation/genetic problem. A single transverse palmar crease or partial syndactyly is an example. Minor anomalies may aid in the diagnosis or recognition of a specific syndrome. Infants with one minor malformation may have a 3% chance of a major anomaly, 10% of babies with two minor malformations may have a major malformation, and 20% to 25% of babies with ***three or more minor malformations*** are at risk for having a major malformation or a syndrome.

3. **Common variants,** These are structural changes that represent one end of normal spectrum, and do not amount to an abnormal development, for example, sacral dimple and broad forehead.

B. Classification of birth defects based on clinical presentation. Birth defects may be a single-system defect (isolated cleft lip/palate, congenital heart disease) or multiple system defect.

Multiple system defects can be classified as follows:

- A **syndrome** consists of a constellation of anomalies that are often seen together and are ***due to single underlying cause***, e.g., Down's syndrome due to trisomy 21 or Turner's syndrome.
- **Associations** are clusters of malformations that occur together more frequently than occur sporadically, but their association is not strong enough to classify as a syndrome. The word association is reserved for malformations occurring together ***with no unifying (common) cause***. For example, VACTERL association (vertebral, anal, cardiac, tracheoesophageal fistula, renal, and limb—radial ray defects), in which **at least three** anomalies are required.

  The CHARGE association is now called CHARGE syndrome, as the specific genetic anomaly (CHD 7) has been identified.
- **Sequence** is defined as a pattern of multiple anomalies derived from a single known or presumed cause, but are embryologically unrelated defects. It may be a cascade due to mechanical factors—Potter sequence and Pierre Robin sequence.
- **Complex** is a multiple system malformation due to a change in the developmental filed (unit).

A developmental field is a group of embryonic structures that ***respond as a unit***. Their development is temporally and spatially controlled and coordinated. The evidence of such developmental fields comes from observation of ***same defects*** due to different causes.

C. Classification of birth defects based on their pathogenic mechanisms

- **Malformation** is reserved for abnormalities caused by **failure or inadequate completion of one or more of the embryonic processes**. An example is neural tube defects caused by failure in the closure of neuropores.
- **Disruptions** are defects due to extrinsic events that alter structures that have already developed normally. These events can be due to **compromise in circulation,** examples - atresia may be due to compromise in gut circulation, amputation of digits by amniotic band may be due to physical compression.
- **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.
- **Dysplasia** refers to abnormal cellular organization or function within a **specific tissue type** throughout the body resulting in abnormality. Examples include skeletal dysplasia and ectodermal dysplasia.

II. INCIDENCE. The Centers for Disease Control and Prevention (CDC) monitor rates of birth defect in the United States (http://www.cdc.gov/ncbddd/birthdefects/data.html). Approximately 1 in 33 children have a birth defect. In the United States, infants

with birth defects account for 20% of infant deaths. As per the WHO March of Dimes report, birth defects account for 7% of all neonatal mortality globally. Major congenital anomalies are noted in 20% to 30% of ***stillbirths.***
In India, the birth defect prevalence varies from 61 to 69 per 1,000 live births.

III. ETIOLOGY. The etiology of approximately 50% of birth defects are unknown. Of the remainder, etiology is attributed as follows: 6% to 10% chromosomal, 3% to 7.5% single-gene Mendelian disorders, 20% to 30% multifactorial and 4% to 5% environmental exposures. The use of molecular diagnostic technique helps to establish the etiology in most cases.

IV. APPROACH TO AN INFANT WITH BIRTH DEFECTS

A. A comprehensive history is an important 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, heart disease (valvular heart disease), myotonic dystrophy, phenylketonuria, autoimmune disorders (Systemic Lupus Erythematosus [SLE]), Graves disease, and hypothyroidism (see Table 10.1 for prenatal exposures and fetal effects) should be documented.

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
Methimazole	Hypothyroidism, aplasia cutis
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

(*Continued*)

Table 10.1. Well-Recognized Human Teratogens *(Continued)*

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
Danazol and other androgenic drugs	Virilization in female fetus
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
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
Parvovirus	Fetal anemia, nonimmune hydrops fetalis
Zika virus	Microcephaly

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

b. Drug exposures include prescribed drugs, such as antihypertensives (angiotensin-converting enzyme inhibitors), seizure medications, antineoplastic agents (methotrexate), anticoagulants (warfarin), and illicit drugs (cocaine). Other drugs that may result in birth defects include misoprostol (used to induce abortions). Timing of the exposure is important. 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 post fertilization, with the exception of severe forms of holoprosencephaly when exposure may occur around or before 23 days (see Appendix B).

c. Infections and immunizations: Ask for clinical features or diagnosis in the antenatal period for infection with toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis (TORCHS), varicella, parvovirus, HIV, hepatitis B, and Zika virus. Enquire the immunization status especially against rubella, varicella, and hepatitis B.

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

e. Nutritional status: Undernutrition, obesity and periconceptional folic acid intake, and any other micronutrient deficiency disorder should be documented.

f. Fertility issues and the use of reproductive assistance (e.g., history of multiple miscarriages, *in vitro* fertilization [IVF], or medications to stimulate ovulation) should be documented. Genetic disorders such as Beckwith–Wiedemann syndrome, Silver–Russell syndrome, and Angelman's syndrome that can be caused by imprinting defects (epigenetic mutations) have been seen more often in children conceived by assisted reproductive technology using intracytoplasmic sperm injection (ICSI).

g. Multiple gestations (see Chapter 11) should be documented.

h. 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.

i. First and second trimester screening include 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 beta subunit (β-hCG) or total hCG. The second trimester screen includes alpha-fetoprotein (AFP), unconjugated estriol (uE3), and free β-hCG for the triple screen, plus inhibin A, as part of the quad screen. The combined or sequential screening is having a detection rate of 80% to 95% depending on the screening strategy with a false-positive rate of 5%. A low maternal serum alpha-fetoprotein (MSAFP) level can be seen in trisomies 21, 18, and 13. A high MSAFP may be a sign of multiple gestation, 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 a low hCG may occur with trisomies 18 and 13.

j. Prenatal studies include ultrasonography (any anomaly detected), magnetic resonance imaging (MRI) and chromosome or microarray studies done

on samples obtained by amniocentesis, chorionic villi sampling (CVS), or percutaneous umbilical blood sampling.

k. Noninvasive prenatal screening (NIPS) is slowly replacing the first and second trimester screens. This technique consists of the analysis of cell-free fetal DNA present in the maternal serum. Massive parallel sequencing of maternal and placental (fetal) fragments of DNA is possible through next-generation sequencing (NGS) platforms. As per the American College of Medical Genetics (ACMG) recommendation, NIPS is the most sensitive screening option for the common trisomies such as trisomy 21 (Down's syndrome, sensitivity 99.4%, specificity 99.9%) and trisomy 18 (sensitivity 97.7%, specificity 99.9%). Sensitivity is lower for trisomy 13 (90.6%) and sex chromosome (92%): NIPS is not recommended for screening other trisomies and copy number variants such as 22q11 deletion syndrome. NIPS is used in high-risk situations such as advanced maternal age and abnormal ultrasound examinations where positive predictive value (PPV) will be high. For low-risk presentations, conventional first and/or second trimester screens are preferred. The American College of Obstetricians and Gynecologists (ACOG) recommend conventional screening methods as the most appropriate choice for first-line screening for most women in the general obstetric population. Before any prenatal screening test, the couple should be informed on various aspects of the test through pretest counseling. If the screening test is positive, they should be offered post-test counseling and offered options for definitive prenatal testing.

l. Newer forms of NIPS include 22q11.2 microdeletions (DiGeorge/velocardiofacial syndrome [VCFS]) and Wolf–Hirschhorn deletion. However, in view of low PPV (0% to 21%) and high false-positive rate (79% to 100%), it should not be used in the general population (not recommended by the ACOG and ACMG). At present, NIPS has little clinical application in the prenatal screening or diagnosis of monogenic disorders.

2. **Family history** should include the following questions:
   - **a.** Are there any previous children with multiple congenital anomalies?
   - **b.** What is the ethnicity of the parents? Some diseases 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.
   - **e.** Three generation pedigree should be constructed.
3. **Prenatal and perinatal events** should be evaluated.
   - **a.** What was the fetal presentation, and for how long was the head engaged? Was there fetal crowding (may occur with multiple gestation) 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. Was there any history of polyhydramnios (gastrointestinal tract [GIT] anomalies) or oligohydramnios (renal dysplasia)?

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

e. 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, asymmetry, or micro/macrocephaly. 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 the section "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; eye examination (micro-opthalmia, cataract, etc.), midface hypoplasia, cleft lip/palate, micrognathia, and short neck; joint contractures (arthrogryposis) and dislocations; spine abnormalities (neural tube defects [NTD], sinus, scoliosis, etc.); genitalia (abnormality, Prader staging); and dermatological (Mongolian spot, bullous lesion, pigmentary lesion, etc.) and limb anomalies (e.g., asymmetry, clinodactyly, brachydactyly, polydactyly). A good clinical description can aid the diagnosis as features can be matched to those in a database such as London Dysmorphology Database or Pictures of Standard Syndrome and Undiagnosed Malformations (POSSUM). Other diagnostic aids are text books (*Smith's Recognizable Patterns of Human Malformations*), web-based (OMIM, Phenomizer), and digital applications (Face2Gene). Some physical findings can be obscured by aspects of clinical care such as endotracheal tube position and taping or intravenous armboard and tape over the limbs. In this case, the infant should be re-examined when these are no longer present.

3. Ancillary evaluations include a hearing screen (otoacoustic emission [OAE] and automated auditory brainstem response [AABR]) that is done typically before discharge from the nursery or neonatal intensive care unit (NICU) and an ophthalmologic evaluation.

C. Laboratory studies

1. Genetic laboratory studies

a. Chromosome studies are typically performed on whole blood drawn into sodium heparin tubes. The T lymphocytes in the blood are stimulated with mitogens, cultured for 72 hours, placed on slides, and karyotype done with 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's syndrome), cell growth may be impaired and cell stimulation fails. In this case, it is preferable to perform a molecule-based assay such as array comparative genomic hybridization (aCGH) (see the 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, as there is delay in obtaining results to several weeks. However, chromosome studies on the skin are reserved in some cases of suspected chromosome mosaicism. Chromosome studies can detect up to 5% of abnormalities. Tables 10.2 and 10.3 list the main clinical findings of the most common chromosome aneuploidies.

b. 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. FISH testing is also useful in the diagnosis of cases with phenotypically suggestive microdeletion syndrome such as 22q11.2 deletion or William's syndrome.

c. aCGH, also known as chromosome microarray, is a molecular technique 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 the exon. This study is based on the comparison of a known genome from a normal individual against the test sample and is often done with a matched sex control. Chromosome microarrays can detect 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. Any loss or gain of genetic material must be confirmed by molecular techniques such as FISH, polymerase chain reaction (PCR), or multiplex ligation-dependent probe amplification (MLPA). Both parents must be studied after the confirmation to determine whether one of them is a carrier and to aid with the interpretation of the finding(s) in case it is a polymorphic variant. 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 10.4.

d. "Specific disease gene panels" is mainly reserved for single-gene disorders. They are caused by inherited or new mutations and often transmitted in a Mendelian fashion, such as autosomal recessive, autosomal dominant,

Table 10.2. Common Chromosome Anomalies (Aneuploidies)

	Trisomy 13	Trisomy 18	Trisomy 21	Turner's 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	Brachycephaly 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 GDD	Microcephaly GDD	Microcephaly global developmental delay (GDD)	Normal
Neurologic	Hypertonia/hypotonia seizures, apnea	Hypertonia, apnea	Hypotonia	Normal tone
Heart	ASD, VSD	Multiple valvular anomalies	AV canal defect, VSD, ASD	Aortic coarctation Bicuspid aotic valve
Abdominal	Multicystic kidneys, horseshoe kidneys, double ureters	Omphalocele, renal anomalies	Duodenal atresia, Hirschsprung's disease	Horseshoe kidneys
Limbs	Polydactyly, nail dysplasia	Overlapping fingers, nail hypoplasia, rocker-bottom feet	Brachydactyly, fifth finger clinodactyly, single transverse palmar crease	Hand and feet lymphedema, deep-set nails
Skin	Scalp defects	Decreased subcutaneous tissue	Cutis marmorata	Multiple nevi

ASD, atrial septal defect; AV, atrioventricular; GDD, global development delay; VSD, ventricular septal defect.

Table 10.3. Other Common Chromosome Abnormalities

	Cri-du-Chat Syndrome	Wolf–Hirschhorn Syndrome	1p36.3 Deletion Syndrome	Killian/Teschler-Nicola Syndrome (Pallister's 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 pigmented 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
Heart	Congenital heart disease (CHD) variable	ASD, VSD	Cardiomyopathy	
Abdominal		Malrotation, absent gallbladder		Diaphragmatic hernia, imperforate anus
Limbs	Nail hypoplasia	Clubfeet, hyperconvex nails		Brachydactyly, broad digits

(*Continued*)

Table 10.3. Other Common Chromosome Abnormalities *(Continued)*

	Cri-du-chat Syndrome	Wolf–Hirschhorn Syndrome	1p36.3 Deletion Syndrome	Killian/Teschler-Nicola Syndrome (Pallister's Mosaic Syndrome)
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 often improve in 50% hearing loss leads to speech delays	Profound ID, no speech, seizures, joint contractures

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

Table 10.4. Common Chromosome Microdeletions Ascertained in the Neonatal Period

	Prader–Willi Syndrome	DiGeorge's Syndrome and Velocardiofacial Syndrome	Williams, Syndrome	Miller–Dieker Syndrome
Chromosomal and genetic defect	15q11q13 deletion 70% UPD 20% to 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 Friendly personality	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

(*Continued*)

Table 10.4. Common Chromosome Microdeletions Ascertained in the Neonatal Period *(Continued)*

	Prader–Willi Syndrome	DiGeorge's Syndrome and Velocardiofacial Syndrome	Williams, Syndrome	Miller–Dieker Syndrome
Limbs	Small hands and feet	Long digits	Normal	Normal
Skin	Lighter pigmentation than that of parents (in deletion cases)	Normal	Normal	Normal
Other		T-lymphocyte dysfunction: frequent infection	Hypercalcemia	
Natural history	Obesity and hyperphagia after 2 to 3 years	Normal life span	Normal life span	Death before age 2 years

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

and/or X-linked disorders. Many of them can present in newborns as life-threatening disorders. These include spinal muscular atrophy (exon 7/8 deletion in *SMN* gene); congenital adrenal hyperplasia (most commonly due to 21-hydroxylase deficiency); congenital myotonic dystrophy (only when inherited from an affected mother); osteogenesis imperfecta due to type I collagen mutations and other rare recessive forms (*CRTAP, LEPRE-1, PPIB*); holoprosencephaly due to mutations in *SHH* (accounts for 30% to 40%), *ZIC2, TGIF, SIX3, PTCH1,* and *GLI2*; cystic fibrosis due to CFTR mutations; and autosomal recessive polycystic kidney disease. 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 connexin 26 and connexin 30 mutations. Blood sample for DNA testing should be collected in *EDTA* Vacutainer.

e. In certain diseases with high clinical variability (symptoms overlapping with other disorders) and genetic heterogeneity (multiple genes associated with the similar phenotype or disease), **next generation sequencing-based multigene panel tests/clinical exome** is appropriate for an efficient and timely molecular diagnosis. For example, diabetes in a child is caused by multiple genes (*ABCC8, KCNJ11, INSZFP57, GCK, IPF1, EIF2AK3,* and others). Exome sequencing studies are performed in the clinical evaluation of children with multiple anomalies who had a normal chromosome microarray study. This test allows the sequencing of all the exons of the genome (20,000 genes approximately) in a single pass using NGS, a technique that reads small stretches of DNA multiple times, making the results more robust. The exons code for proteins and are the best known components of the genes. Exome sequencing detects the etiology in approximately 26% of patients, in whom etiology was not detected by previous studies. In a small minority of situations, whole genome sequencing may be used, when intronic variants are expected.

f. Mitochondrial disorders have extreme phenotypic heterogeneity and can have any mode of inheritance (autosomal recessive or mitochondrial). Prematurity, intrauterine growth restriction, hypotonia necessitating ventilator support, neonatal seizures, and elevated lactate levels are characteristic of mitochondrial disorders. When mitochondrial disorders are suspected, either **targeted mitochondrial mutation testing** or panel testing of nuclear and mitochondrial genes associated with mitochondrial disorders is appropriate.

g. **Methylation testing** is the first test recommended for disorders in which alteration in DNA methylation in specified regions is the pathogenic mechanism (Prader–Willi syndrome, Angelman's syndrome, Beckwith–Wiedemann syndrome, and Russell–Silver syndrome).

2. Other laboratory studies

a. **Infection.** Toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCHS) infection may be suspected in children with microcephaly, cataracts, deafness (cytomegalovirus, rubella, toxoplasmosis), and congenital heart disease (rubella). In that case, immunoglobulin G (IgG) and

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

b. 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 29 conditions for testing. Most of these conditions can be managed by medications and/or special diets, and treatment in many can be lifesaving. A neonate with a suspected metabolic disorder should be investigated for hypoglycemia and absent urine ketones (fatty acid oxidation disorder), nonglucose-reducing substance in urine (galactosemia), plasma ammonia and urine orotic acid (urea cycle disorder), arterial blood gas (ABG) with anion gap (acidosis with increased anion gap), plasma lactate and pyruvate (mitochondrial disorders), urine organic acids (organic acidemia), plasma amino acids for aminoacidopathies (e.g., phenylketonuria, tyrosinemia, nonketotic hyperglycinemia), and tandem mass spectroscopy for acylcarnitine profile (fatty acid oxidation disorders). Additional metabolic studies considered for the diagnosis of IEM include very long-chain fatty acids for peroxisomal disorders (Zellweger's syndrome), sterol panel (Smith–Lemli–Opitz syndrome associated with low 7-dehydrocholesterol levels), and urine succinylacetone (tyrosinemia). Appropriate precaution should be taken during specimen collection; measure lactic acid in whole plasma from a free-flowing blood sample (ideally arterial). It is important to note that many IEM will not manifest symptoms until the infant is receiving milk feedings (see Chapter 60).

D. Ancillary evaluations

1. Imaging studies

a. Ultrasonography, brain imaging to detect major malformation and intracranial hemorrhage; abdominal ultrasonogram to detect major liver and kidney anomalies, and 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 and hemangiomas

e. Skeletal survey in children with intrauterine growth restriction (IUGR), poor linear growth, and especially if 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.
2. 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 (including photograph) should be obtained and radiographs should be considered in addition to pathologic exam. Blood sample should be collected for karyotype (should be done within 24 hours) and DNA analysis (stored at –20°C to –70°C for future testing) for the confirmation of diagnosis and genetic counseling. In a suspected metabolic disorder, a urine sample can be collected and stored at –70°C for future studies (metabolic autopsy).
3. 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. Patients with birth defects 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 to 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 or early childhood intervention programs.

Suggested Readings

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11 Multiple Births

Melinda Markham

KEY POINTS

- Twin birth rates continue to climb slowly, whereas higher-order multiple gestation pregnancies are declining.
- Prematurity and low birth weight are the most common complications of multiple births.
- Complication rates are higher in monochorionic than in dichorionic twin pregnancies.
- Laser ablation is the intervention of choice for the treatment of advanced stages of 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 on 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 South Asia is 9 to 16/1,000 live births. Twin birth rates in India are lesser at 7.7/1,000 live births. However, the rate of twin birth has been relatively stable over the past 10 years.

1. The rate of MZ twinning has remained relatively constant (3.5 per 1,000 births).
2. The rate of DZ twinning is approximately 10 in 1,000 births. This rate is influenced by several factors such as ethnicity, parity, maternal age, and the use of fertility-enhancing therapies. The frequency of DZ twinning has a genetic tendency that is affected by the genotype of the mother and not that of the father. In India, approximately three-fourth of twins are DZ.

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.

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. A **dichorionic diamniotic** placenta results when early splitting occurs on 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 on 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 types is 30% dichorionic diamniotic, 70% monochorionic diamniotic, and <1% monochorionic monoamniotic. On day 14 and thereafter, the primitive streak begins to form and late splitting of the embryo at this time results in **conjoined twins**.

B. DZ pregnancies 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 ultrasonography can best determine the chorionicity of a multiple gestation; chorionicity is more difficult to determine in the second trimester. From weeks 10 to 14, a fused dichorionic placenta may often be distinguished from a true monochorionic placenta by the presence of

an internal dividing membrane or ridge at the placental surface (lambda sign or twin-peak 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, and the intertwin membrane abruptly ends at the placental site in a "T"-shaped configuration. One placenta, same-sex fetuses, and absence of a dividing septum suggest monoamniotic twins.

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. There is also an increasing evidence on the possibility of cell-free fetal DNA testing from the maternal blood to determine zygosity. Postnatally, DNA typing should optimally be performed on the umbilical cord tissue, buccal smear, or a skin biopsy specimen rather than on 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 in 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. 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. Monochorionic twins are assumed as monozygous with a single risk of aneuploidy provided for the pregnancy. Since majority of dichorionic twins are dizygous, a risk for each twin is provided based on the first-trimester nuchal translucency value. The detection rate for Down's syndrome is lower than in a singleton pregnancy (86% for dichorionic and 87% for monochorionic twins).

C. A second-trimester ultrasonography exam is important in surveying each fetus for **anatomic defects**. **Second-trimester amniocentesis** and **first-trimester CVS** can be safely performed on multiples and both are accurate diagnostic procedures for determining aneuploidy. Cell-free fetal DNA testing on maternal blood in screening for trisomy 21 can be performed in twin pregnancies and it is superior to the first-trimester combined screening test (detection rate 98%, false-positive rate 0.05%). Evidence in screening for trisomy 13/18 is lesser.

VI. MATERNAL COMPLICATIONS

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

B. Spontaneous abortion occurs in 8% to 36% of multiple pregnancies with reduction to a 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 a 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. Incompetent cervix occurs in up to 14% of multiple gestations.

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 in 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 a 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 36, 33, and 29 1/2 weeks, respectively, for twins, triplets, and quadruplets. The **likelihood of a birth weight <1,500 g is 8 and 33 times greater in twins and triplets** or 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 that of singletons. Fetal growth restriction is defined by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) as an estimated weight of one fetus <10th centile or the intertwin weight discordance >25%. Selective IUGR (poor growth of one twin) can be stratified based on umbilical artery flow. The mechanisms of IUGR 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, perinatal morbidity, and 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 and perinatal death. Five percent to 15% of twins and 30% of triplets have fetal growth discordance that is associated with a sixfold increase in perinatal morbidity and mortality.

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 four to six times greater in MZ pregnancies. Death of one twin can affect the other.

1. Death of one of the MZ twins. 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 on death of the co-twin.
2. Death of one of the DZ twins. Because their circulation is not shared, the death of one DZ twin usually has minimal adverse effect on the surviving co-twin. In this case, the co-twin is either completely resorbed if death occurs in the first trimester or compressed between the amniotic sac of its co-twin and the uterine wall (fetus papyraceous).
3. Other complications of death. The complications affecting the surviving twin might include stillbirth, preterm birth, neonatal demise, placental abruption, and chorioamnionitis.
4. In the event of demise of one monochorionic twin, immediate delivery of the surviving co-twin should be considered after fetal viability. However, this does not seem to change the outcome as neurologic injury is thought to occur at the time of the co-twin's death. Women who retain the dead fetus are at an increased risk of preeclampsia and hypertensive disorders. Disseminated intravascular coagulopathy is a very rare complication in women who retain the dead fetus for more than 3 weeks. Monitoring of maternal blood pressure, proteinuria, and coagulation profiles is recommended.

E. Neonatal mortality. Twin birth is associated with an increased risk of neonatal mortality compared to singleton births at all gestational ages. Prematurity and low birth weight are the predominant factors that increase the rates of mortality and morbidity for multiple births. But the risk of stillbirth in twin pregnancies increases with advancing gestational age, so delivery is typically considered at 37 to 38 weeks of gestation.

In a retrospective cohort study (*of matched US multiple birth and death data from 1995 to 2000 in infants without congenital anomalies*), the perinatal mortality rate was greater in twins, and increased threefold and fourfold for triplet and quadruplet births, respectively. In a large population-based study, Euro-peristat (29 countries, 5,074,643 births) project, multiple birth rates were found to vary across regions from as low as 9.1 in Romania to 26 in Cyprus. The prematurity

rate was 9 times more, fetal loss was 2.4 times more, and neonatal mortality was 7 times higher with multiple births. The study clearly demonstrated that efforts to reduce multiple gestations will decrease perinatal mortality. Restricting the number of babies (embryo transfer) in ART and reduction to twins from a higher number of babies has resulted in better perinatal outcomes. In Turkey, after a regulation restricted the number of embryo transfers, twins and triplets decreased, mean gestation and weight of twins increased, and NICU admissions decreased significantly.

F. Neonatal morbidities. Prematurity and growth restriction are associated with an increased risk of morbidities such as bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, and intraventricular hemorrhage (IVH).

G. Long-term morbidities such as cerebral palsy (CP), cognitive deficits, and autism spectrum disorders are more in twins and higher-order multiples than in 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. The prevalence of CP in twins is 7.4%, compared with 1% in singletons. The higher prevalence of CP among twins compared to among singleton births is due to a greater frequency of prematurity and low birth weight in twins. 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 same-sex pairs, 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.

H. Impact of ART on outcomes. In the United States, 19% of twin births and 32% of triplet or higher-order births result from ART. Multiple reports noted increased adverse maternal and perinatal outcomes associated with ART. However, the extent to which the increased frequency of multiple births following ART, (~44% with ART vs. ~3% with natural conception) contributes to this risk requires further study. Recent population-based studies in the United States demonstrate an increased risk of adverse perinatal outcomes in twin versus in singleton ART births, including prematurity, low birth weight, and very low birth weight. A meta-analysis on ART babies (64 studies, 60,210 IVF/intracytoplasmic sperm injection [ICSI] vs. 146,737 spontaneously conceived multiple births) showed a higher incidence of adverse pregnancy outcomes (APO), prematurity, IUGR, NICU admissions, and perinatal mortality.

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 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's syndrome. However, larger prospective cohort studies are required to definitively relate these rare conditions to ART.

VIII. UNCOMMON COMPLICATIONS OF MULTIPLE GESTATIONS

A. Congenital malformations occur in approximately 6% of twin pregnancies or 3% of individual twins. The risk in MZ twins is approximately 2.5-fold greater than in DZ twins or singletons. 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. Twin reversed arterial perfusion** (TRAP sequence) is a rare problem (in 1% of monochorionic twins). One twin is normal and the other twin is a poorly developed mass of tissue. One twin is the pump twin and the other is an acardiac twin (no heart). The abnormal 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.
   - **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's syndrome (facio-auriculo-vertebral defects), or Poland sequence. 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.

   Twin pregnancies should be evaluated for anomalies by fetal ultrasonography or more invasive procedures if indicated. Congenital anomalies are concordant only in a minority of cases, even in MZ twins.

B. Chromosomal anomalies occur at a higher frequency in offspring of multiple gestations. **Advanced maternal age** contributes to the increased risk of chromosomal anomalies. The risk in MZ twins is equivalent to that in a singleton.

The risk in DZ twins is independent for each fetus, so the risk of chromosomal abnormality in at least one DZ twin is twice that in a singleton fetus.

C. 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 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. Decisions regarding separation are complex and depend on anatomic factors, associated anomalies, and parental wishes. Fewer than 20% of conjoined twins survive.

D. TTTS occurs only in monochorionic gestations.

1. The **pathophysiology** of TTTS is not completely understood, but placental vascular anastomoses, unequal placental sharing, and abnormal umbilical cord insertions are all necessary for TTTS to occur. Vascular connections occur in 85% of monochorionic placentas. Ten percent to 20% of monochorionic placentas have sufficient circulatory imbalance to produce TTTS. 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 ischemic lesions, 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, fetal hydrops, and demise.
2. Diagnosis is usually made between 17 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.
3. **Fetal treatment** interventions depend on the gestational age and stage at the time TTTS is identified. Most cases are detected in the second trimester at more advanced stages. Many pregnancies with stage I TTTS can be managed expectantly because more than 75% regress or remain stable with no invasive intervention, and perinatal survival is approximately 86%. However, worsening polyhydramnios, maternal discomfort, shortening of cervix, and cardiac changes in recipient are indicators of emergency intervention. Most experts

recommend fetoscopic laser photocoagulation or radiofrequency ablation of placental anastomoses for stages II to IV at <26 weeks' gestation, although data are limited. In the 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. In a systematic Cochrane review, the two trials that compared amnioreduction to laser ablation found no difference in death. In follow-up at 6 years of age, no additional deaths occurred in the group of infants alive at 6 months. Normal neurologic evaluation was similar between groups (82% and 70% in the laser and amnioreduction groups, respectively, $P = 0.12$), but due to the increased survival at 6 months of age, more infants were alive without neurologic abnormality at 6 years of age in the laser group. An alternative management of severe TTTS (hydropic recipient/severe IUGR with critically abnormal Dopplers of the donor) involves selective reduction of the sick fetus using bipolar cord coagulation or radiofrequency ablation.

4. Neonatal management may include 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.
5. Persistent pulmonary hypertension of the newborn (PPHN) is more common in TTTS.
6. Twin anemia polycythemia sequence (TAPS) is another rare complication of monochorionic twins. This is diagnosed based on discordant MCA Doppler abnormality, suggesting fetal anemia in one and polycythemia in the other twin. Possible cause is unequal nutrition and oxygen flow to the twins from a common placenta.

E. Velamentous cord insertion and vasa previa occur six to nine times more often in twins than in 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.

F. 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.

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

H. Social and family impact. Caring for twins or higher-order multiples contributes to increased family physical, emotional, and financial stress; parental anxiety and depression is often not recognized. Professional and social life of mothers is significantly affected compared with mothers of singletons. Multiples are more likely to have medical complications (i.e., prematurity, congenital defects, IUGR)

that result in prolonged hospital stays and contribute further to problems of two newborn babies. Social services, lactation support, 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

Chauhan SP, Scardo JA, Hayes E, et al. Twins: prevalence, problems, and preterm births. *Am J Obstet Gynecol* 2010;203:305–315.

Khalek N, Johnson MP, Bebbington MW. Fetoscopic laser therapy for twin-to-twin transfusion syndrome. *Semin Pediatr Surg* 2013;22:18–23.

Simpson L. What you need to know when managing twins: 10 key facts. *Obstet Gynecol Clin North Am* 2015;42:225–239.

12 Maternal Drug Use, Infant Exposure, and Neonatal Abstinence Syndrome

Stephen W. Patrick

KEY POINTS

- Information on drug abuse is difficult to obtain, unexplained situations may cause suspicion:
  - Maternal characteristics that may be associated with drug use: teen pregnancy, poor antenatal care.
  - Neonatal characteristics that may be associated with maternal drug use: unexplained microcephaly, dysmorphism, stroke, pulmonary hypertension.
- Verbal screening for substance use should occur in every pregnancy.
- Opioid use in pregnancy is increasingly common and can result in drug withdrawal.
- Every birth hospital should have a protocol in place to screen, evaluate, and treat substance-exposed infants.
- An opioid (morphine or methadone) should be the first choice for opioid withdrawal if pharmacotherapy is required.

I. MATERNAL DRUG USE

A. Use of illicit substances. Data from the National Survey of Drug Use and Health (NSDUH) suggest that at least 5.4% of pregnant women use illicit drugs in pregnancy. Illicit drug use is highest among younger women, with the highest rate (14.6%) in 15- to 17-year-old girls. Overall, the rate of illicit drug use in pregnant women is nearly half that of the general population (11.4%), and women are less likely to use drugs in the third trimester (2.4%). This suggests that, although illicit drug use in pregnancy is common, becoming pregnant may motivate some women to engage in the treatment of substance use disorders. The NSDUH reports that the most common illicit drugs used as a percentage of the US population >12 years old in the United States are marijuana (7.5%), psychotherapeutics used illicitly (2.5%), cocaine (0.6%), hallucinogens (0.5%), inhalants (0.2%), and heroin (0.1%). The maternal abuse of narcotics has increased because of "liberal prescription of opiates in pregnant women in some countries to treat acute and/or chronic pain." The reported incidence of drug abuse in pregnancy in Iran is 0.2% to 5.4%. However,in a study from Iran,on random urine sampling of 200 pregnant ladies, 23% had positive urine screening test. Similar observations were reported from Thailand too. Understandably, the reported numbers from South East Asia are not accurate because of the stigma attached

to substance abuse in this region and fear of reprisal. Increase in drug abuse has been reported from other Asian countries including metropolitan cities in India.

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 the risk of fetal effects are limited for many. Prescribed medications include atypical antipsychotics (e.g., risperidone), antidepressants (e.g., sertraline), and opioids (e.g., hydrocodone). In addition, the NSDUH reports high use by pregnant women of alcohol (9.4%) and cigarettes (15.4%). In many South east Asian countries, adverse obstetric outcomes and even maternal deaths have been associated with substance overdose. 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 should include the use of illicit drugs, prescription drugs, tobacco, and alcohol. The American College of Obstetricians and Gynecologists recommends the use of a validated screening tool for drug use such as the 4 *P*s or CRAFFT (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. Nonspecific maternal and infant associations with illicit drug use include the following:

1. Maternal

- **a.** Poor or no prenatal care
- **b.** Preterm labor
- **c.** Placental abruption
- **d.** Precipitous delivery

2. Infant

- **a.** Dysmorphic features: Fetal alcohol syndrome, barbiturates
- **b.** Small for gestational age (heroin, nicotine, cocaine)
- **c.** Microcephaly
- **d.** Neonatal stroke
- **e.** Persistent pulmonary hypertension (in mothers on selective serotonin reuptake inhibitors [SSRIs])

The risk factors for substance abuse in the study of pregnant women from Iran were age at the first pregnancy of less than 20 years, living in rural areas, unwanted pregnancy, lack of health care during pregnancy, and having a spouse and/or first-degree family member with substance abuse.

B. Diagnostic testing can be useful to supplement standardized verbal screening tools. Testing should be considered in infants with signs consistent with neonatal abstinence, severe intrauterine growth restriction without an identified etiology, intracranial hemorrhage or stroke, or placental abruption. 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.

Table 12.1. Clinical Screening Tools for Prenatal Substance Use and Abuse

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—Substance Abuse Screen for Adolescents and Young Adults

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 in TROUBLE while you were using alcohol or drugs?
Scoring: Two or more positive items indicate the need for further assessment.

Center for Adolescent Substance Abuse Research, Children's Hospital Boston. *The CRAFFT Screening Interview*. Boston, MA: CeASAR; 2009. http://www.ceasar.org/CRAFFT/pdf/CRAFFT_English.pdf. Retrieved February 10, 2012. *Source*: American College of Obstetricians and Gynecologists Committee opinion no. 524: opioid abuse, dependence, and addition in pregnancy. *Obstet Gynecol* 2012;119(5):1070–1076.

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) for 3 to 5 days. Drugs administered during labor may cause difficulty in interpreting results.
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 similar data to meconium, although collection and storage of the umbilical cord at birth can be resource intensive.

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).

Management of pregnant woman on substance of abuse. It is most important to counsel the mother to use agonist therapy at the most effective dose to stabilize maternal and fetal withdrawal symptoms and reduce cravings for drugs, and she should also be encouraged to come for antenatal clinic visits.

III. NONOPIOID SUBSTANCE EXPOSURE.

Substance use in pregnancy may result in abnormal psychomotor behavior in the newborn that is consistent with toxicity or withdrawal, as summarized in Table 12.2.

IV. NEONATAL ABSTINENCE SYNDROME FOLLOWING OPIOID EXPOSURE IN PREGNANCY

A. Because of the high prevalence of opioid use during pregnancy, 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. Adherence to such protocols appears to impact clinical outcomes more than pharmacotherapy. Neonatal abstinence syndrome (NAS) can result from a variety of opioids including prescription opioids (e.g., hydrocodone), illicit opioids (e.g., heroin), or medication-assisted treatment (e.g., methadone). Although medication-assisted treatment increases an infant's risk of NAS, the infant's risk of being born preterm or low birth weight is less than with continued heroin use. As a result, the American College of Obstetrics and Gynecologists recommends medication-assisted treatment.

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, which becomes less with buprenorphine, followed by a long-acting opioid (MS Contin, morphine sulfate extended release), and then a short-acting opioid (hydrocodone). Adjunctive use of tobacco, SSRI, atypical antipsychotics, and benzodiazepines increases the likelihood of NAS or makes it more severe.

C. **Timing of presentation**. The initial presentation of NAS depends on when the drug was last used in pregnancy, infant metabolism, and half-life of the opioid used. In addition, for reasons that are uncertain, 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 4 to 7 days after birth.

D. **Site of care**. There is increasing evidence that processes of care that keep mother and infant together (e.g., rooming in) promote bonding and breastfeeding, and may reduce infant symptomatology and decrease NAS severity. Where possible, infants should not be separated from their mothers.

E. **Assessment**. Infants at risk for drug withdrawal should be assessed for drug withdrawal using an available scoring tool. We use the modified Finnegan Neonatal Abstinence Score Tool (NAST) (see Table 12.3). Scoring should begin soon after admission and continue every 3 to 4 hours, reflecting the preceding period and depending on the frequency of feedings, recording of vital signs, and provision of care. If infants appear hungry, we provide half of the feeding volume and then complete scoring. Infants are scored for a total of 4 days if pharmacologic intervention is not required. We continue to score infants who require pharmacologic

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, poor sleeping pattern, hyperphagia, diaphoresis; onset of signs at birth	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 to weeks	9 months; 11/2 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 to 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
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 to days	1–4 weeks

SSRI, selective serotonin reuptake inhibitor.
*Prescription indicates that the infant was treated with pharmacologic agents, and the natural course of the signs may have been shortened.
Source: Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129:e540–e560.

Table 12.3. Neonatal Abstinence Score Tool Score

Score	Action	
≥8 for two to three times	Determine NAS level and dose.	
<8	Continue same dose for 24–48 hours and then consider weaning.	
8 for two times	Go to next higher level and dose.	
Oral Morphine Dosing Tool		
NAS Level	**NAST Score**	**Morphine Dose (0.4 mg/mL)**
1	8–10	0.04 mg/kg/dose q3h
2	11–13	0.06 mg/kg/dose q3h
3	14–16	0.09 mg/kg/dose q3h
4	≥17	0.11 mg/kg/dose q3h

NAS, neonatal abstinence syndrome; NAST, Neonatal Abstinence Score Tool.

therapy for the duration of therapy and for 48 to 72 hours after the drug is discontinued to ensure that symptoms do not redevelop. We typically score infants who do not require pharmacologic intervention for a total of 4 days.

1. Signs of withdrawal 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), and 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 scores. Treatment begins with nonpharmacologic measures. Infants with severe withdrawal are treated with an opioid (morphine or methadone) as a first-line agent. Examples of treatment protocols using morphine (Vanderbilt University School of Medicine) and methadone (University of Michigan) are shown in the text and Figure 12.1.

1. Nonpharmacologic interventions are implemented for NAST scores <8.
   - **a.** Decrease stimulation by reducing lights, noise, and touch.
   - **b.** Promote infant self-regulation by encouraging pacifier use, non nutritive sucking, and swaddling.
   - **c.** Room in with the mother if possible.
   - **d.** Encourage holding, especially skin-to-skin.

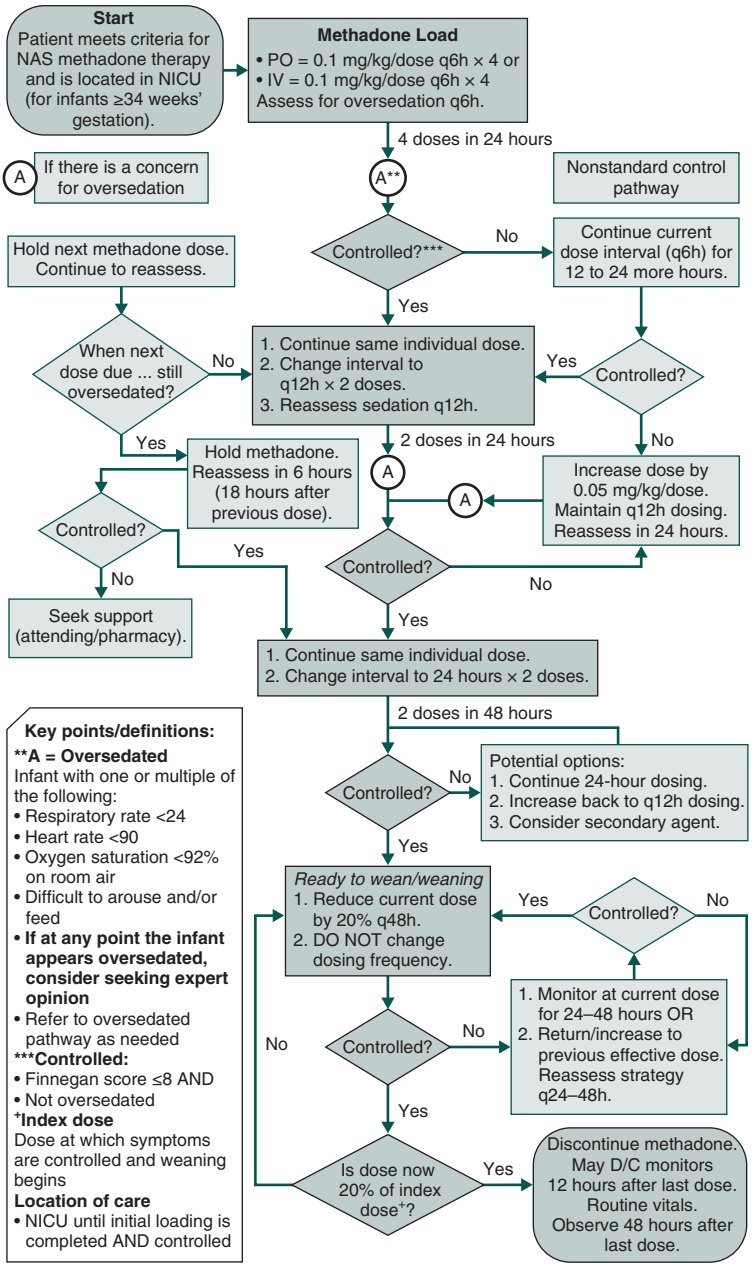

Figure 12.1. Neonatal abstinence syndrome treatment protocol used at the University of Michigan (methadone for pharmacologic treatment). D/C, discontinue; IV, intravenous; NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit; PO, orally.

e. Encourage breastfeeding.

Breastfeeding is contraindicated only with mothers actively abusing drugs such as cocaine, marijuana, and phencyclidine (PCP).

2. Pharmacologic interventions are implemented for NAST scores ≥8, and nonpharmacologic interventions are continued. Infants treated with an opioid should be on a cardiac and respiratory monitor, particularly in the initial period, to ensure that there are no clinical signs of respiratory depression.

a. We use morphine as the first-line drug, although methadone is an appropriate alternative. We use a dosing interval of 3 hours, although, depending on the feeding schedule, some infants benefit from alternative dosing intervals to provide the same 24-hour total dose (e.g., a baby feeding every 4 hours could be dosed every 4 hours).

i. Morphine dose is adjusted based on the NAST score as shown in Table 12.3.

ii. One rescue dose of oral morphine 0.05 mg/kg is available for each infant until appropriate dosing changes are made. It may be given only once and must then be reordered by the clinician after reassessment of the maintenance dose. If scores are ≥8 following weaning, one rescue dose can be considered with return to the previous dose/dosing level. One rescue dose may be considered before adding clonidine.

Sublingual buprenorphine under the tongue followed by a pacifier (starting with 4.5 μg/kg/dose q8h) has proved to shorten the opioid weaning time compared to conventional regimens.

Phenobarbital, diazepam, and diluted tincture of opium are generally not used anymore in combination with morphine.

b. Adjunct management

i. We re-evaluate infants who reach level 4 and continue to score ≥8 and consider addition of clonidine, as shown in Table 12.4.

ii. If we are unable to wean morphine after 3 weeks of treatment, we consider adjunct management with oral phenobarbital.

Table 12.4. Use of Clonidine as an Adjunct

Initial clonidine dose	1 μg/kg/dose PO every 6 hours
Dose titration	If scores continue ≥8 for two measurements and blood pressure is stable, increase dose to 2 μg/kg/dose every 6 hours.
	If scores remain elevated, consider dose increase to maximum of 3 μg/kg/dose every 6 hours.
Monitor	Monitor blood pressure every 6 hours during treatment to assess for hypotension; monitor for 48 hours after stopping to assess for rebound hypertension.

PO, orally.

c. Weaning begins when the average daily score is <8 without a single score of ≥14. Morphine is typically weaned by dose, not interval. If treatment includes clonidine, we wean the morphine first.

i. If the NAST score remains <8 for 48 hours, we wean morphine by 10% of the maximum dose every 48 hours if the average score continues to remain <8. We consider a faster wean after 24 hours if the NAST score remains <8.

ii. We discontinue morphine if the score remains <8 on 25% of the maximum morphine dose for 48 hours and continue to score for 48 to 72 hours. If the score is ≥8, we increase to the previous dose.

iii. If the morphine has been weaned off and scores are ≥8, we consider one rescue dose and return to the previous dose/dosing level.

iv. Clonidine weaning depends on the maximum dose used and the volume of measurable doses. Assistance by a pharmacist in generating a weaning plan is helpful if available. We begin to wean clonidine when morphine has been discontinued for 24 to 48 hours, continue to wean every 48 hours if the NAST score remains <8, and discontinue at the final step if the score is <8 for 24 hours.

3. Educational interventions

a. Caregivers and families should be provided verbal and written education about NAS.

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.

c. The family should be engaged in the care of the infant, including infant scoring (Tables 12.5 and 12.6; Fig. 12.1).

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 NAS.

A. We encourage breastfeeding in the following circumstances:

1. The mother is on treatment for substance abuse and allows newborn providers to discuss progress in treatment and plans for postpartum treatment with substance abuse provider.

2. Substance abuse treatment provider endorses that the mother has been able to achieve and maintain sobriety prenatally.

3. The mother plans to continue substance abuse treatment in the postpartum period.

4. The mother has abstained from illicit drug use or illicit drug abuse 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

Table 12.5. Neonatal Abstinence Scoring Tool														
Date: _____														
Signs & Symptoms	**Time:**													**Comments**
Central Nervous System Disturbances														
Excessive High-Pitched Cry	2													
Continuous High-Pitched Cry	3													
Sleeps <1 Hour After Feeding	3													
Sleeps <2 Hours After Feeding	2													
Sleeps <3 Hours After Feeding	1													
Hyperactive Moro Reflex	2													
Markedly Hyperactive Moro Reflex	3													
Mild Tremors: Disturbed	1													
Mod-Severe Tremors: Disturbed	2													
Mild Tremors: Undisturbed	3													
Mod-Severe Tremors: Undisturbed	4													
Increased Muscle Tone	2													
Excoriation (Specific Areas)	1													
Myoclonic Jerks	3													
Generalized Convulsions	5													

(*continued*)

Table 12.5. Neonatal Abstinence Scoring Tool (*continued*)

Date: _____

Signs & Symptoms	Time:													Comments
Metabolic/Vasomotor/Respiratory Disturbances														
Sweating	1													
Fever: 37.2–38.3°C	1													
Fever: 38.4°C and Higher	2													
Frequent Yawning (>3)	1													
Mottling	1													
Nasal Stuffiness	1													
Sneezing (>3)	1													
Nasal Flaring	2													
Resp. Rate >60/min	1													
Resp. Rate >60/min with Retractions	2													

(*continued*)

Table 12.5. Neonatal Abstinence Scoring Tool (*continued*)

Date: _____

Signs & Symptoms	**Time:**												**Comments**
Gastrointestinal Disturbances													
Excessive Sucking	1												
Poor Feeding	2												
Regurgitation	2												
Projectile Vomiting	3												
Loose Stools	2												
Watery Stools	3												
Total Score:													
Initials of Scorer													

Signature: _____ Initials: _____ Date: _____ Time: _____

Source: Courtesy of Vanderbilt Children's Hospital.

Table 12.6. Definitions of Scoring Items on Neonatal Abstinence Scoring Tool

Scoring Item	Definition
Excessive high-pitched cry	Unable to self-console in 15 seconds or continuous up to 5 minutes despite intervention
Continuous high-pitched cry	Unable to self-console in 15 seconds or continuous >5 minutes despite intervention
Sleep	Based on longest period of sleep (light or deep) after feeding
Hyperactive Moro reflex	Elicit from a quiet infant; jitteriness that is rhythmic, symmetric, and involuntary
Markedly hyperactive Moro reflex	Elicit from a quiet infant; jitteriness that is rhythmic, symmetric, and involuntary AND clonus of hands/arms; may test at hands or feet if unclear (more than 8–10 beats)
Mild tremors when disturbed	Involuntary, rhythmical, and equal strength in hands or feet only while being handled
Moderate to severe tremors when disturbed	Involuntary, rhythmical, and equal strength in arms or legs while being handled
Mild tremors when undisturbed	Involuntary, rhythmical, and equal strength in hands or feet only while NOT being handled; should be assessed while unwrapped 15–30 seconds after touching the infant, not while sleeping
Moderate to severe tremors when undisturbed	Involuntary, rhythmical, and equal strength in arms or legs while NOT being handled; should be assessed while unwrapped 15–30 seconds after touching the infant, not while sleeping
Increased muscle tone	Perform pull-to-sit maneuver if tolerated; no head lag with total body rigidity. Do not test while asleep or crying.
Excoriation	Reddened areas from increased movement present at nose, chin, cheeks, elbows, knees, or toes. Do not score for reddened diaper area related to loose/frequent stools.
Myoclonic jerks	Involuntary twitching of face/extremities or jerking at extremities which is more pronounced than jitteriness of tremors
Generalized convulsions	Tonic seizures with extension or flexion of limb(s); does not stop with containment; may include few clonic beats and/or apnea
Sweating	Wetness at forehead, upper lip, or back of neck; do not score if related to the environment.
Fever <101°F	37.2–38.3°C
Fever >101°F	38.4°C and higher
Frequent yawning	More than three to four times, individually or serially, over scoring interval/time period

(Continued)

Table 12.6. Definitions of Scoring Items on Neonatal Abstinence Scoring Tool (*continued*)

Scoring Item	Definition
Mottling	Pink and white marbled appearance present at chest, trunk, arms, or legs
Nasal stuffiness	With or without runny nose
Sneezing	More than three to four times, individually or serially, over scoring interval/time period
Excessive sucking	Rooting with more than three attempts noted to suck fist, hand, or pacifier before or after feeding
Poor feeding	Excessive sucking as above but infrequent or uncoordinated with feeding, or gulping with frequent rest periods to breathe
Regurgitation	Effortless, not associated with burping; more than two episodes
Loose stools	Loose, curdy, seedy, or liquid watery
Watery stools	Soft, liquid, or hard with watery

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, has engaged in treatment, and the provider team, including the infant's provider, and the mother's substance abuse treatment provider deem it appropriate.

2. Active substance use while not in substance abuse treatment or refusal to allow communication with substance abuse treatment provider

3. Positive maternal urine toxicology testing for drugs of abuse or misuse of licit drugs at delivery

4. No confirmed plans for postpartum substance abuse 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 (or in conjunction with medication-assisted treatment): 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 NAS may last for months, and infants with NAS are 2.5 times as likely as uncomplicated term infants to be readmitted to the hospital within 30 days of discharge. The following should be done to help ensure a safe discharge home:

- **A.** Pediatrician follow-up within a few days of discharge and on a long-term basis
- **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 NAS
  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 12.7.

Table 12.7. 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.
Source: Behnke M, Smith VC. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 2013;131:e1009–e1024.

Suggested Readings

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13 Care of the Extremely Low-Birth-Weight Infant

Steven A. Ringer

KEY POINTS

- Survival of extremely low-birth-weight (ELBW) babies is very high, and many have good long-term development if optimal perinatal care is offered.
- Some babies born extremely small may have innate problems—genetic/infection—and are at a high risk of death/disability.
- **Quality:** Uniformity of care processes (standard protocols) and periodic audits of patient-relevant short-term outcomes (mortality, BPD [bronchopulmonary dysplasia], NEC [necrotizing enterocolitis], ROP [reitnopathy of prematurity], sepsis rates) and long-term outcomes (child development) are the most important aspects of care of ELBW infants.
- **Place of birth:** Extremely premature infants should be delivered in a facility with a high-risk obstetric service and a level 3 neonatal intensive care unit (NICU), unless delivery is imminent and cannot be postponed.
- **Preparing the family**: The family should be provided complete information on the expected survival and morbidities; at gestations ≤24 weeks, parental decisions regarding aggressive resuscitation and intensive care must be respected; at 25 weeks and more, they must be encouraged to standard intensive care.
- **Resuscitation room care**: Resuscitation planning includes experienced personnel, room temperature 26°C, plastic wrap/bag for thermoregulation, delayed cord clamping, blended oxygen (21 to 30 FiO_2 to start), target saturations 90 to 95 only after initial 10 minutes, and early continuous positive airway pressure (CPAP).
- **In NICU**: Careful attention should be given to detail and frequent monitoring, because critical changes can occur rapidly. Fluid volume, glucose, blood gases and electrolytes should be monitored frequently. Optimal nutrition should be started at birth itself as minimal enteral nutrition and high dose parenteral nutrition.
- **Equipment:** This includes humidified incubator and volume-limit ventilation.
- **Variations in practices:** These may determine outcomes, for example, patent ductus arteriosus (PDA) closure practices are highly variable; a selective, echocardiography-guided approach with paracetamol/ibuprofen is preferred over prophylaxis by most.

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); these infants are so physiologically immature that they are extremely sensitive to small changes in respiratory management, 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.

Table 13.1. Elements of a Protocol for Standardizing Care of the Extremely Low-Birth-Weight (ELBW) Infant

Prenatal consultation
Parental education
Determining parental wishes when viability is questionable
Defining limits of parental choice; need for caregiver–parent teamwork
Delivery room care
Define limits of resuscitative efforts
Respiratory support—early CPAP in delivery room
Low tidal volume ventilation strategy
Prevention of heat and water loss
Ventilation strategy
Low tidal volume, short inspiratory time, right positive end-expiratory pressure
Avoid hyperoxia and hypocapnia—volume-targeted ventilation
Early surfactant therapy as indicated and early caffeine
Define indications for high-frequency ventilation
Fluids
Early use of humidified incubators to limit fluid and heat losses
Judicious use of fluid bolus therapy for hypotension
Careful monitoring of fluid and electrolyte status
Use of double-lumen umbilical venous catheters for fluid support
Nutrition
Initiation of parenteral nutrition shortly after birth
Early initiation of trophic feeding with maternal milk
Advancement of feeding density to provide adequate calories for healing and growth

(Continued)

Table 13.1. Elements of a Protocol for Standardizing Care of the Extremely Low-Birth-Weight (ELBW) Infant *(continued)*

Cardiovascular support
Maintenance of blood pressure within standard range
Use of dopamine for support as indicated
Corticosteroids for catecholamine-unresponsive hypotension
PDA
Avoidance of excess fluid administration
Consider medical therapy when hemodynamically significant PDA is present
Consider surgical ligation after failed medical therapy
Infection control
Scrupulous hand hygiene, use of bedside alcohol gels
Limiting blood drawing, skin punctures
Protocol for CVL insertion and care, minimize dwell time
Minimal entry into CVLs, no use of fluids prepared in NICU

CPAP, continuous positive airway pressure; CVL, central venous line; NICU, newborn intensive care unit; PDA, patent ductus arteriosus.

II. PRENATAL CONSIDERATIONS. If possible, extremely premature infants should be delivered in a facility with a high-risk obstetric 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 (*in utero*) transport must of course be weighed against the risks of transport of a sick, newly born ELBW baby (see Chapter 17). Prenatal administration of corticosteroids (betamethasone or dexamethasone) to the mother, even if there is no time for a full course, reduces the risk of respiratory distress syndrome (RDS) and other sequelae of prematurity and is strongly recommended. Antenatal magnesium sulfate is neuroprotective.

A. Neonatology consultation. If delivery of an extremely premature infant is expected, a neonatologist should consult with the parents, preferably with the obstetrician present. The parents must be guided on the expected outcomes, long hospital stay, need for intensive care unit (ICU), and risk of death/disability. There are no reliable systems or prognostic scores that allow one to make firm predictions about an individual case, because outcomes are affected by multiple factors. These include perception of health care team; this determines the first step—optimal resuscitation at birth of these infants. The most useful current data are based on a study of ELBWs born in NICUs participating in the Eunice Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Network. This study reported that 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 corticosteroids, and (iv) singleton or multiple gestation. Using these data, the NICHD developed 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 glucocorticoids, 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, tempered by 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 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. Large databases for survival data among ELBW infants are lacking in the South east Asian region but from recent studies ELBW survival in Taiwan, Singapore, Sri Lanka, and India was 80%, 80%, 77%, and 62%, respectively. Among extreme preterms (≤28 weeks), survival was 77%, 80%, 68%, and 50%, respectively. Assessments based solely on the best obstetric estimate of the gestational age do not allow for the impact of other factors, whereas those based on birth weight (a more accurately determined parameter) do not 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 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. If this information is not known, gestational age estimates for appropriate-for-gestational-age (AGA) fetuses can be roughly converted as follows: 650 g = 24 weeks; 750 g = 25 weeks; 850 g = 26 weeks; 950 g = 27 weeks; 1,100 g = 28 weeks (WHO Intergrowth 21st Growth chart). Although prevalence of term small for gestational age (SGA) is 41.5%, preterm SGA accounts for only 3.0% of live births in the South Asian region; so birth weight may be used as a surrogate for approximate gestation age assessment after birth. Second, there may be important additional information in individual cases that will significantly impact the prognosis, such as the presence of anomalies, infection, chronic growth restriction, or evidence of deteriorating status before birth. Clinical experience must be used to guide interpretation of the impact of such factors.

2. For antenatal counseling, it may also be important to interpret published data in the light of local results. The best neonatal outcomes at early gestational ages may vary between institutions, and local practices and capabilities may

significantly affect both mortality and morbidity in ELBW infants. Within individual institutions, practitioners tend to not agree on the gestational age at which an infant has any hope of survival, and this can in effect make prognostication pragmatic; the gestation at which good outcomes are expected are best described as a range, rather than a single number. In counseling, practitioners must strive to improve, but at the same time remain cognizant of the current institutional capabilities.

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. We advocate attempting resuscitation of all newborns who are potentially viable, but recognize that the personal views of parents regarding what might be an acceptable outcome for their child will vary, and thereby impact decisions about offering resuscitation. Currently, we inform them that resuscitation at birth has been technically feasible at gestational age as low as about 23 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, we stress that within these parameters, delivery room resuscitation alone has a high (but not absolute) chance of success, but that this 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. We also 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. We assure parents that initial resuscitation is always followed by frequent reassessment in the NICU and discussions with them and that intensive support may be discussed if the response to therapy appears poor or if catastrophic and irreversible complications occur. Parents are counseled that the period of highest vulnerability may last several weeks in infants at the lowest gestational ages. Once all these components are discussed, a recommendation can be made regarding an approach to initial resuscitation.

If parents disagree with this recommendation, differences may be resolved by ensuring that they understand the medical information and that their views and concerns are understood. Almost always, a consensus on a plan of care can be reached, but if an impasse continues, consultation from the institutional ethics service may be warranted (see Chapter 19). If the baby is delivered before parents and medical team reach a consensus, then standard resuscitation is carried out. At gestations <23 weeks and expected fetal weight of 400 g, resuscitation and full care may be attempted after detailed discussions, only if parents desire so.

3. **Morbidity.** 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. We explain the risk of RDS and the potential need for ventilatory support. Support may include 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.

4. **Potential morbidity.** During prenatal consultation, it is generally recommended to avoid giving parents detailed information on every potential sequela of extreme prematurity because they may be too overwhelmed to process extensive information during this time. We do specifically discuss those problems that are most likely to occur in many ELBW infants or will be screened for during hospitalization. These include apnea of prematurity, intraventricular hemorrhage (IVH), nosocomial sepsis (or evaluations for possible sepsis), and feeding difficulties as well as long-term sensory disabilities. We make a point of briefly discussing the risks of retinopathy of prematurity and subsequent visual deficits and the need for hearing screening and the potential for hearing loss. These complications are not diagnosed until late in the hospital course, but we find that giving parents some perspective on the entire hospitalization is helpful to them.

5. **Parents' desires.** In most instances, parents are the best surrogate decision makers for their child. We believe that, within each institution, there should be a uniform approach to parental demands for attempting or withholding resuscitation at very low gestational ages. 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. When counseling parents around an expected birth at <24 weeks, we specifically offer them the choice of limiting delivery room interventions to those designed to ensure comfort alone if they feel that the prognosis appears too bleak for their child. We encourage them to voice their understanding of the planned approach and their expectations for their soon-to-be born child. We reassure them that the strength of their wishes does 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 above, in the absence of other factors, we very strongly advocate for attempting resuscitation and make this clear to parents.

III. DELIVERY ROOM CARE.

The resuscitation team should include a trained (neonatal resuscitation program provider certified) and experienced pediatrician or neonatologist, particularly when the fetus is of <28 weeks, gestational age. The approach to resuscitation is like that in more mature infants (see Chapter 4). Special attention should be paid to the following:

A. Warmth and drying. The ELBW neonate is at particular risk for hypothermia. Better temperature control may be achieved with at least one of the following techniques: (i) immediately wrapping the *undried* baby's body and extremities in plastic wrap or placing them in a plastic bag (we have had most success using a

large sheet of plastic and quickly wrapping the baby in a swaddling fashion, not to forget to cover the head as it constitutes a significant body surface in the neonate, more so in a preterm), (ii) the use of an exothermic mattress, and (iii) ensuring that the delivery room temperature has been set at 26°C. Use of two modalities increases the likelihood of avoiding hypothermia. Care must be taken to avoid overheating the baby, especially when more than one of these modalities is employed.

B. Timing of umbilical cord clamping is an important first step during early stabilization in the delivery room; delaying cord clamping by at least 60 seconds or more has showed a significant reduction in mortality for preterm infants (RR, 0.68; 95% confidence interval [CI] 0.52 to 0.90).

C. Respiratory support. Most ELBW infants require some degree of ventilatory support because of pulmonary immaturity and limited respiratory muscle strength. Blended oxygen and air should be available to help avoid prolonged hyperoxia after the initial resuscitation, and it should be used in conjunction with pulse oximetry, using a probe placed on the right upper ("preductal") extremity. Studies have demonstrated that a blend of oxygen and air is preferable; it is recommended that resuscitation usually start with 21% to 30% oxygen and titrate the concentration based on measured oxygen saturation. Oxygen saturation should be targeted as identified for all babies in the first several minutes after birth (see Table 4.1), and thereafter oxygen concentration adjusted so as to keep the saturation level the same as that used during NICU care for all babies <32 weeks (suggested target of 90% to 95%). Preterm babies with RDS will usually try to breathe during transition at birth, although they may subsequently struggle to maintain adequate alveolar aeration. "Supporting transition" rather than "resuscitation" is therefore in most cases is the preferred term in RDS management. If the neonate cries vigorously at birth, the infant is observed for signs of distress. If an ELBW infant requires oxygen in the delivery room or has even minimal respiratory distress, it is preferable to consider early initiation of CPAP (very early CPAP or delivery room CPAP).

Many of these infants will require some ventilatory support because of apnea or ineffective respiratory drive. If the infant is breathing spontaneously, albeit with distress, initial respiratory support can be provided by either positive-pressure ventilation (PPV) or CPAP. In trials comparing CPAP with intubation and ventilation with or without surfactant (n = 2,364 neonates), CPAP resulted in a small but clinically significant reduction in the incidence of BPD and death (Number Needed to Treat [NNT] = 20). There was also a clinically important reduction in the need for mechanical ventilation and the use of surfactant in the CPAP group by half. We therefore favor using CPAP (with T-piece resuscitator) at 6 to 8 cm H_2O as initial support, although infants may require a breath or two with bag and mask before they breathe spontaneously. If the infant is not breathing spontaneously, PPV must be started using preset pressures, quickly titrated to provide a just visible chest rise (adequacy of PPV is assessed by a normal heart rate). Judgment is required regarding ongoing support, depending on the baby's status; if PPV is required, care should be taken to use the smallest tidal volumes and peak pressure possible while still adequately ventilating the infant. Most centers employ a T-piece device for providing PPV or CPAP instead of hand-bagging via bag and mask because it ensures adequate and regulated

positive end-expiratory pressure and regulated inflation pressures. Administration of exogenous surfactant therapy is not an emergency and is often not necessary in the delivery room. Based on recent evidences, the American Academy of Pediatrics Committee on Fetus and Newborn recommends that, "the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy." Exogenous surfactant, if required, may be safely administered once correct endotracheal tube position has been confirmed clinically. The pediatrician should reassess the response to respiratory support at short intervals of 15 to 30 minutes and adjust (decrease) the supports; the response to surfactant therapy is dramatic and most babies need very low pressures and oxygen (FiO_2 0.21) within minutes of surfactant therapy.

If the infant fails to respond, the team should recheck that all support measures are being effectively administered. If there is no positive response to resuscitation after a reasonable length of time, we consider limiting support to comfort measures alone. In all cases, communication with the parents should be maintained through a designated member of the care team.

D. Care after resuscitation. Immediately after resuscitation, the plastic-wrapped infant should be placed in a prewarmed transport incubator for transfer to the NICU. Within practical limits, we encourage as much interaction of parents with the baby, starting from the delivery room itself. In the NICU, the infant is moved to an incubator/radiant warmer combination unit when available (the unit is very expensive and not available even in tertiary care centers in most units in South east Asia) where a complete assessment is done and treatment initiated. The infant's temperature should be rechecked at this time and closely monitored. As soon as possible, the unit is closed to function as an incubator for continued care. Humidity is maintained at 70% for the first week of life and 50% to 60% thereafter up to 32 weeks, corrected gestation. In addition to reducing insensible fluid losses and thereby simplifying the fluid therapy, the use of incubators aids in reducing unnecessary stimulation and noise experienced by the baby.

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 can occur rapidly. Balance has to be achieved between large fluid losses and fluid intake, high and low blood glucose levels, high and low saturation and carbon dioxide levels, early treatment of shock and risk of overtreatment, etc. 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 in ELBW infants 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 or cardiovascular support or who have encephalopathy (poor tone, spontaneous movement, alertness and response to external stimuli) are assessed continuously, and their chances for ongoing survival are evaluated as part of this process. If caregivers and the 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 consider comfort care alone and refrain from futile escalation of intensive care.

B. Respiratory support. Most ELBW infants require initial respiratory support.

1. **CPAP.** In our population, a very large majority of ELBW infants have been exposed to antenatal corticosteroids, and respiratory support may be accomplished with CPAP alone. It is generally initiated at 6 cm H_2O pressure, and the pressure increased in 1-cm increments to a maximum of 8 cm if the oxygen requirement exceeds 30% to 40%. 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, mechanical ventilation and surfactant therapy are indicated.

2. **Conventional ventilation.** We generally use conventional pressure-limited synchronized intermittent mandatory ventilation (SIMV), usually in a volume guarantee mode, as our primary mode of mechanical ventilation (see Chapter 29). The lowest possible tidal volume (4 to 5 mL/kg body weight) to provide adequate ventilation and oxygenation and a short inspiratory time (0.3 to 0.35 seconds) should be used. One very important part of ELBW infant mechanical ventilation is choosing the right positive end expiratory pressure (PEEP) to recruit lungs adequately to achieve the optimum functional residual capacity (FRC). Special effort should be made to avoid hyperoxia (>95% saturation). 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. 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%. We aim for a target range of 90% to 95%. We encourage close monitoring including observation to determine whether oxygen saturation outside the range will correct without intervention, thereby decreasing the tendency for too frequent manipulation of ventilator settings. It is hypothesized that limiting hyperoxia may also reduce the incidence or severity of chronic lung disease. Recent evidence showed that neonates who received volume-targeted ventilation had a lower incidence of BPD (NNT = 8), pneumothorax (risk is half), hypocarbia, and abnormal neurosonogram compared with neonates treated with pressure-limited ventilation. It is important as well to avoid hypocapnia, although the potential benefit of permissive hypercapnia as a ventilatory strategy remains unproven.

3. **Surfactant therapy** (see Chapter 33). We administer surfactant to infants with RDS who are ventilated with a mean airway pressure of at least 7 cm H_2O and have an inspired oxygen concentration (FiO_2) of 0.3 or higher in the first 2 hours after birth. The first dose should be given as soon as possible after birth after intubation, preferably within the first hour, although with an increased use of CPAP as the initial therapy, the timing of surfactant therapy

may be delayed. We have found that many treated infants can be rapidly transitioned to support with CPAP shortly after surfactant administration.

4. **High-frequency oscillatory ventilation (HFOV)** is used in infants who fail to improve after surfactant administration and require conventional ventilation at high mean airway pressures. For infants with an air leak syndrome, especially pulmonary interstitial emphysema (see Chapter 38), high frequency may be the preferred mode of ventilation. Some units use HFOV as a primary mode of ventilation in extremely preterm babies; they have reported lower BPD rates.

5. **Caffeine citrate**. Prophylaxis, soon after admission, has become standard based on cohort studies showing that earlier initiation of caffeine (2 hours to 3 days) at standard doses (see Appendix A) is associated with a lower incidence of BPD and lesser duration of mechanical ventilation among less than 28 weeks preterm infants. In view of more CPAP use, early administration of caffeine will help in reducing CPAP failure. Recent studies showed that early (<2 days age) caffeine therapy is associated with better neurodevelopmental outcomes at 18 to 24 months when compared with late caffeine therapy in preterm infants born at <29 weeks' gestation.

C. Fluids and electrolytes (see Chapters 23 and 28). Fluid requirements increase as the gestational age decreases <28 weeks, owing to both an increased surface area–body weight ratio and immaturity of the skin. Renal immaturity may result in large losses of fluid and electrolytes that must be replaced. Early use of humidified incubators 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 incubator top is only rarely opened.

1. **Route of administration.** Whenever possible, a double-lumen 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 to 10 days and then replaced by peripheral arterial lines if needed. Because of an increased risk of infection, the dwell time for umbilical venous catheters (UVC) in most cases is limited to 10 days. Catheter related blood stream infections (CLABSI) are higher with increasing dwell time; a reasonable approach is to remove UVC early (by day 4) to decrease infection rate among extreme preterm infants. These are often replaced by percutaneously inserted central venous catheters (PICC) if continued long-term intravenous (IV) access is required.

2. **Rate of administration.** Table 13.2 presents initial rates of fluid administration for different gestational ages and birth weights when humidified incubators 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 at the age of 12 to 18 hours and often at every 12 hours on the first 2 to 3 days, until the levels are stable, and then daily for few days. 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 thickens and dries over the first few days of life.

Table 13.2. Fluid Administration Rates for the First 2 Days of Life for Infants on Radiant Warmers*

Birth Weight (g)	Gestational Age (weeks)	Fluid Rate (mL/kg/day)	Frequency of Electrolyte Testing
500–600	23	110–120	8 hourly
601–800	24	100–110	q8h 8–12 hourly
801–1,000	25–26	80–100	q12h

*Rates should be 20% to 30% lower when a humidified incubator is used. Urine output and serum electrolytes should be closely monitored to determine the best rates.

3. **Fluid composition.** Initial IV fluids should consist of dextrose solution in a concentration sufficient to maintain serum glucose levels >45 to 50 mg/dL. Often, immature infants do not tolerate dextrose concentrations >10% at high fluid rates, so use of dextrose 7.5% or 5% solutions is frequently needed. Usually, a glucose administration rate of 4 to 10 mg/kg/minute is sufficient. If hyperglycemia results, lower dextrose concentrations should be administered; hypo-osmolar solutions (dextrose <5%) should be avoided. If hyperglycemia persists at levels above 180 to 220 mg/dL with glycosuria, an insulin infusion at a dose of 0.05 to 0.1 unit/kg/hour may be required and adjusted as needed to maintain serum glucose levels at acceptable levels (see Chapter 24). Extreme caution must be exercised with the use of insulin; there is high risk of severe, damaging hypoglycemia even with the lowest doses.

   ELBW infants are more prone to postnatal growth restriction, in view of their increased energy demands because of immaturity, growth needs, high risk of hypothermia, anemia, and infection. Healthy preterm neonates require 110 to 120 kcal/kg/day for their adequate growth. If sufficient amount of nonprotein energy is not provided, amino acids are catabolized for energy production. Adequate balance between nitrogen and nonprotein energy sources (protein/energy ratio: 3 to 4 g/100 kcal) is needed to promote protein accretion. To achieve this, we start parenteral nutrition (PN) immediately on admission to the NICU for all infants with a birth weight <1,250 g (30 weeks). (Threshold and methods of delivering PN may be customized to unit resources and practices, with an aim to achieve target protein and calorie needs as a bare minimum. Some units mix the amino acid, dextrose and electrolytes into a single bag. We use each of these without tampering with the factory pack; we run them into separated iv lines. Thus decreasing mixing and wastage. Most units in Asia have no access to a pharmacy to prepare PN. Some neonatal units prepare PN in the NICU itself, a few of these units have a laminar flow hood, most have no facility for sterile mixing of PN components,most do not have either. Components such as trace elements and buffering agents are also not available. Skills to insert central lines and maintain them may be suboptimal.) Multivitamin solutions are not included in this initial PN because of shelf-life issues but are added within 24 hours after delivery. No electrolytes are added

to the initial solution other than the small amount of sodium phosphate needed to buffer the amino acids. The solution is designed so that the administration of 60 mL/kg/day (the maximum infusion rate used) provides 2 to 3 g of protein/kg/day. Additional fluid needs are met by the solutions described earlier. Customized PN, including lipid infusion (1 to 3 g/kg/day), is begun as soon as it is available, generally within the first day.

4. **Skin care.** Immaturity of the skin and susceptibility to damage requires close attention to the 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 disagreement 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, we accept mean blood pressures of 26 to 28 mm Hg for infants of 24 to 26 weeks' gestational age in the transitional period after birth if the infant appears well perfused and has a normal heart rate. Early hypotension is more commonly due to altered vasoreactivity than hypovolemia, so therapy with fluid boluses is generally limited to 10 to 20 mL/kg, after which pressor support, initially with dopamine, is begun. Stress-dose hydrocortisone (1 mg/kg every 12 hours for two doses) may be useful in infants with hypotension refractory to this strategy (see Chapter 40). Delayed cord clamping has been shown to decrease the incidence of early hypotension in premature infants.

2. **Patent ductus arteriosus (PDA).** The incidence of PDA is as high as 70% in infants with a birth weight <1,000 g. The natural timing of presentation has been accelerated by exogenous surfactant therapy so that a symptomatic PDA now commonly occurs between 24 and 48 hours after birth, manifested by an increasing need for ventilatory support or an increase in oxygen requirement. 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. All three medical management strategies in preterm neonates have their own disadvantages.

   - In the prophylactic group, we end up treating 50% infants who are not destined to develop hemodynamically significant PDA (hSPDA).
   - Closing an echocardiography-proven PDA when symptoms and complications develop is too late as it also results in less closure rate (50% to 80% and sometimes reopens).

- Adopting an "early targeted treatment" is possibly the best approach which balances between prophylactic and late symptomatic treatment; however, the chance of overtreating (20 % increase in treated infants) who are not destined to develop hSPDA is still there.

We thus remain vigilant for the presence of a PDA but delay pharmacologic therapy until an echocardiogram has been performed and the PDA is noted to have left to right shunt, ductal diameter 1.4 mm/kg body weight, and left atrium to aorta (LA/Ao) ratio >1.4 to 1.6 which suggest that the duct is widely patent or shown to be causing a diminution in the left ventricular function (left ventricle output to superior vena caval [LVO/SVC] flow >4) and retrograde diastolic flow in the descending aorta. If the initial medical therapy fails to eliminate the hemodynamic impact of the PDA, we administer a second course of pharmacologic therapy (ibuprofen or IV paracetamol). 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. In a recent meta-analysis, it was noticed that paracetamol was as efficacious as ibuprofen and indomethacin in accelerating PDA closure in premature infants. In comparison to ibuprofen, it showed shorter mean days needed for closure, a lower percentage of gastrointestinal (GI) bleeding, and a lower risk of hyperbilirubinemia. Surgical ligation is infrequently necessary and should be considered only if there is clear evidence of a significant left to right shunt after medical management.

E. Blood transfusions. These 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 a few transfusions in the first few weeks of life. Donor exposure can be successfully limited by delayed cord clamping (DCC), microsampling techniques, reducing laboratory testing to the minimum necessary level, employing strict uniform criteria for transfusion, and 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. Delayed cord clamping may help in reducing early need of packed RBC transfusion. Unnecessary fresh frozen plasma and platelet transfusion can also be reduced with following a strict protocol; these blood products can act like a Trojan horse and carry infection.

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. We almost always screen for infection immediately after birth in cases in which there are perinatal risk factors for infection and treat with prophylactic antibiotics (ampicillin and gentamicin) pending culture results. In India, many of the microbes associated with early-onset infections are resistant to ampicillin and gentamicin, and neonatologists often use amikacin or other combinations (see Chapter 53). ELBW

infants are particularly susceptible to hospital-acquired infections (occurring at >72 hours after birth), with about half due to coagulase-negative *Staphylococcus* (Gram-negative bacteria, *Staphylococcus aureus* in India). In a large study from India, commonest agents of neonatal sepsis were multidrug-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* with fatality rate of 59% in culture-positive sepsis newborn. Risk factors for late-onset infection include longer duration of mechanical ventilation, presence of central catheters, and PN 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 spots 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. We use only PN solutions that have been prepared under laminar flow and never alter them after preparation. 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, we have an observer monitor the PICC insertion technique and immediately identify deviation or omission from a standard checklist. 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 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. Fluconazole prophylaxis is recommended in units where baseline incidence of fungal infections is high. Probiotics have been shown to decrease late onset neonatal sepsis (LONS) consistently across studies, but controversies on best dose schedule and best patient selection are some of the reasons that many units still do not use them as a routine.

G. Nutritional support (see Chapter 21)

1. **Initial management.** In all infants who weigh <1,000 to 1,200 g at birth, PN is begun shortly after birth using a standard solution administered at a rate of 60 mL/kg/day (see section IV.C), resulting in protein administration of 2 to 3 g/kg/day. On subsequent days, customized parenteral solutions are formulated to increase the protein administration rate to a maximum of 3 to 4 g/kg/day. Parenteral lipids are begun on day 1 at 1 g/kg/day and advanced each day to a maximum of 3 g/kg/day as allowed by triglyceride levels (there is no evidence for the stepwise escalation, some practice 3 g/kg lipid on day 1). Enteral feeding is begun as soon as the patient is clinically stable. Nonprotein

calorie should be provided at 20 to 30 kcal for each gram of protein with carbohydrate to fat source ratio of 60:40.

2. The safe initiation of enteral feeds begins with the introduction of small amounts of expressed breast milk (10 to 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 the 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 advanced as per protocol. A standardized approach to feeding advancement may reduce the risk of feeding intolerance or necrotizing enterocolitis (NEC) (see Chapters 21 and 27). As feedings are advanced, signs of feeding intolerance such as abdominal distention, vomiting (which is rare), and increased gastric residuals should be monitored. It is important but often difficult to differentiate the characteristically poor GI motility of ELBW infants from signs of a more serious GI disorder such as NEC (see Chapter 27). At least two-thirds of ELBW infants have episodes of feeding intolerance that result in interruption of feeds, including small bilious gastric residuals as feeds are begun. Once successful tolerance of feedings is established at 90 to 100 mL/kg/day, caloric density is advanced to 24 cal/30 mL, and then the volume advanced to 150 to 160 mL/kg/day (see Chapter 21). This eliminates a drop in caloric intake as PN is weaned while feedings advance. Once tolerance of full feedings of 24 cal/30 mL is established, the density of feedings may be advanced if needed for adequate growth by 2 cal/30 mL/day up to a maximum of 30 cal/30 mL, although this higher caloric density is rarely required. Protein powder may be added to a total protein content of 4 g/kg/day because this promotes improved somatic and head growth over the first several weeks of life. Adequate protein and calorie intake can be achieved by fortification of human milk–derived or bovine milk–derived fortifiers. Once neonate reaches 60 to 100 cm^3 mL/kg feed, one sachet of milk fortifiers can be added to 25 mL of expressed breast milk or pasteurized donor milk. Many extremely small infants may benefit from restriction of total fluids to 130 to 140 mL/kg/day. This minimizes problems with fluid excess while still providing adequate caloric intake.

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14 Developmentally Supportive Care

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KEY POINTS

- The sensory experiences of a preterm baby should be appropriate to the development stage, similar to what the fetus would have experienced in utero.
- Developmentally supportive care aims at adapting the NICU environment and care processes to improve physiologic stability, decrease stress, protect sleep, and promote behavior organization.
- Intense stimuli like severe/frequent pain, intense light, loud sound, strong smell, and frequent sleep interventions may have devastating influence on developing brain.
- Evidence supports improvement in short-term development outcomes in preterm babies who receive development care.
- Individualized care: timing of examination, feeding, care like diaper change, sampling should be based on infant cues (behavior state), rather than by schedule.
- Family-centered care: involve parents very early (from day1) in care of the baby, it is beneficial to both the baby and the parents. The family experiences are better and transition to home is smoother.
- NICU design must aim to minimize noise and optimize light to minimum, when not needed.
- Kangaroo care (KC) has multiple benefits and all NICUs must have policy to support and promote KC.
- Nonnutritive sucking, massage, swaddling, facilitated tuck, positioning to promote flexion, midline posture, and parents speaking to their baby are all supportive development.

I. INTRODUCTION. The key principles of developmentally supportive care (DSC) are a development-supportive environment, family-centered care, and individualized care. It provides a gentler care environment which simulates *in utero* experiences of the fetus, and encourages and guides the developmental organization of the premature or critically ill infant. Family participation starts with the birth of the baby. Implementing the principles of family-focused DSC in a neonatal intensive care unit (NICU) environment facilitates family adaptation and aims to improve neurodevelopmental outcomes. DSC promotes a culture that respects the personhood of preterm and medically fragile term infants.

A. 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 (position, diaper change, orogastric feeding) may contribute to this increased morbidity; noxious stimuli such as pain, bright light, and loud sounds may alter the neurotransmitters and bioactive factors resulting in developmental aberrations. Changes in cerebral oxygenation and blood volume measured with near-infrared spectroscopy (NIRS) that occur during diaper changes with elevation of the legs and buttocks, endotracheal tube (ET) suctioning, repositioning, routine physical assessment, and gavage feedings have been associated with early parenchymal brain abnormalities. DSC helps to minimize these disturbances. For implementing DSC, the following aspects need to be understood:

1. Assessment of the baby's behavioral state—stress and self-regulatory responses
2. The goals and principles of DSC
3. The components and methods of DSC

II. ASSESSMENT OF STRESS AND SELF-REGULATORY BEHAVIORS. Identification of an infant's stress responses and self-regulating behavior 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 the care plan is modified as needed to lower stress and promote stability. Acutely ill term infants have responses to stress and pain similar to 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 stress responses to various stimuli are assessed in the domains of autonomic, motor, state organization, and attention/interaction signs.

1. Autonomic signs of stress include changes in color, heart rate, and respiratory patterns, as well as visceral changes such as gagging, hiccups, vomiting, and stooling.
2. Motor signs of stress include facial grimacing, gaping mouth, twitching, hyperextension of limbs, finger splaying, back arching, flailing, and generalized hypertonia or hypotonia.
3. State alterations suggesting stress include rapid state transitions, diffuse sleep states, irritability, and lethargy.
4. Changes in attention or interaction, exhibited by closing or blinking eyes, 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 or foot bracing; sucking; bringing the hands to the face; flexed positioning; cooing; and grasping of linens, tubing, or own body parts. Because painful procedures may overwhelm an infant's ability to self-console, support of the infant by parents or staff during these activities is needed.

III. GOALS AND PRINCIPALS 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 physiologic disturbances. The individual

Table 14.1. Neurobehavioral Organization and Facilitation

System	Signs of Stress	Signs of Stability	Interventions
Autonomic			
Respiratory	Tachypnea, apnea, 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, changing colors	Stable, overall pink color	Use hand containment and pacify 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.
			Position appropriately for neuromotor development and comfort; use nesting/boundaries or swaddling as needed to reduce tremors, startles.
			Manage pain appropriately.

(continued)

Table 14.1. Neurobehavioral Organization and Facilitation *(Continued)*

System	Signs of Stress	Signs of Stability	Interventions
Motor			
Tone	Either hypertonia or hypotonia; limp/flaccid body, extremities, and/or face; hyperflexion	Tone consistently appropriate for 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; crying facial expression; 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.
			Encourage sucking or 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.

(continued)

Table 14.1. Neurobehavioral Organization and Facilitation *(Continued)*

System	Signs of Stress	Signs of Stability	Interventions
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;3:229–243; 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;6:3–55; 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.

caregiver must learn to recognize and appropriately respond when an infant communicates stress, pain, or the need for attention. The core principles of DSC are stimulation of early developing senses such as tactile and olfactory–gustatory and protecting the later developing senses such as auditory and visual by appropriate protective measures for optimal growth of the brain and musculoskeletal system. The goal is to maximize rest, minimize stress, and optimize healing and growth in a framework that supports family participation as described in the subsequent text.

A. Supporting autonomic system stability. Because the autonomic and visceral systems cannot be accessed directly, interventions are used to 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 guide the pace of a feeding are strategies that will elicit less stress behaviors during feeding and may result in better feeding 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.

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. Positioning during care requires close attention, as a preterm infant cannot sustain a flexed, aligned posture with midline orientation that is ideal and comforting. 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 and also need positioning support. Movement is necessary for musculoskeletal growth and development. Thus, it is imperative that boundaries or swaddling provide containment without being restrictive.

C. Creating environments that cultivate state organization. Preterm infants have a reduced ability to maintain a stable behavior state and have frequent transitions between states compared to term infants. Environmental modifications are made to promote quiet periods and restful sleep. 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.

IV. THE COMPONENTS AND METHODS OF DSC

A. Team collaboration and consistent care plan. Developmental care should be considered as a part of routine care. The unpredictable nature of care in the NICU can be diminished by consistent caregivers who are familiar with an infant's clinical condition and behavior, 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. 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.

By providing a developmentally supportive NICU environment, neonatal caregivers can support neurologic and sensory development and potentially minimize later developmental issues in preterm and medically fragile 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 respond appropriately to an infant's ongoing requirements. Environments on a larger, more complex scale are planned 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. When possible, anticipation of an infant's environmental needs prior to admission is ideal. The influence of the environment is of practical concern for short- and long-term development (e.g., both light and sound impact sleep). The main components of DSC are the following:

1. Developmentally supportive activities of daily living (ADL)
2. Healing environment
3. Protected sleep
4. Pain protection
5. Family-centered care
6. Infant follow up and early Intervention programs

1. **Developmentally supportive ADL.** These are caregiving activities that are important for the infant's growth, development, hygiene, and general well-being. The activities include dressing and undressing, diaper change, sponging, massage, skin care, non-nutritive sucking (NNS), and feeding. Involving and encouraging parents and extended family members to actively participate during caregiving activities fosters bonding between them and their infant. ADL should be carried out according to the readiness of the baby by looking at the infant's state of alertness, sleep cycles, communication cues, medical condition, and family presence and not be protocol driven. During these activities, care should be taken to position the preterm infant to ensure that it supports symmetric development by following the below-mentioned steps:

   a. **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 skill 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 are able to feed their infant. Progression to oral feeds is highly contingent on elements of DSC and occurs predictably in several phases. 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' postmenstrual age (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 and gain the same amount of weight as controls. 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.

   i. Dim the light, and reduce noise and other distractions.

   ii. Caregivers should not be distracted and talk to others while feeding their infant.

   iii. While feeding with paladai or spoon, the infant must be awake and not asleep.

   iv. Do not wake infants by pinching, tickling, pulling, or flicking their ears or soles.

   v. The infant's head, neck, and trunk should be well supported by the caregiver's arm or body.

   vi. Swaddling the infant during feeding reduces startles and unnecessary arm and leg movements and associated stress.

b. Skin care

   i. Avoid using lotions and soap.

   ii. Care should be taken to avoid pressure and device-related sores and during removal of adhesive tapes.

c. Massage. Gently apply oil for very preterm and ELBW infants instead of massaging. In supine, prone and side-lying positions, start massaging from the head, move to the face, then the chest, the abdomen, and finally the limbs. Fingers should be placed flat on the infant's body and the massage should be done with moderate pressure using long, firm yet gentle strokes. Gentle extending and flexing of limbs can be done during the massage. Light feathery touch should be avoided.

d. Diaper change. Make sure that clean diapers and wet cotton swabs are ready and near the infant. Open the dirty nappy and pick up both the legs

of the infant, flexing them toward the abdomen; clean from the front to the back in gentle strokes.

2. **Healing and stimulating environment**. It is important for stress reduction and early stimulation of olfactory, vestibular, vision, and auditory 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 above disrupt sleep and may impact brain development occurring during both active/light sleep and quiet sleep. The development of sleep state organization may also be altered. The American Academy of Pediatrics (AAP) recommends that NICU sound levels should not exceed an hourly equivalent sound level of 45 dB and hourly L_{10} (noise level exceeded for 10% of 1 hour) of 50 dB. Transient sounds should not exceed 65 dB. 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.

   A DSC program includes systematic efforts to manage environmental sound (e.g., low conversational tones, discussions away from the bedside, placing pagers on vibrate mode, care in opening and closing portholes). Baseline sound levels need to be measured occasionally during the year along with an evaluation of sources contributing to noise intensity or sudden loud sounds. Random monitoring of sound levels is helpful in sustaining noise abatement.

   Limited information is available on the impact of sound frequencies on infants in the NICU. Early investigations have reported frequencies ranging from <500 to 16,000 Hz or more over 50% of the time in the NICU. Inside the womb, the fetus is exposed to frequencies of <500 Hz until later in gestation when the womb thins closer to delivery. Around 33 weeks, fetuses can respond to high-frequency sounds; however, the effects of repeated exposure over time are unknown. The preterm infant may experience high-frequency, high-intensity sounds repeatedly throughout his or her hospital stay without the natural protection of the mother's womb; this may influence the developing architecture and functional organization of cortical auditory connections. Because the effects of such exposure are unknown at this time, spectral analysis along with sound intensity requires further study. As a precaution, both sound intensity and frequency should be monitored in the NICU and a plan developed to minimize the infant's exposure to potentially deleterious levels of sound. The most natural source of sound for the infant is the mother's voice. If a baby cannot distinguish the maternal voice from ambient noise, auditory development may be altered from the natural evolution that occurs in the womb.

   Doctors, nurses, and family should talk softly near the infant's bassinet or move slightly away while medical intervention is being discussed. Shouting instructions across the room and chairs being dragged rather than lifted are a constant source of stress for the infant. Other simple measures taken for reducing auditory overload are lifting the chairs without dragging, handling steel vessels carefully without falling (trays, paladai, etc.), reducing

the volume of telephone ring, attending monitor alarms promptly, setting the volume of the alarm at a lower level, and closing the incubator doors quietly. Tapping or writing on incubator should not be allowed. Mother's speaking or singing softly is the best auditory stimulation. It comforts the infant and blocks out some of the stress sounds present in the environment. Do not hang baby chimes or put toys with loud nursery rhymes near the infant.

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 a concurrent reduction in environmental noise and less 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. Protection from light for the early preterm infant can be accomplished with thick, quilted covers that have a dark material on the side facing the incubator. Lighting for staff needs to be at a level that allows safe and efficient functioning. Lights should be dimmed during the day if there are no procedures. Preterm infants should not be placed under direct bright light. Encourage a day–night light rhythm in the NICU to develop circadian rhythm. The mother's face is the best visual stimulus for the preterm infants. During procedures, the infant's eyes should be protected from direct light using blanket tents or other methods that do not require tactile input. Eye covers should be used only when phototherapy is indicated. 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. These are relatively short-term outcomes; long-term effects of early, atypical lighting and visual stimulation are unknown.

The AAP guidelines for perinatal care recommend 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. Procedure lights need to be focused so they do not alter the illumination of other infants.

The AAP also supports the recommendations of both the Illuminating Engineering Society and the 2012 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 night-time 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 are 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. **Gustatory sensation.** Preterm infants are very sensitive to noxious smell (hand rubs) which causes stress. The mother's smell and the smell of her breast milk are the best olfactory stimulants. These also help in reducing infant stress.

d. **Vestibular sensation.** Abrupt position change will negatively affect the infant's physiological parameters and optimal development. Stress can be reduced if the caregiver gently moves his/her body instead of rocking or swinging the infant. Gently move the body toward you when lifting up. The mother's rhythmic breathing and chest movement is one of the most soothing experiences for the preterm neonate while in kangaroo care. The caregiver should bend his/her body forward, holding the baby close to his/her body.

e. **Kangaroo care (KC).** Sometimes referred to as skin-to-skin holding, KC 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. KC 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 cap. 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. Kangaroo care impacts several developing sensory systems including tactile (skin), olfactory, and vestibular (rise/fall of chest). Soft speech by the parent a 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 KC. Parents can be with their infant earlier in a way that is satisfying for them and supportive for their baby.

f. **Tactile stimulation/touch.** This includes positioning, nesting, swaddling, facilitated tuck, and massage. 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, swaddling, and nesting. **Swaddling** is a technique of wrapping the baby in a sheet in such a way that the infant feels safe, secure, and contained. It facilitates sleep and promotes growth and development. **Nesting/creating boundary** is preparing a nest like an oval boundary around the infant using sterilized sheets. Nesting holds and contains the infant, simulating *in utero* environment. This technique stabilizes the infants and promotes protected sleep. Nesting needs to allow sufficient room for the infant to push against boundaries, to facilitate continuing development of the neuromotor and skeletal systems. Nesting and swaddling are also 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.

g. **NICU design.** Single family rooms support the infant and family bond and create an environment that is readily adapted to meet an individual infant's requirements. Whether single family rooms are more beneficial than the traditional open-bay design is not certain. In one study, preterm infants cared for in single family rooms were found to have delayed cerebral maturation on magnetic resonance imaging (MRI) at term and significantly inferior language scores at 2 years of age compared to a peer cohort cared for in open bays. These results are thought to be related to sensory and social deprivation. On the other hand, another study noted that infants cared for in single family rooms experienced a lower infection rate, decreased stress, better weight gain, improved feeding tolerance, and better attention and tone. Regardless of design, thoughtful consideration of the needs of an individual infant must be considered to provide an environment that supports optimal outcomes.

3. **Protected sleep.** An infant's undisturbed sleep is very important for his/her brain growth. Apart from KC, the other measures such as providing nesting, clustering of ADL, massage, and having a healing environment help to promote sleep of infants. The containment that the uterus provides to the fetus instills a sense of safe and secure environment. The fetal position enables the fetus to develop appropriate muscle tone and patterns of movement. Unfortunately premature infants are unable to maintain this position themselves due to their low tone and the gravitational pull. External help is needed to simulate the *in utero* environment to enable the newborn to develop and grow appropriately. Leaving an infant without boundary or nesting disturbs the infant's sleep and aggravates pain and stress.

   Newborn babies admitted in the NICU are constantly handled which disturbs their sleep pattern. So, to ensure that the infants get enough undisturbed sleep, the daily routines such as cleaning the baby gently, changing of diapers, oil massage, weighing of the baby, putting cap, gloves, and socks, giving antibiotic, and feeding can easily be done together in a cluster when the infant is awake instead of disturbing the sleep by doing these activities individually at different times.

   It is important to remember that all caregiving activities are modified according to the infant's cues rather than protocol driven. While changing clothes or nappy, do not make sudden changes in the position; stop and calm the newborn if stress signs are seen.

4. **Pain protection and stress management.** Pain assessment and management is a basic right of all patients. Evidence-based assessment and practice guidelines facilitate the use of pain management by physicians, nurses, and other practitioners. A streamlined approach using algorithms may enhance utilization at the bedside.

   Pain. Effective nonpharmacologic interventions incorporate developmental principles such as swaddling, NNS, kangaroo holding, hand containment/facilitated tuck, breastfeeding, and administration of an oral sucrose solution (see Chapter 70). Nonpharmacologic measures are used as an adjunct to

pharmacologic treatment of moderate-to-severe pain. **Containment** is holding and calming a baby placed in a bassinet/incubator during a painful procedure. One hand of the caregiver is placed firmly yet gently on the head of the baby while the other hand can be placed on the lower back, buttocks, or soles of his/her feet.

The AAP and the Canadian Pediatric Society advocate management of both pain and stress. High-stress situations need to be identified and modified to minimize the impact on the ill or preterm infant. Examples of potential high-stress conditions include delivery room care, transport to NICU, admission process, and diagnostic procedures that often produce pain or discomfort along with stress. During stressful events, developmental support based on infant cues guides the NICU team's care and needs to be ongoing with every episode of care.

5. **Family-centered care with parent support/education.** Effective DSC is dependent on implementation of the principles of family-centered care during NICU stay as well as on transition to home.
   a. **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, promotion of family participation in infant care, creation of parent advisory boards, implementation of parent support groups, and comfortable rooming-in areas for parents.
   b. **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.
   c. **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 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 Early Intervention (EI) program before the infant's discharge and collaboration between NICU and EI professionals to create a developmentally supportive transition plan.
6. **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.

District early intervention centers. As a part of the infant follow-up and disability reduction, the Government of India has introduced district-level early intervention centers (DEIC) under the Rashtriya Bal Swasthya Karyakram (RBSK) scheme. It provides holistic care with the help of multidisciplinary team under one roof and is primarily aimed at children younger than 6 years.

The major interventions include the following:

- Screening and assessment for the 4 D's—defects at birth, diseases, deficiencies, and developmental delays and disability
- Domain-specific intervention
- Review and follow-up
- Referral to tertiary centers if needed

The multidisciplinary team includes the following:

- Medical and dental services
- Audiology and speech therapy
- Occupational therapy and physical therapy
- Cognition and psychological services
- Vision services
- Sensory services and special education

Babies admitted to the newborn care units, who are at a high risk for developmental delays and neuromotor disability, will be followed up in the DEICs and early intervention will be initiated. All the services are coordinated by the DEIC manager and children older than 6 years will be referred to specific rehabilitation centers.

7. **Developmental care-evidence.** Recent systematic review (GRADE process) included 13 studies that reported interventions in NICU intended to support development (RCT reporting Bayley Scale of infant development at 12 or 24 months were included). Both psychomotor developmental index and mental developmental index were better in the intervention group, although quality of evidence was limited.

   Single family room (SFR). Nursing preterm babies in single rooms with all family members, rather than in large NICU bays was associated with better parent presence, participation, skin-to-skin care, and lower NICU-related stress.

Suggested Readings

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15 Temperature Control

Kimberlee E. Chatson

KEY POINTS

- Immediate postnatal hypothermia is a worldwide issue with implications of significant morbidity and mortality.
- The preterm infant is especially vulnerable, and extra measures need to be taken to provide a neutral thermal environment.
- Practice kangaroo care to prevent hypothermia; it has benefits in improving breastmilk feeding, better weight gain, less infections, and early discharge from hospital.
- 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 activities (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 and innervated by sympathetic neurons. When these infants face cold stress, norepinephrine levels increase and act in the brown fat tissue to stimulate lipolysis. Most of the free fatty acids (FFAs) are re-esterified or oxidized; both reactions produce heat. Factors that can increase risk for hypothermia include prematurity, intrauterine growth restriction, asphyxia, and certain congenital anomalies (e.g., abdominal wall defects, central nervous system [CNS] anomalies).

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:

1. A higher ratio of skin surface area to weight
2. Highly permeable skin which leads to increased transepidermal water loss
3. Decreased subcutaneous fat with less insulative capacity

4. Less-developed stores of brown fat and decreased glycogen stores
5. Poor vasomotor control
6. Challenges with adequate caloric intake to provide nutrients for thermogenesis
7. Limited oxygen delivery if pulmonary conditions coexist

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. Thermistor probes available with radiant warmers or incubators can identify and alert the physicians to the occurrence of hypothermia (by alarms activated whenever skin temperature falls 0.5°C to 1°C below the set temperature).

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 support regarding the thermal environment and practices needed to minimize heat loss. 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 higher than the core temperature or setting it to 36.5°C 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 and should be carefully evaluated and treated for possible infection, bleeding, or injury.

D. Hyperthermia, defined as an elevated core body temperature (>37.5°C), 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 of the same temperature and the infant appears vasodilated. In contrast, infants with sepsis are often vasoconstricted and the extremities are cooler than the trunk. Dehydration fever is seen in hot climates, especially if feeding is not established,

it is characterized by excessive weight loss and hypernatremia. Management includes frequent breast feeds/expressed breast milk/formula milk and removing excess layers of clothing. Ensure the baby does not have infection.

E. Induced hypothermia. In recent years, there is experimental and clinical evidence that induction of controlled hypothermia can reduce neuronal loss and subsequent brain injury after a hypoxic-ischemic insult. 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 ≤7.0/base deficit ≥16 on cord gas or gas obtained within 1 hour of life, 10-minute Apgar score ≤5, or assisted ventilation initiated at birth and continued for at least 10 minutes. Target temperature range is 33°C to 34°C. Core temperature (typically measured rectally at the referring hospital and on transport) should be monitored every 15 minutes (see Chapter 55).

III. MECHANISMS OF HEAT LOSS

A. Radiation. Heat dissipates from the infant to a colder object in the environment.

B. Convection. Heat is lost from the skin to moving air. The amount lost depends on air speed and temperature.

C. Evaporation. Heat is lost through conversion of water to gas. The amount of loss depends primarily on air velocity and relative humidity. Wet infants in the delivery room are especially susceptible to evaporative heat loss.

D. Conduction. Heat is lost due to transfer of heat from the infant to the surface on which he or she lies.

IV. NEUTRAL THERMAL ENVIRONMENTS

minimize heat loss. Thermoneutral conditions exist when heat production (measured by oxygen consumption) is minimal and core temperature is within the normal range.

V. MANAGEMENT TO PREVENT HEAT LOSS

A. Healthy term infant

1. Standard thermal care guidelines include maintaining the delivery room temperature at 72°F (American Academy of Pediatrics [AAP])/25°C (World Health Organization [WHO]), immediately drying the infant (especially the head), removing wet blankets, and wrapping the newborn in prewarmed blankets. It is also important to prewarm contact surfaces and minimize drafts. A cap is useful in preventing significant heat loss through the scalp.
2. Examination in the delivery room should be performed with the infant by the mother's side. Examination under a radiant warmer with a skin probe attached to the right hypochondrium in servocontrol mode to maintain skin temperature at 36.5°C (97.7°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.

Warm chain

Set of ten interlinked steps.
1. Warm delivery room –25 to 28°C with no draughts
2. Warm resuscitation
3. Immediate drying with warm linen
4. Skin-to-skin contact
5. Breast feeding
6. Postpone bath
7. Appropriate clothing and bedding
8. Rooming in – mother and baby together
9. Warm transportation
10. Training of health personnel and awareness raising

B. Premature infant

1. Standard thermal care guidelines should be followed.
2. Additional interventions immediately after birth can optimize thermoregulation.

   Thermal care bundles include room temperature, plastic wrap, and prewarmed warmer.

   a. Barriers to prevent heat loss should be used in extremely premature infants. Very preterm infants should be placed in a polyethylene bag immediately after birth, without drying. Plastic wraps and plastic caps are also effective in infants born at <32 weeks.

   b. A radiant warmer should be used during resuscitation and stabilization. A heated incubator should be used for transport.

   c. Combination of interventions such as plastic wraps as well as external heat sources such as transwarmer mattresses have demonstrated a reduction in the risk of hypothermia in extremely preterm neonates (<28 weeks).

   d. Whenever positive-pressure ventilation is required, the use of heated humidified gases may be optimal.
3. In the neonatal intensive care unit (NICU), infants require a thermoneutral environment to minimize energy expenditure and optimize growth; skin mode or servocontrol 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. Once the baby is discharged from NICU, parents can assess the baby's temperature by touching the baby's abdomen and feet with dorsum of their hand, both should feel warm. Cold feet indicate that the environment is cold; the baby should be wrapped, and reassessed in 30 minutes. If a skin probe cannot be used, the incubator may be used in air mode for short periods.
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. Servocontrolled 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 (sunflower seed oil or coconut oil in resource-limited settings) prevents 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, IN) and the Giraffe OmniBed (Ohmeda Medical, Madison, WI). 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.
8. Premature infants in a 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. Stable preterm infants can be kept warm by the use of kangaroo care (KC) and newer innovations such as phase change material used as a cocoon warmer. In KC, the preterm baby is placed in skin-to-skin contact on the chest of the mother, father, or caretaker. KC has been associated with a significant decrease in hypothermia in preterm neonates.
9. Phase change material (cocoon warmer) has been shown to keep babies warm in between KC sessions. This allows stable preterm babies to be nursed without radiant warmer/incubator.

VI. HAZARDS OF TEMPERATURE CONTROL METHODS

A. Hyperthermia. A servocontrolled 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. Servocontrol 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.

Suggested Readings

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16 Follow-Up Care of Very Preterm and Very Low-Birth-Weight Infants

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KEY POINTS

- Very preterm (VPT) babies are at a high risk of medical and surgical morbidities, that need care even after discharge from hospital.
- VPT babies are at a high risk of neurodevelopmental and neurosensory impairments, these may become evident only in infancy or childhood.
- VPT babies have an increased risk for learning disabilities and attention problems requiring special educational services.
- VPT babies have an increased risk of abnormal visual and auditory function and require early screening in NICU and evaluations after discharge, in the first years of life.
- Follow up (FU) is the process of structured surveillance of medical, surgical, and developmental health from birth to childhood.
- Start the process of FU early, at birth (of an at-risk baby) itself.
- Early diagnosis and intervention, starting in NICU and continuing after discharge, will mitigate disability.
- A check-list that integrates development supportive care with medical (intensive) care ensures best compliance and development outcomes (common document, blue book).
- Ensure continuum of care after discharge: Use a predischarge checklist to ensure good continuum of care from NICU to home.
- FU till school: Continue FU of a VPT baby till (at least) the child enters school (6 years of age).
- Risk stratification: The intensity of FU must be based on the anticipated risk.
- Best tools for development assessment are based on the availability of expertise and anticipated risk (risk stratification).
- Timely referral and early specific intervention can minimize childhood disability.

I. INTRODUCTION. VPT babies (defined as <32 weeks' gestational age) account for majority of admissions to current day NICU, although they are only 2% of all births. They have special medical and development needs; they are at a higher risk of medical morbidities and development deviation. Advances in obstetric and neonatal care have resulted in survival of more than 95% of VPT babies. This vulnerable population saved after weeks of intensive care is at an increased risk for long-term complications including neurodevelopmental sequelae, such as cognitive delay, cerebral palsy, motor coordination problems, learning disabilities, visual impairments, 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 structured, long-term follow-up (FU) care.

Both parents and medical teams desire that a VPT baby survives without disability. The term "follow-up" encompasses structured surveillance of ***medical and developmental health***. The ultimate purpose is early intervention to minimize childhood disability and morbidities. The process starts from birth of the baby and continues till at least 6 years of age (school entry).

Early Interventions in NICU

In a recent systematic review, early interventions in NICU were evaluated under four heads

- Parent delivered motor intervention program (PDMI) - they were most effective. Daily PDMI were associated with improved motor and cognitive outcomes in short-term; some benefits were demonstrable even on long-term follow up.
- Therapist delivered posture control interventions (TPDCI) - short-term improvement in motor outcomes and infant behavior were noted.
- Developmental care - short-term improvement noted in infant behavior, no improvement in motor and cognitive outcomes.
- Oral motor interventions - no evidence for improvement in development outcomes.

In a randomized controlled trial from India, early stimulation therapy was associated with better development outcomes (Bayley Scale of Infant Development, BSID scores), the infants were followed till adulthood and the benefits lasted.

Follow up of VPT babies check list

In a public -private partnership quality initiative, Kerala Institute of Medical Sciences and Child development Centre, Trivandrum, India, have evolved a checklist for follow up of VPT babies called the "blue book", this is being followed in more than 200 NICUs of India. This model has evolved over the last 15 years into an easy-to-use guide for the medical team and the family of an NICU baby.

We will discuss the checklist of structured FU of a VPT baby from birth to 6 years. The ***blue book*** is organized as a diary from birth to 6 years. It starts at birth and takes the team through to 6 years.

- Page 1: Information
  - Education and occupation of parents. It is well established that cognitive outcomes are associated with parents' (especially maternal) education.
  - Family support. List the members available for immediate care and care after discharge to home. They must be included in the education program. Language development, behavior, and cognitive outcomes improve if good family support is available.
  - Obstetrician/referring pediatrician. Ensure two-way communication with the physician who cared for the baby before he/she was managed by your team. This will ensure complete medical information.
  - Primary care physician after discharge. Often babies managed in a tertiary NICU go back to the community and continue care with their primary care (family) physician. The NICU team must give a referral note and call the family doctor to ensure seamless transfer. This ensures compliance to FU for development/medical care.
  - Address and contact details (phone numbers/email) of the family members

- Page 2: Birth details
  - Gestation
  - Birth weight (BW)
  - Gender
  - Place of birth
  - Date and time of birth
  - Expected date of birth. This allows both parents and physicians to calculate the age corrected for prematurity on development FU; this is necessary to avoid overestimation of age and incorrect diagnosis of development delay.
- Page 3: List antenatal and neonatal risk factors
  - List all antenatal problems, with relevance to development.
    - Neuroprotective factors such as antenatal steroids, magnesium sulfate, and treatment for twin to twin transfusion syndrome (TTTS) must also be documented.
  - List the neonatal morbidities and major interventions during NICU stay else these details will be forgotten and valuable information will be lost.
- Page 4: Risk stratification based on perinatal risk factors. The risk factors that may affect development are arranged in ascending severity (Table 16.1). The model is intuitive and reasonably predictive. The table helps in documenting all risk factors in real time and planning the intensity of FU. In a study from India, the risk stratification model was able to identify 12% of VPT babies to be at a higher risk (risk of disability 18%) and assign 88% to a lower risk (risk of disability 4.5%). This allows better management of resources and reduces burden of repeated visits to the family, in as many as 88% of babies; the low-risk babies may be followed up in the community and referred to early intervention services, only if necessary. The model is only illustrative, and can be customized to the needs of any NICU.
- Page 5: Growth chart
  - Growth monitoring. Serially plot the weight, length, and occipitofrontal circumference (OFC) weekly from birth to term age on a growth chart for preterm babies (Fenton/Intergrowth 21). A dropping OFC or rapidly increasing OFC must be investigated. Poor weight gain may prompt investigation and is a predictor of severe retinopathy of prematurity (ROP).
- Page 6: In-NICU checklist
  - This checklist integrates development supportive care and development screening routines and medical (intensive) care.
  - Always encourage the mother to express breast milk.
  - Record risk factors on a real-time basis from birth to discharge from NICU.
  - Day 1
    - Introduce benefits of early parent participation (EPP) program.
    - Neonatal services that included parents early in NICU and continued their participation through to home have shown benefits on development outcomes, both cognitive and motor. The most proven ones are kangaroo care (KC), mother-infant transaction program (MITP), and infant health development program (IHDP). We have a modular program called the early parent

participation program (EPPP) that is organized as training modules, these are introduced at appropriate times of NICU stay (listed as page 7 of blue book).
    - Promote breast milk feeding.
    - Record antenatal and birth risk factors.
    - Plot BW.
  - Days 3–7
    - Record OFC.
    - First thyroid function test (newborn screen for metabolic diseases)
    - Ensure good infant position (Infant Positioning Assessment Tool).
    - Encourage parents to touch and talk to the baby. Train them in orogastric feeding, diaper change, taking weight of the baby, massage, and giving nutrient supplements. (We have modules for parent education.)
  - Days 7–14
    - Neurosonogram
    - Repeat thyroid function test
    - Serial record of OFC
    - Kangaroo care (KC) and non-nutritive sucking (NNS)
    - Human milk fortifier (HMF) and other nutrient supplements
  - Weeks 3–4
    - ROP screening
    - Early intervention (massage and passive movements)
    - Serially record OFC.
    - Start iron.
    - Lab tests—hemoglobin, phosphorus, and alkaline phosphatase
  - Weeks 5–8
    - ROP FU
    - Assess neurobehavior.
    - Vaccination
  - Post menstrual age (PMA) 36–40 weeks
    - Repeat neurosonogram.
    - Hammersmith Neonatal Neurological Examination (HNNE)
- Page 7: Health education sessions for parents by development FU team
  - Hand hygiene and NICU routines
  - Breast milk (importance, expression, storage, paladai, and orogastric feeding)
  - ROP screening and refraction (on FU)
  - Hearing screening including otoacoustic emission (OAE), brainstem evoked response audiometry (BERA [language milestones later])
  - Need for periodic assessment of development till at least 6 years of age
  - Daily care issues (bathing, skin care)
  - Danger signs and basic life support
  - Managing stress and introduce them to NICU parent support groups

- Page 8: List medications (calcium phosphate, iron, HMF, and any others such as antiepileptic drugs [AED] and thyroxine)—when to start and stop, and the dosing schedule.
- Page 9 Test reports - labs and imaging
  - Reports of blood tests tabulated (thyroid function, hemoglobin, phosphorus, alkaline phosphatase, ferritin)
  - Reports of neuroimaging tabulated (7 to 14 days, 36 to 40 weeks)
- Page 10. Examination before discharge
  - Neuroexamination before discharge: HNNE at 36 to 40 weeks (before discharge)
  - Physical examination checklist—new murmur, oral thrush, hemangioma, hernia, skin injuries, genitalia, dysmorphism, markers of intrauterine infection, etc.
- Page 11: Predischarge checklist (tick each bullet carefully after verification)
  - Active medical problems at discharge (e.g., on AED, oxygen). Emergency card must be issued - if the child has risk of seizures, severe hypoxia, aspiration due to neurologic handicap, cyanotic spells, or other serious health conditions. This may help a family doctor/emergency room doctor to quickly and safely address the needs of the infant with complex health issues.
  - Growth (OFC and weight) tracking/not
  - ROP findings of last examination and FU appointment scheduled
  - BERA—give appointment for the test before the baby is 3 months old.
  - Summary of neurosonogram/other neuroimaging findings, FU dates scheduled.
  - Summary of lab tests and FU scheduled
  - Immunizations given and FU date scheduled
  - Nutritional supplements doses checked and plan explained
  - Physical examination
  - Neurologic examination
- **After discharge from NICU**
  - Page 12: Vision assessment
    - ROP screening form—findings, intervention given (laser/anti–vascular endothelial growth factor [VEGF]), and FU appointment
    - Annual assessment of refraction starting from 6 to 9 months of age
    - Exclude squint at each visit.
  - Page 13: Hearing screening
    - OAE
    - BERA or automated auditory brainstem response (AABR)
    - Language milestones
  - Page 14–19: One page each for Development assessment at 4, 8, 12, 18, and 24 months of corrected age, and then annually till 6 years of age. Each page lists the age appropriate plan for development assessment and medical care. The choice of tool for development assessment and neuroexamination depends on expertise available and also the anticipated risk of disability.

The choice of tool for development assessment and and neuroexamination depends on the available expertise and anticipated risk.

- General Movement Assessment, Hammersmith Infant Neurological Examination (HINE), the Child Development Center Grading (Trivandrum) for detection of motor disorders (cerebral palsy, motor coordination disorder)
- Bayley Scale of Infant Development (BSID) for multidomain development evaluation for babies stratified as severe risk (Table 16.1). This test requires expertise in interpretation and requires about 1 hour time to complete.

Table 16.1. Risk Stratification Model (KIMS–Child Development Center) for Development Outcomes

	Mild	Moderate	Severe Risk
Gestation (in weeks)	33–34	30–32	<30
Birth weight (g)	>1,500	1,250–1,500	<1,250
Fetal growth restriction	>10th centile	3rd to 10th centile	<3rd centile
Antenatal risk	Medical/obstetric complications not as severe as columns to right	Abnormal NST/BPP Maternal fever DC twins Preterm labor	Eclampsia (seizures) MC twins, triplets or higher order, cord prolapse, chorioamnionitis, abruptio placentae Absent/reversal of umbilical artery Dopplers
Antenatal steroids	Completed	Partial	Not given
Magnesium sulfate (<32 weeks)	Given		
Need for resuscitation at birth	No resuscitation required/initial steps/PPV		Chest compression/medications
Ventilation	Noninvasive/short ventilation	Pneumothorax, longer than 7 days of ventilation	BPD
Shock	Nil	Saline bolus	Inotropes/hemodynamic significant PDA closure
Hypoglycemia	No	Asymptomatic	Symptomatic
Encephalopathy		Seizures	Discharged on AED/encephalopathy >24 hours
NEC			Stage 2 or more

(continued)

Table 16.1. Risk Stratification Model (KIMS–Child Development Center) for Development Outcomes *(continued)*

	Mild	Moderate	Severe Risk
Neonatal jaundice			Exchange transfusion/ encephalopathy
Neurosonogram			Grade 3 IVH/paren-chymal bleed PVL 2 or more

Mark risk factors on the chart on a weekly basis (ideally mark the risk factor, as it occurs). The highest risk in any row is used to classify the baby's risk; even one factor marked in severe column indicates a high risk of development problems.
AED, antiepileptic drugs; BPP, biophysical profile; BPD, bronchopulmonary dysplasia; DC, dichorionic; IVH, intraventricular hemorrhage; KIMS, Kerala Institute of Medical Sciences; MC, monochorionic; NEC, necrotizing enterocolitis; NST, nonstress test; PDA, patent ductus arteriosus; PPV, positive pressure ventilation; PVL, periventricular leukomalacia.

- Denver Development Screening Tool (DDST, Denver II) is not an ideal tool for screening high risk preterm babies. DDST has benefits that it takes only 15 minutes to complete and can be performed even by a pediatrician, with little training. Infants at a lower risk are assessed by DDST; if an infant shows deviation on the screening tool, we do a formal assessment with BSID.
- Beyond infancy, we use modified checklist for autism in toddlers (M-CHAT) tool for autism screening, Child Behavior Checklist (CBCL) for behavior assessment, and Vineland Social Maturity Scale (VSMS) for social adaptation.
- Special focus on language and communication assessment (Language Evaluation Scale, Trivandrum [LEST]). LEST allows assessment of children from age 0 to 6 years. Early language interventions are associated with better communication outcomes.

II. MEDICAL CARE ISSUES

A. Respiratory issues (see Chapter 34). VPT infants are at a high risk for respiratory ailments, especially during the first year.

Wheezing following minor infections is common and some have recurrent/chronic wheezing requiring preventors for asthma.

Admissions during the first year of life are most commonly for respiratory illness among VPT and very low-birth-weight (VLBW) infants.

Approximately 23% of VLBW infants and 40% of extremely low-birth-weight (ELBW; BW <1,000 g) infants develop bronchopulmonary dysplasia (BPD). VPT infants with BPD are at risk of pulmonary hypertension and should have an ECHO on follow up. They are at risk of growth failure and development delay. Infants with significant BPD may be discharged home on supplemental oxygen, bronchodilator, steroid, and/or diuretic therapy. Some infants discharged home from the NICU on supplementary oxygen may be weaned off within the first few months following discharge, whereas others may remain on oxygen for years. Infants on home oxygen are at a higher risk of death, acute exacerbations

of hypoxia with minor illness or agitation. Infants with the severest form of BPD may require treatment with tracheostomy and long-term ventilator support.

Children born VPT who do not develop BPD are also at an increased risk of frequent respiratory illnesses. Rehospitalization, emergency room, and outpatient visits are common. VLBW infants are four times more likely to be rehospitalized during the first year; viral (respiratory syncytial virus [RSV]) and bacterial infections are common. RSV is an 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. This is too expensive and not available in most units in Asia. The American Academy of Pediatrics (AAP) recommends treatment during RSV season for at least the first year of life for infants born ≤28 weeks' gestation and for at least the first 6 months of life for those born between 28 and 32 weeks' gestation. 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; until then, care providers in close contact with the infant should strongly consider receiving the influenza vaccine. The COVID-19 pandemic has placed preterm babies in hospitals and homes at risk of infection from NICU staff and family members alike. Symptomatic infections seem to be less common among newborns, despite the fact that they cannot protect themselves by wearing a mask.

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 oxygen content in the cabin air. If an infant's PaO_2 is ≤80 mm Hg, supplemental oxygen will be needed while flying.

B. Immunizations. VPT infants should receive their immunizations according to the same schedule as term infants, with the exception of hepatitis B vaccine. Medically stable, thriving infants should receive the hepatitis B vaccine as early as 30 days of age regardless of gestational age or BW. 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. Many of the extreme preterm babies will be 8 weeks old in the NICU itself; they must be vaccinated while in the NICU itself. There is a risk of apnea following vaccines (apnea risk seems to be higher following DTwP than after DTaP). Pneumococcal conjugate vaccines (PCV) are expensive and not yet supplied universally by the government. Parents of preterm babies must be encouraged to take PCV. Although studies evaluating the long-term immune response to immunizations have shown antibody titers to be lower in preterm infants, most achieve titers in the therapeutic range.

In a systematic review, BCG vaccine given to preterm babies was found to be safe and effective even if given within 7 days of life; in this review, babies as small as 700 g BW and 27 weeks' gestation were included. The systematic review found similar rates of scar formation and tuberculin skin test positivity rates as in babies vaccinated later; lymphadenitis and mortality rates were similar. A study from India showed OPV vaccine to have modest efficacy when given at 34 to 35 weeks' gestation.

C. Growth and nutrition. VLBW infants have a high incidence of feeding and growth problems for multiple reasons. Infants with severe BPD have increased protein and calorie needs. 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. Fenton's growth chart and Intergrowth 21 charts are specific to preterm babies. Growth should be followed carefully on standardized growth curves (the World Health Organization [WHO] International Growth Curves 2006) after term age, 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 or multicomponent HMF with increased protein, calcium, and phosphate (either added to human milk or used alone) should be considered for VPT infants. ELBW infants may demonstrate growth that is close to or below the fifth percentile. However, if their growth runs parallel to the normal curve, they are demonstrating a healthy growth pattern. Infants whose growth curve plateaus or whose growth trajectory falls off warrant further evaluation. Monitoring for excessive weight gain is also recommended. There is some evidence that links rapid weight gain of low-birthweight (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 VPT with potential neurodevelopment disability. Long-term feeding problems are frequent in this population of children, and they often require specialized feeding and oral motor therapy to ultimately wean from gastrostomy tube feedings.

Specific nutritional issues

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, starting at least by 4 weeks of age.
2. **Rickets.** VLBW infants are at risk of nutritional deficits of calcium, phosphorous, or vitamin D and resulting rickets. Infants at highest risk are those treated with long-term parenteral nutrition and furosemide. Infants with rickets diagnosed in the NICU may need continued supplementation of calcium, phosphorous, and vitamin D during the first year of life.

D. Sensory issues that need special FU include vision and hearing.

1. **Ophthalmologic FU** (see Chapter 67). Infants with severe ROP are at an increased risk of 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 extended monitoring for a few months 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 in term infants. Myopia is the most common problem and may be severe. Hyperopia also occurs more commonly in premature infants. Vision may need correction with specs.

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, amblyopia may result from severe strabismus, anisometropia, or high refractive error. Permanent loss of vision may happen, due to amblyopia, if these problems are not corrected within 6 to 10 years 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. Strabismus may be treated with eye patching, atropine drops, corrective lenses, or surgery.

d. Anisometropia, defined as a substantial difference in refractive error between the two eyes, occurs more often in premature than in 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 eyeglasses.

In patients 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.

All VLBW infants should have FU with an ophthalmologist who has experience with ophthalmologic problems related to prematurity. Assessments should occur by 6 to 9 months of age and then annually. Cortical visual impairment (CVI) can further impair visual function; it is challenging to make a diagnosis and correct this impairment.

2. Hearing and language. 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 an increased risk for auditory dyssynchrony (also called auditory neuropathy) and central auditory processing problems. Early language intervention programs help toddlers to improve communication gaps.

E. Neuromotor problems. The incidence of cerebral palsy is 7% to 12% in VLBW infants and 11% to 15% in ELBW infants. The most common type of cerebral palsy is spastic diplegia. This correlates with the anatomic location of the corticospinal tracts in the periventricular white matter. VLBW infants are also at risk for other types of abnormal motor development including motor coordination problems and later problems with motor planning.

Early diagnosis of motor problems must be followed up with referral to a pediatric neurologist and orthopedic surgeon. Both transient and long-term motor problems in infants require assessment and treatment by physiotherapists and occupational therapists.

Some infants with cerebral palsy 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. Hippotherapy (horseback riding therapy) and aquatherapy are also beneficial for young patients with cerebral palsy.

F. Cognitive impairment. Risk of cognitive disability in preterm infants is associated with degree of prematurity, presence of cerebral injury on neuroimaging, low parental education, and socioeconomic status. Progress is typically assessed by development quotient (DQ) assessed by Bayley Scales of Infant Development or the Mullen Scales of Early Learning. Additional instruments are available but their psychometric properties may not be as robust. Scales with excellent psychometric properties such as the Stanford -Binet Intelligence Scales for Early Childhood (fifth edition) can be used in older children.

VPT 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 between 5% and 20% for VLBW infants and between 14% and 40% for ELBW infants. Most studies report the status of children younger than 2 years. Among older children, the percentage with school failure or school problems is as high as 50%. 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 (even without neurologic problems) compared to term infants of similar sociodemographic status. There is also increasing evidence that VLBW schoolchildren have significant difficulties with simultaneous processing when compared to term children, thereby having an impact on visual motor integration and logical reasoning. 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 some of the studies report lower rates of educational achievement, lower income, and higher level 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. Likewise, studies assessing VLBW teen and young adults in their perception of their quality of life report positive values comparable to term controls. Further longitudinal FU of these children into early adulthood and assessing quality of life measures in addition to the incidence of neurodevelopmental disability is essential.

G. Social and communication development difficulties are also increasingly a concern in the population of preterm infants. Several recent studies have noted prematurity as a risk factor for autism and have noted that in prospective studies of preterm infants at the toddler age, they are more likely to screen positive for autism spectrum disorders (ASD). Neuroimaging techniques, diagnostic instruments, and biologic markers geared to accurately assess ASD at the earliest possible age have been developed. Psychometric instruments such as the Autism Diagnostic Observation Schedule (ADOS) and early electroencephalographic signatures promise better sensitivity and specificity than previously available. During school-aged years, these children and their parents report more social difficulties with their peers, with risk being higher in children with cognitive and behavioral development problems.

H. 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. Smaller preterm infants may have the lightest sleep related to their brain immaturity, and their potential exposure in the NICU to an environment with light and noise that is not conducive to appropriate sleep–wake cycle routines.
2. **Behavior.** VLBW children are at an increased risk for behavior problems like hyperactivity and/or attention deficit. Recent research findings indicate that parenchymal lesions/ventricular enlargement during the neonatal period predict attentional difficulties without hyperactivity in these children, a finding that is important for developing interventions. The risk factors for behavioral problems also include stress within the family, maternal depression, financial difficulties, and smoking. Behavior problems can contribute to school difficulties. In relation to both school problems and other health issues, VLBW children are seen as less socially competent than normal BW children. Formal tools may be used to detect behavioral problems, especially if parents/teachers express concern. The youngest children for whom such standardized scales are available are 2 years old. 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 psychology services. Screening of NICU mothers for postpartum depression or post-traumatic stress disorder is also recommended; the incidence of depressive symptoms in mothers who have delivered a premature infant is higher and, when identified, provides an opportunity for intervention that will enhance both maternal and child health. Many pediatric hospitals have behavioral medicine specialists who focus not only on the baby's individual needs but also on the impact that a new preterm baby can have on each of the family members.
3. **Mental health.** VLBW children tend to experience internalizing problems, such as depression and anxiety, more often than term born babies.

I. Coordination of services. Infants with multiple disorders (motor, sensorineural handicaps, behavioral) require coordination of clinical services and developmental programs. The nodal person (neonatologist or developmental pediatrician) should organize the screening and timely referral to specialists. He then interprets the expert opinion and ensures that the advice is implemented. For older children, consultation with the schools and participation in an educational plan are equally important. If available, referral to a structured FU and early intervention service at the time of discharge from the NICU allows early identification of children with development delay and referral for therapy to physiotherapist, occupational therapist, speech and language pathologist, and educational specialist as appropriate. The Government of India has established district early intervention centres (DEIC). Children with severe development problems may benefit from advances in technology, for example, children with severe language delay will benefit from referral to centers that use adaptive technology to enhance language and communication. Caretakers will traditionally require significant assistance not only in understanding the importance of specialized interventions but also

in navigating the complex programs. 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 developmental critical period.

J. Family/parent support. Having a premature infant is often an extremely stressful experience for the parents. Support to families starts even before the preterm baby is born, and continues through NICU care and even after discharge.

- Antenatal counseling. If preterm birth is expected, the neonatologist is invited by the obstetrician. Together they discuss the care plan and the need for preterm delivery. The neonatologist informs the family the expected survival rates, risk of disability, hospital stay duration, and costs of care (most parents in India pay out of pocket). This prepares the family for long in-hospital care.
- First communication. Immediately after birth of the baby, the parents are introduced to NICU routines, common medical terms, and therapeutics that may be frequently used. Parents and family members are allowed unrestricted visit to their baby.
- Parent participation. Parents are encouraged to take part in care of the baby, including feeding through orogastric tube, paladai, or direct breastfeed as appropriate. They help in all routines such as diaper change, taking weight, and comforting the baby by talking to the baby, caressing the baby, and KC.
- Parents may experience fear when the baby is critically ill and may need support of the extended family, psychologists, and religious leaders.
- Physical and emotional exhaustion are compounded by financial burdens and blame game resulting in marital conflicts. Counselors may be invited, if undue emotional burnout is recognized.
- Parents may need guidance on insurance, source of special assistance such as home oxygen, etc.

K. Development specialists and services

Survival of neonates with complex health care issues has necessitated that the neonatologist has optimal knowledge of development assessment tools, early intervention and scope of departments that may help the child with special needs. The NICUs must incorporate a developmental therapist, nurse, speech language pathologist, and a developmental pediatrician as full time staff who are involved in developmental care from start. All NICUs must have database of outcomes of NICU babies for at least 1 year to start with and target follow up till school age as the follow-up services become better. The national neonatology forum of India has included follow-up services in their mandatory criteria for accreditation of NICUs.

Research in neonatology has recognized the need to report development outcomes at an age of at least 18 to 24 months for all therapeutic interventions (example caffeine, steroids for BPD).

L. Quality Improvement in follow up

As early as 2006, evidence-based quality-of-care indicators for follow up of VLBW babies were published. Seventy indicators were reported with the purpose of guiding pediatricians and specialists in improving follow up of VLBW babies. Most quality initiatives in neonatology stop at NICU discharge. A recent project by the New England Follow-up Network showed a low rate for clinical

follow-up (52%). It demonstrated many opportunities to improve post-discharge follow-through specific to NICU-based care.

The California Perinatal Quality care collaborative undertook a web-based high risk infant follow-up program. They identified high risk babies, and planned early referral to specialists, if needed. The program resulted in dramatic improvement in timely referral to nearly 95%. The improvement was greatest from NICUs with low or medium load of sick babies. This study demonstrates that it is possible to identify babies at higher risk of disability, screen them periodically and refer them for modifiable factors so that childhood disability may be minimized,

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17 Neonatal Transport

Monica E. Kleinman

KEY POINTS

- Whenever possible, transport of the mother and fetus prior to delivery (*in utero transfer*) is preferable to a postnatal transport.
- The risk of interfacility transport can be reduced by the use of specially trained and equipped neonatal transport teams/protocols.
- Preparation, documentation, and communication are critical to safe transfer.
- There are very few private/government neonatal transport services in India and most of Asia. Safe transfer is a critical link in management of sick neonates and their outcomes.

I. INTRODUCTION. Regionalization of perinatal services necessitates that newborn babies requiring intensive care or specialty treatment be transported between facilities. Most experts agree that whenever possible, it is preferable to safely and expeditiously transfer 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 identified prior to birth, and others deliver too quickly to permit maternal transfer. It is important that a system exists for timely referral, clear communication of information, and recommendations. The transfer system provides access to specially trained personnel who can support local staff to provide neonatal resuscitation and stabilization before the transport team arrive. The latter then seamlessly take over these responsibilities and tasks following a comprehensive patient handover.

It is vital to recognize that transport medicine is different to unit-based neonatal practice. Fundamental differences include the following:

A. Impact of movement, noise, and vibration on patient stability

B. Limited space in the transfer vehicle

C. Lack of prior familiarity with the patient

D. Limited equipment

E. Frequent occurrence of high-stress scenarios

F. Requirement for consistently excellent communication, conflict resolution, and teamwork skills

II. INDICATIONS

A. Escalation of care (uplift). 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 infants at birth or in the immediate newborn period are proficient in basic neonatal resuscitation and stabilization. If the ongoing clinical needs of the infant cannot be met at the birth hospital, then uplift transfer should be arranged. This may be in the context of a newborn with anticipated needs related to prematurity, birth weight, or known congenital abnormality. It may be in the context of an unexpected scenario, e.g., undiagnosed congenital abnormality or perinatal asphyxia. Transfer to the regional tertiary neonatal center should be expedited following initial stabilization. Medical personnel from the referring center should contact their affiliated neonatal intensive care unit (NICU) or regional transport service to arrange transfer and to discuss a management plan to optimize the patient's condition before the transport team's arrival.

Urgent escalation may also be in the context of a stable infant who develops an unexpected complication, for example, necrotizing enterocolitis or septicemia.

B. Repatriation (step-down). After a period of intensive care, infants may need transfer back to their birth hospital for ongoing management leading up to discharge home. This allows easier visiting for parents as their child is closer to home. The local clinical team will also become familiar with the patient should he/she return to hospital either as an emergency or for follow-up.

C. Wait and return. Many infants who are still inpatients need transfer from local to specialist hospital to access specialty clinics or investigations that may not be available in the birth hospital. This may simply need a day visit but will involve transfer both ways by a trained team.

D. 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 perinatal centers outlining criteria for perinatal consultations and neonatal transfer. Conditions that typically require transfer to a center that provides neonatal intensive care include the following:

1. Prematurity (<32 weeks' gestation) and/or birth weight <1,500 g
2. Respiratory distress requiring 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

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 ■ Care of extremely preterm infants ■ Management of complex congenital abnormalities ■ Subspecialty medical and surgical expert consultation ■ Mechanical ventilation (all forms) ■ Diagnostic imaging capabilities
Level 4* (regional neonatal intensive care units) Highly specialized centers	Level 3 capabilities plus: ■ Specialized surgical capabilities for repair of congenital or acquired conditions, e.g., cardiac, neurosurgical, and ECMO services ■ Critical care transport services and outreach education

ECMO, extracorporeal membrane oxygenation.
Source: American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics* 2012;130:587–597, reprinted with permission.
*In India, the National Neonatology Forum of India has organized levels of care at three levels.

9. Other conditions that may be indications for neonatology consultation and/or transfer.

a. Severe hyperbilirubinemia that may require exchange transfusion

b. Infant of a diabetic mother with hypoglycemia or other complications

c. Severe intrauterine growth restriction

d. Birth weight between 1,500 and 2,000 g and gestational age between 32 and 36 weeks

e. Procedures or therapies unavailable at the referring hospital (echocardiography [ECHO], surgery, extracorporeal membrane oxygenation [ECMO], etc.)

III. ORGANIZATION OF TRANSPORT SERVICES

A. The 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, which should be reviewed on a fixed basis. A medical control physician, who may be the attending consultant neonatologist or fellow, 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.

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 transport of such patients with sufficient frequency to maintain their expertise. Such teams typically consist of a combination of at least 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 and competencies should be assessed, and procedural and situational training should be part of routine ongoing education.

C. Types of transport teams

1. Unit-based transport teams consist of personnel (nurses, respiratory therapists, neonatal nurse practitioners, etc.) who are involved in routine patient care in the NICU and are deployed when a request for transport is received. If few infants are transported to the NICU, 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 transport teams are staffed separately from NICU personnel specifically for the purpose of transport of patients to and from the hospital or between hospitals in the region. These personnel do not have patient assignments, although they may assist NICU 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 personnel to maintain specialized skills for transport and facilitates rapid mobilization to transport requests.

   High-volume services may benefit from having on-site ambulance personnel and vehicles for rapid dispatch.

D. Modes of transport include ambulance by road, rotor-wing (helicopter) aircraft, and fixed-wing (airplane) aircraft. The type of vehicle operated depends on the availability of resources, distance of transports anticipated, acuity of patients, and geographic terrain to be covered by the vehicle. In India, most of the interhospital transfer is by road; the air transfer that happens when long transfers are necessary is also mostly on commercial passenger planes with customization. Most interhospital transfer is done in India by ambulances that are common to all health care emergencies (108); they are not currently dedicated to neonatal needs in terms of equipment or personnel. The 102 ambulance is to be used for transfer of pregnant women and children from home to health care facility and back, or

between health care facilities. Many transfers are unfortunately still made by ambulances or personal vehicles not able to support sick patients. Some hospitals in private sector have neonatal transport facilities and transport protocols in place. The vehicles chosen must be outfitted to conform to standards that ensure safety and efficiency of transport. The vehicles should be large enough to allow the transport team to adequately assess and treat patients as needed *en route* to the referral 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. **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, and the option to stop the vehicle to assess the patient or perform procedures. **Rotor-wing transport** has the advantage of a rapid response with hospital-to-hospital service for patients up to a distance of ~100 to 150 miles or less each way, although a rotor-wing service is more expensive to operate, has limitations with regard to weather and weight, and has inherently more safety considerations. **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. Units must prepare packs or other containers should be stocked by members of the transport team, to find required items promptly. The weight of the stocked packs should be documented for air transport (Tables 17.2 to 17.4).

All equipments should be subjected to a daily check of stock levels and functionality to minimize adverse events on transport.

F. Legal issues. The process of neonatal transport may raise legal issues, which vary among states. 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. Professionals undertaking transport work should be appropriately indemnified and covered under a suitable accident policy.

G. Quality assurance and performance improvement activities should be performed routinely using established benchmarks whenever possible.

H. 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.

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, 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
Nitric oxide tank and delivery equipment
Infusion pumps
Gel-filled mattress
Glucometer or other 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 to 4.0 mm
Magill forceps
Laryngeal mask 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
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

CPAP, continuous positive airway pressure.

Table 17.3. Medications Used during Neonatal Transport
Adenosine
Albumin 5%
Ampicillin
Atropine
Calcium chloride
Calcium gluconate
Dexamethasone
Dextrose 10% in water ($D_{10}W$)
Dextrose 5% in water (D_5W)
Dobutamine
Dopamine
Epinephrine (1:10,000; 0.1 mg/mL)
Erythromycin eye ointment
Fentanyl
Fosphenytoin/antiepileptic drug
Furosemide
Gentamicin
Heparin
Lidocaine
Lorazepam
Midazolam
Morphine (narcotic drug, issued as per hospital policy)
Naloxone
Normal saline (0.9% NaCl)
Phenobarbital
Potassium chloride
Prostaglandin E_1 (requires refrigeration)
Rocuronium
Sodium bicarbonate 4.2% (0.5 mEq/mL)
Sterile water for injection
Surfactant (bovine surfactant products require refrigeration)
Vecuronium
Vitamin K_1

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

$$FiO_2 \text{ required} = \frac{F_iO_2 \times BP_1}{BP_2}$$

FiO_2, fraction of inspired oxygen patient is currently receiving; BP_1, barometric pressure prior to flight; BP_2, barometric pressure at altitude.

I. Ambulance regulations vary from state to state and may conflict with transport team goals. For example, some states require that an ambulance stop at the scene of an unattended accident to render aid until a second ambulance arrives.

IV. REFERRING HOSPITAL RESPONSIBILITIES

A. Identify the appropriate tertiary care facility for transfer. If it is known before birth that the infant will need transfer to a tertiary care facility (e.g., an infant with congenital cyanotic heart disease), both the parents and the appropriate tertiary care facility can be prepared for the transfer. Prompt notification of the receiving hospital will allow timely deployment of the transport team and verify that the required services are available. Any risk posed by the patient for communicable diseases must be disclosed to the tertiary center at the time of the request for transfer.

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. Transport team documentation begins on 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 (receiving unit) should ***obtain a sufficiently detailed summary*** on phone/email/fax from the referring clinician to decide the appropriate team composition, equipment, and medications required (e.g., prostin and antiepileptic drug).

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 whether there is any additional equipment or medications that might be needed.

C. On 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*** and signed over. Use of checklists for communication decreases the likelihood of important items being overlooked during handoff (e.g., vitamin K, BCG, hepatitis B, mother's blood group, last dose of antibiotics).

E. The teams should work collegially and be ***objective in their assessment and stabilization***.

F. ***Parents should be given an opportunity to see the infant*** before the team leaves the referring hospital. Some services prioritize the conveyance of a parent to minimize anxiety and facilitate consent if emergency surgery is required at the receiving hospital. If parents do travel with their child, it is imperative that they are medically fit to travel and discharged from inpatient care themselves. While meeting with the family, the team should obtain ***consent for transfer and other anticipated procedures*** (including blood transfusion, if indicated), as well as review the team's policy regarding parents traveling with their newborn on transport.

G. 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 and simulation training.

VI. MEDICAL MANAGEMENT BEFORE TRANSPORT

A. Stabilize before transport. 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 urgency of the patient's condition as well as the resources available at the referring hospital. In general, pretransport interventions should focus on thermal, respiratory, cardiac, neurologic, and metabolic stabilization. These should be limited to those necessary for a safe transfer, not for ongoing definitive care.

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. Establish stable vascular access (umbilical/peripherally inserted central venous or arterial catheters).
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 copies of radiographic studies.
8. Prepare the parents for transport of their infant and, if possible, allow them time to visit with their infant.

VII. MEDICAL MANAGEMENT DURING 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 work on both AC and DC (battery). 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. 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 or reduce mortality. In the event of sudden patient deterioration, the team should be trained through simulation/drills in rapid problem solving which may involve immediate division into parallel tasks of patient assessment and intervention and equipment troubleshooting.

C. Communication. The transport team should notify the medical control physician and receiving hospital 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. 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 with signatures will ensure that relevant information is not inadvertently omitted.

B. A team member should telephone the parents to let them know that their infant has arrived safely unless they have traveled with their child.

C. Relevant documentation regarding the transport should be completed and a copy added to the patient's medical record, including contact information for the parents.

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 medical director 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. Ideally, a chest x-ray should be obtained after intubation and prior to surfactant delivery to avoid administration of surfactant into one lung. However, aide-memoires may assist with predicted tube lengths. 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 and minimize the risk of pneumothorax.

B. Hypoxic respiratory failure and pulmonary hypertension. Management should focus on ensuring optimal lung recruitment using ventilatory strategies and, in some cases, surfactant administration, while avoiding injurious ventilator settings and/or hyperventilation. If the infant has signs of severe pulmonary hypertension (e.g., tachycardia, preductal and postductal oxygen saturation difference, systemic hypotension), 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. In India, inhaled nitric oxide is often not available at the referring hospital or in ambulance.

C. Cardiac disease. Ideally, a 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 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 infants with single ventricle physiology.

D. Surgical conditions. 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.*

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 operate at an equivalent altitude of 5,000 to 8,000 ft where barometric pressure is decreased.

A. Alveolar hypoxia (Dalton's law). As altitude increases, the barometric pressure and partial pressure of oxygen in the air decrease (see Table 17.4), leading to a decrease 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's 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 sea level. To prevent decompensation in flight, pneumothoraces should be drained and the stomach vented with a nasogastric tube before an 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. Simulation-based training allows teams to practice working together to enhance their interactions and efficiency in a safe environment. Neonatal apps are especially useful in assistance with drug and fluid calculations, tube and line length, etc. They can provide helpful disease-specific pretransfer checklists.

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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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;16:711–717.

Tette EMA, Nuertey BD, Akaateba D, Gandau NB. The Transport and Outcome of Sick Outborn Neonates Admitted to a Regional and District Hospital in the Upper West Region of Ghana: A Cross-Sectional Study. *Child Basel Switz* 2020;7(3).

Watson H, McLaren J, Carlisle N, Ratnavel N, Watts T, Zaima A, et al. All the right moves: why in utero transfer is both important for the baby and difficult to achieve and new strategies for change. F1000Research. 2020;9.

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 take their infants home.
- Follow the tenets of family-centered care involving the family from start, as a member of the team as much as possible.
- Include a structured family education program.

I. INTRODUCTION. A successful transition from the neonatal intensive care unit (NICU) to home is critical to ensure a safe and confident home for newborns and their families. This requires involving the family from the start of the NICU journey and organized discharge planning. The optimal safe and successful discharge requires mutual participation between the family and the medical faculty and should begin at admission and follow through the infant's hospital stay. This chapter discusses the 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 in infant care by the primary caregivers. NICU **discharge preparation** is the process of facilitating discharge readiness. Discharge readiness is the desired outcome, and discharge preparation is the process.

II. INFANT'S DISCHARGE READINESS. The transition to home should 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. Free of apnea for at least 5 days, after stopping caffeine (may be longer, up to 2 weeks in extreme preterms) (see Chapter 31)
2. Able to take all feedings by breast/paladai/bottle without respiratory compromise
3. Able to maintain temperature in an open environment
4. Demonstrate steady weight gain evidenced by a weight gain of 15 to 20 g/day for 3 consecutive days

Discharge criteria are best guided by physiology; a minimum gestation of 34 weeks postmenstrual age (PMA) helps in discharge date planning; some units also include a minimum weight (e.g., 1,400 g).

B. Complete routine screening tests according to local and regional guidelines (Table 18.1).

For all infants

- Immunizations administered according to national guidelines based on chronologic age, not PMA
- Newborn screening (see Chapter 8)
- Hearing screening

For preterm infants

- Cranial ultrasound and ophthalmologic evaluation as indicated (see Chapter 67)

C. Ongoing medical issues. When planning discharge, it is important to consider the infant's complex medical needs based on the discharge diagnosis. Parents should be given sufficient supply of special medications (sachet of medications not available in strengths that parents can prepare at home, such as valganciclovir and thyroxine), and dietary supplements such as iron, calcium, and vitamin D, and taught dispensing, schedules, and stop dates of these medications. If an infant will require in-home respiratory support, make a referral to a reliable medical equipment company. A respiratory therapist (RT) or an equally qualified person must prepare the family with requisite needs such as large and small oxygen cylinder, pulse oximeter, emergency care numbers, and chest physiotherapy, if necessary. It will be ideal to evaluate the home environment and primary care physician/facility especially for babies who need specific/lifesaving care after discharge (e.g., baby with gastrostomy, tracheostomy, seizures).

III. PARENT'S DISCHARGE PREPARATION.

There should be a dedicated team and process that plans and guides parents for care of the infant at home and ensures arrangements for high-risk infants. The families should be given a written plan and educated regarding surveillance of growth and development, till at least 6 years of age (school entry). Follow-up in school for scholastic and behavioral issues is also desirable.

Discharge planning is a multidisciplinary process involving medical personnel such as ophthalmologist and nursing and team members from development/follow-up services. Parents spend a few days with the baby in a room in the hospital, after the baby is shifted out from the NICU, and act as primary carers (Figure 18.1). They are provided with a booklet (such as the *Blue Book* from KIMS and CDC, Trivandrum), which gives them the directions for caring at home, information on follow-up arrangements, assessment tools for each visit until 6 years of age, and danger signs to look out for in case of emergency. The Rashtriya Bal Swasthya Karyakram (RBSK) program by the Government of India under National Health Mission aims at early identification and early intervention for children with development delays (vision impairment, hearing impairment, neuromotor impairment, motor delay, cognitive delay, and language delay) as one of its components. The District Early Intervention Center (DEIC), consisting of pediatrician, speech therapist, physiotherapist, etc., identifies and manages these children, especially those younger than 6 years.

A. Discharge teaching concepts

1. **Identification of caregivers**. Involve all individuals who will be closely involved with the infant's care (often includes parents, grandparents, and close relatives).
2. **Family-centered care** (FCC) is the concept that parents are an integral part of the care team who work in partnership with the medical providers on decision

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
■ Day 3 or discharge (D/C) date (whichever comes first) ■ Screening for congenital hypothyroidism—repeat at 2 weeks (and at 4 weeks/term gestation)
Cranial ultrasound (see Chapter 54)
Criteria
■ All infants with gestational age (GA) <32 weeks
Initial
■ Days 7 to 10 (earlier in critically ill infants, when results of an earlier ultrasonography may alter clinical management)
Follow-up (minimum if no abnormalities noted)
■ If no hemorrhage or germinal hemorrhage, only week 4 and at 36 to 40 weeks postmenstrual age ■ 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 indicated, for example, encephalopathy, severe cardiorespiratory deterioration
Audiology screening (see Chapter 68)
Criteria
■ All infants being discharged home from NICU
Timing
■ Examine at 34 weeks, gestation or greater. ABR in NICU and confirmatory BERA must be completed before baby is 3 months chronologic age
Ophthalmologic examination (see Chapter 67)
Criteria
■ All infants with birth weight ≤2,000 g or GA <34 0/7 weeks (see RBSK guidelines for India, in ROP chapter 67) ■ Bigger infants (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

Table 18.1. Guidelines for Routine Screening, Testing, Treatment, and Follow-Up at Neonatal Intensive Care Unit (NICU) *(Continued)*

Newborn screening
Timing of initial exam
■ First screening examination should be carried out at 4 weeks of PMA or at 2 to 3 weeks in babies at risk of APROP
Follow-up (based on most recent exam findings)
■ Follow-up examinations should be recommended by the examining ophthalmologist based on retinal findings classified according to the international classification. ■ Follow-up after resolution of ROP depends on the severity of the active phase of ROP but should occur by age 6 to 12 months.
BCG vaccine—at discharge to home
Hepatitis B vaccination (see Chapter 48)
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 g and unstable: Defer vaccination until the infant's clinical condition has stabilized ■ If weight <2,000 g: Vaccinate at discharge
Synagis RSV prophylaxis (not available in India)
Neurodevelopmental follow-up program
Criteria
■ BW <1,200 g ■ GA <32 weeks ■ NICU admission >5 days ■ 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
Timing
■ Follow-up frequency according to anticipated severity of risk
ABR, auditory brainstem response; APROP, aggressive posterior retinopathy of prematurity; BERA, brainstem evoked response audiometry; BW, birth weight; NICU, neonatal intensive care unit; PMA, postmenstrual age; RBSK, Rashtriya Bal Swasthya Karyakram; ROP, retinopathy of prematurity; RSV, respiratory syncytial virus.

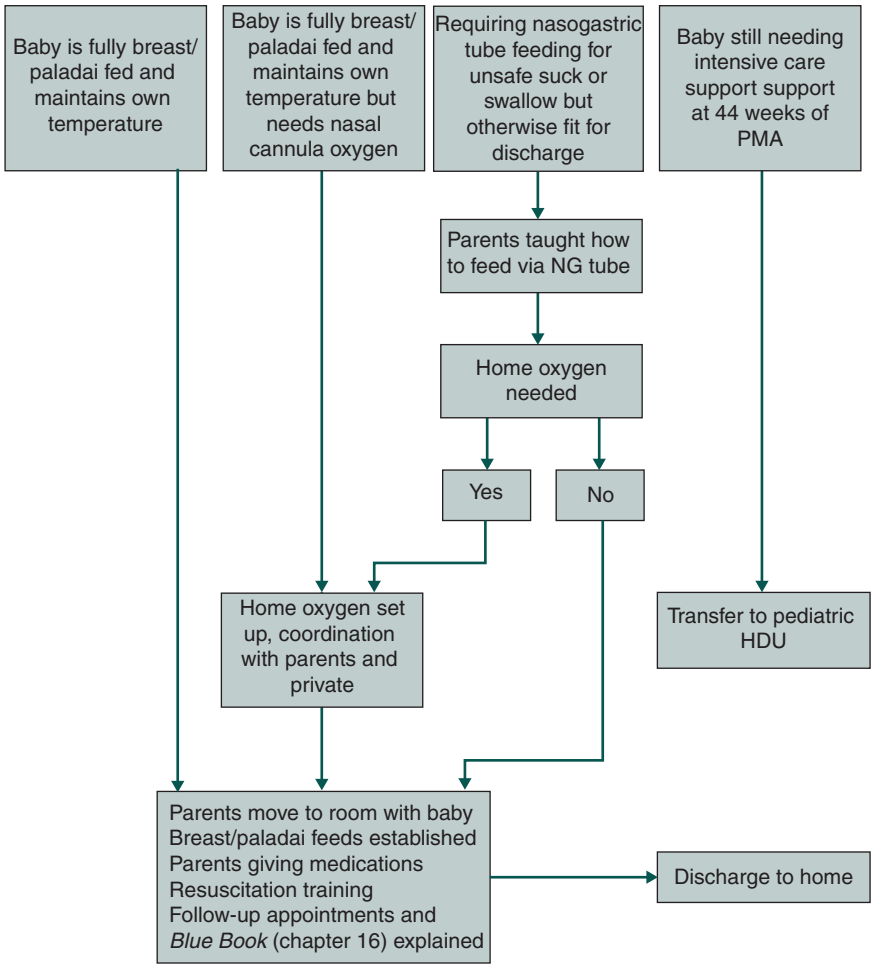

Figure 18.1. Discharge planning for PMA >34 weeks and weight above 1,400 g.

making and providing care for the infant. FCC may ameliorate the stressors that families experience due to the separation of family and infant and inability to experience a traditional parenting role.

a. The early establishment of parents as partners and participants in their infant's care helps promote an easier transition home. In our checklist, early parent participation features on day 1.

b. Family's presence/participation in medical rounds is an easy opportunity to help promote FCC.

c. The four central tenets of FCC are dignity and respect, information sharing, family participation in care, and collaboration with the family.

d. 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.

e. FCC should be incorporated in all aspects of discharge preparation for the families.

3. Discharge planning team includes the following:

a. Family

b. Staff including combination of the following as per the diagnosis and discharge condition: clinical nurses; physicians (primary neonatal consultants/registrars); and multi disciplinary team members such as development pediatrician, physiotherapist, speech and language therapists, psychologists from the follow-up team, and primary care physician (to whom the baby is referred back to)

4. Support of families with language interpreters

a. Families with limited English/regional language (families from another Indian state/other countries) proficiency are at an increased risk for not understanding discharge teaching and to have poor transitions home.

b. Support for families with language barriers 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 where possible

iv. Involving other family members who follow the regional language in discharge planning

B. 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 and competence. It should offer opportunities to interact. We include the following:

- Hand hygiene and NICU routines
- Skin-to-skin care, cuddling, kangaroo care
- Learning to change nappies
- Importance of breast milk expression and storage
- Common medical terms
- Common procedures and emergencies
- Retinopathy of prematurity (ROP) and follow-up for refraction and squint
- Hearing tests (otoacoustic emissions [OAE] and brainstem evoked response audiometry [BERA])
- Dietary supplements

- Immunization of the neonate
- Family vaccination
- Need for development surveillance, schedule
- Emergency care (basic life support)

3. Checklist can be helpful to make sure that the 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

Table 18.2. Sample Family Discharge Checklist

Going Home from the NICU

Baby's name in hospital: _____ **Baby's name after discharge:** _____

	Please check off items as they occur.	Additional Information	Parent Initials
In NICU	Discharge planning meeting		
	Pediatrician chosen Dr. _____ # _____		
	Baby added to insurance policy		
	CPR class complete		
	Handouts received and/or discussed with nurse ☐ Protecting babies from infection	☐ Temperature taking ☐ When to call the pediatrician ☐ Flu/pertussis vaccines for families/caregivers ☐ Suction bulb use ☐ Bathing techniques ☐ Tummy time and activities for 1st year	
Preparing for Home	Supplies at home		
	• Diapers, wipes, ointments		
	• Thermometer, suction bulb		
	• Feeding supplies	☐ Breast pump (if needed) ☐ Nipple/bottles ☐ Formula (if needed)	
	• Circumcision care education	☐ N/A	
	Hearing screen results received*	*If referral needed, add to specialists.	
	Written home feeding plan received		
	Recipe for breast milk/formula received		
	Pediatrician visit date: __ / __ / __ Time: __ : __	Visiting nurse date: __ / __ / __	
	Early intervention arranged with _____		
	Specialists: _____ Name: _____ Date: __ / __ Time: __ : __ Name: _____ Date: __ / __ Time: __ : __		
Going Home	Med: _____ Dose/frequency: _____ Med: _____ Dose/frequency: _____ Med: _____ Dose/frequency: _____	☐ Medications/syringes obtained ☐ Medication teaching complete	
	Received immunization booklet (blue book)		
	Parents Completed Discharged Readiness Questionnaire		

staff providing family education to be aware of which topics already have been and which ones need to be covered (see Table 18.3).

4. Skills demonstration
   - **a.** Provide parents with adequate opportunities to practice skills initially under direct supervision and then with supervisory support as needed.
   - **b.** Repetition and return demonstrations (i.e., teach-back technique) can be used to increase parental retention of the education content.
   - **c.** Provide specific, practical information with examples that are meaningful to the family's everyday experiences.
   - **d.** Supplement discharge teaching with other materials to reinforce the teaching and increasing retention of the material.
     - **i.** Written information presented in a manner that is simple, clear, and devoid of medical jargon, with complex words and concepts defined in precise terms
     - **ii.** Some families may have limited functional health literacy; therefore, pictographs, visual aids, multimedia, and recorded information are helpful to illustrate key concepts.

C. Discharge teaching content. Parents need instruction in all of the following:

1. **Technical infant care skills**
   - **a.** Breast/paladai/bottle feeding and mixing 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 breast and paladai-feeding patterns commonly seen, normal bowel and bladder function, and usual infant sleep–wake cycles.
   - **b.** Some typical preterm infant behaviors are normal but may seem abnormal to those not accustomed to preterm infants. Specifically, preterm infants frequently do not engage socially in the same way as term infants including being less active, alert, and responsive as well as more irritable and having more gaze aversion.
   - **c.** Changes in behavior that may be signs of illness that require close monitoring are the following: not hungry or eating less well than baseline, sleepier or less active than usual, and more irritable or fussy than usual (Table 18.4).
   - **d.** Physical signs that may be signs of illness that require close monitoring are the following: changes from the infant's normal breathing pattern; cyanosis (blueness) of the lips or mouth; flushed, very pale, or mottled (spotted or blotched) skin; or lower muscle tone than usual (Table 18.4).
   - **e.** Abnormal signs and symptoms that should prompt a discussion with the medical home are the following: vomiting and/or diarrhea, dry diapers for more than 12 hours, no stool for more than 4 days, bright red stool, a rectal temperature

Table 18.3. Sample Nurse Discharge Planning Worksheet

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					
Pediatrician chosen					
No later than 1 week prior to anticipated discharge					
Early intervention (EI) arranged			☐	☐	
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: ____
Vaccines information given					
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				☐	
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: _____			☐		

(continued)

Table 18.3. Sample Nurse Discharge Planning Worksheet *(Continued)*

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				☐	
Family learned how to administer home medications			☐	☐	
Hearing screening complete Passed ☐ Referred L ☐ R ☐					
Discharge newborn screen sent					
Family attended CPR class				☐	
Family offered CPR refresher video				☐	
When to call your baby's doctor 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:

Courtesy of Dr Vincent Smith, Beth Israel Deaconess Medical Center.

over 100°F, or an axillary (armpit) temperature over 99.6°F or below 97°F, cold feet despite appropriate covering, and decreased activity than usual.

3. Home environment preparation

a. Equipment and supplies to acquire, in anticipation of discharge:

i. Feeding-related supplies: Breast pump, paladai, nipple shield, formula milk if top-up feeds are needed

ii. Crib or bassinet (bedding in with the mother has benefits over crib care)

Table 18.4. Warning Signs

Guidelines for when parents should call their infant's doctor
Significant changes in infant's usual patterns of behavior:
■ Increased sleepiness ■ Increased irritability ■ Poor feeding
Any of the following (IMNCI signs):
■ Breathing difficulty ■ Blueness around lips, mouth, or eyes ■ Fever (by rectal temperature) over 100.0°F or (under the arm) over 99.6°F or low temperature (rectal) under 97.0°F ■ Vomiting or diarrhea ■ Dry diaper for >12 hours ■ No bowel movement for >4 days ■ Black or bright red color in stool

IMNCI, integrated management of neonatal and childhood illness.

iii. Diapers
iv. Infant clothes
v. Thermometer (axillary or forehead for common use)

4. **Anticipatory guidance**
   a. Provide a realistic idea of what their home life will be like during the immediate and long-term period following discharge including the following:
      i. Anticipated and potential infant developmental or growth-related issues
      ii. Expected number and type of physician visits for routine infant health maintenance and illness
   b. Families must be taught how to cope with and soothe their crying infant.
   c. Families may also be given anticipatory guidance related to potential parental mental health issues such as 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 nearest hospital and primary care physician (pediatrician). This will help optimize appropriate emergency response. Helping the family to prepare a succinct 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.
   b. Emergency management at home: Management of a life-threatening emergency associated with equipment malfunction, instruction on emergency procedures (e.g., CPR), and a list of relevant individuals or organizations to call with questions and concerns
   c. Home nursing care

In India, in the absence of a state-operated network of nurse practitioners, the parents must be guided to a primary care physician (preferably a pediatrician) who is available within 10 minutes from home.

D. Family assessment. Family assessment is a key component of a successful discharge process. It should address the following questions:

1. Who will be the primary caregiver(s) for the infant?
2. What is the family structure? Do they have a support system? Does one need to be developed or strengthened?
3. What are the financial concerns? Will the family's income change? If so, what resources are available to compensate?
4. How is the family coping—well adjusted/too anxious/needs to be appraised of the seriousness of special health care needs? Information should be shared understanding this aspect.
5. What are the actual and perceived complexities of the skills required to care for the infant?
6. How do they learn best? The nursing team should maximize the use of educational tools, written materials, visual props, and demonstrations.
7. How do previous or present experiences with the infant's care affect the family's ability to oversee care after discharge?
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. 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.

E. Discharge summary

1. 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.
2. Discharge summary suggested content (Table 18.5)
   - **a.** The pertinent maternal history
   - **b.** Infant's birth history (need for resuscitation)
   - **c.** NICU medical course synopsis
   - **d.** Infant's discharge diagnoses
   - **e.** Infant's condition at discharge
   - **f.** Prognosis if guarded
   - **g.** Home feeding plan
   - **h.** Discharge medications, dosage start and stop dates, and intervals
   - **i.** Medical equipment needs (e.g., oxygen, gastrostomy tube)
   - **j.** Follow-up appointments that were either arranged prior to discharge or recommended but not yet arranged
   - **k.** Newborn hearing screen, ROP results, and follow-up appointments

Table 18.5. Sample Neonatal Intensive Care Unit (NICU) Discharge/Interim Summary Dictation Guideline/Discharge Summary Content

1. Name of attending consultant(s)
2. Service ("Neonatology")
3. Patient's name as it appears in the hospital records
4. Patient's medical record number
5. Date of birth
6. Date of admission
7. Date of discharge
8. Birth gestation/birth weight/gender
9. History
   a. Maternal history including prenatal labs, pregnancy, labor, and birth history
   b. Reason for admission
10. Physical examination at discharge including weight, head circumference, and length with percentiles plotted serially from birth on special growth charts
11. 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. Echo/ECG reports.
    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, transfusion summary, most recent hemoglobin
    f. *Infectious disease:* Sepsis screen reports, cultures, antibiotic courses
    g. *Neurology:* Neurobehavior assessment (HNNE), describe findings on head imaging.
    h. *Psychosocial:* Relevant observations of family coping and psychosocial needs
    i. *Sensory*
       i. *Audiology:* "Hearing screening results." *(If did not pass, indicate date/place of follow-up test. If not done, schedule test date.)*
       ii. *Ophthalmology*
    a. Indicate if infant has not yet been examined but does require exam.
    b. If ROP was ever detected, include maximum stage of ROP and date of that exam.
    c. For all, include date and results of last exam.
    d. If not mature, state date and time of scheduled appointment.
    e. If mature, state time frame for routine follow-up.
12. Newborn screening (metabolic disorders), hemoglobin, phosphorus, alkaline phosphatase
13. Condition at discharge (e.g., "stable") including prognosis if guarded
14. Discharge disposition (e.g., "home," "chronic care")
15. Name of primary pediatrician. Phone no.
16. Care/recommendations
    a. Feeds at discharge including volume, caloric density, and frequency
    b. Medications including each medication's dose, route, frequency
    c. Medical equipment and supply needs
    d. Immunizations received including dates
    e. Follow-up appointments scheduled/recommended
17. Discharge diagnoses list
18. Emergency contact number

CPAP, continuous positive airway pressure; ECG, electrocardiogram; echo, echocardiogram; GI, gastrointestinal; Hct, hematocrit; HNNE, Hammersmith Neonatal Neurological Examination; ROP, retinopathy of prematurity

l. Imaging details (e.g., cranial ultrasound findings and next due date, MRI brain, echocardiogram [echo])

m. Any immunizations administered

n. Any pending test or lab results

o. Referrals made to community service programs (e.g., early intervention services)

F. Early intervention

1. Early intervention programs such as the District Early Intervention Centre offer multidisciplinary services for children.

2. They provide multidisciplinary services including physical therapy, occupational therapy, and speech and feeding therapy.

IV. 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.

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 place for parents to room in. Both options can offer more opportunities for families to be together to participate in care and have more time to learn.

B. If the child requires intensive care support beyond 44 weeks of corrected gestation age, then transferring to a pediatric intensive care unit (pediatric intensive care unit/ward)/ward may be the preferred option.

Suggested Readings

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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, incorporating the most current medical evidence along with parental values and perspectives.
- Good ethics begin with good facts. Take time to accumulate the relevant data and consult the relevant subject expert.
- Parental authority may be challenged when parental medical decisions clearly oppose their child's best interests.
- Withholding and withdrawing life-sustaining interventions are morally equivalent and ethically acceptable in certain situations in the neonatal intensive care unit (NICU), 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 instituting, withholding, or withdrawing life-sustaining therapy in patients with irreversible or terminal conditions such as extreme immaturity, severe hypoxic-ischemic encephalopathy, certain congenital anomalies, or other conditions that are refractory to the best available treatments.

A. The **ethical principles** that must be considered in the decision-making process in the neonatal intensive care unit (NICU) care include beneficence, nonmaleficence, respect for autonomy, justice, and other principles and ethical frameworks associated with the physician–patient relationship, such as narrative ethics, feminist ethics, or care ethics. Other principles that must be considered include the following:

1. Treatment decisions must be based on the infant's best interests, free from considerations of race, ethnicity, ability to pay, 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 with 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.
3. The physician 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 physician to involve the court system when he or she perceives that the infant's interests are inappropriately threatened by the parents' decision (Fig. 19.1).

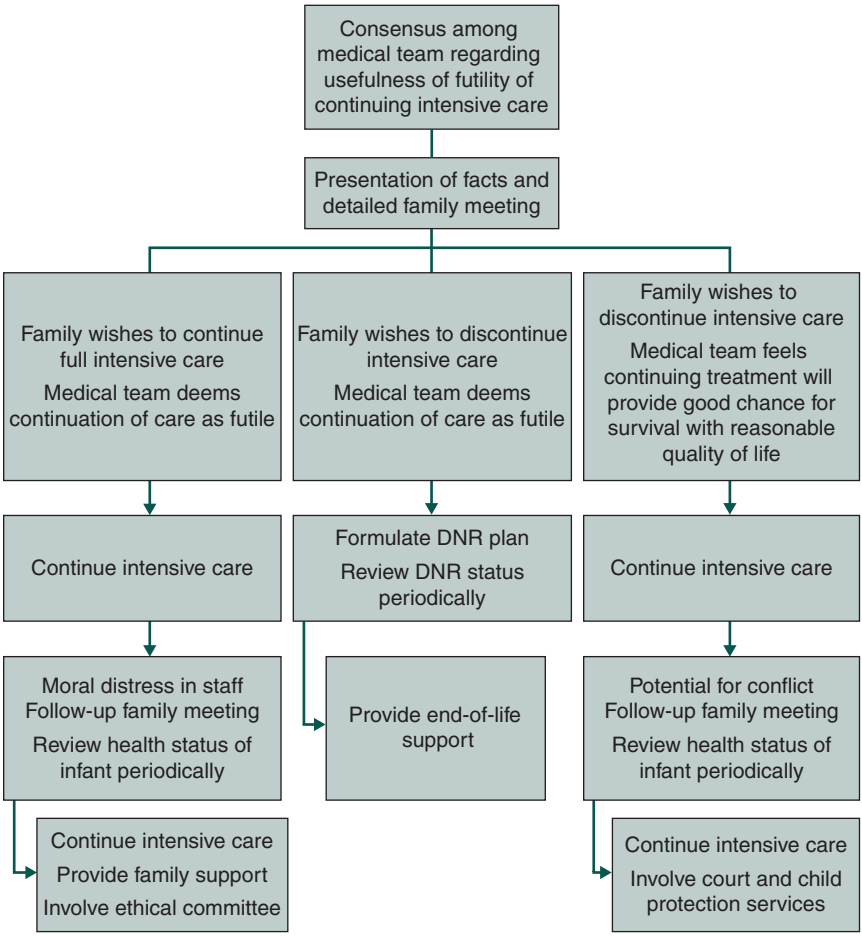

Figure 19.1. Role of parents and physicians in conflict resolution.

B. There is considerable debate on how to define the "best interests" of the infant. 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). 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 adequate 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" embraced the concept of parental permission. In India, section 89 of the Indian Penal Code permits consent of parent or legal guardian for a child younger than 12 years. Parental permission, such as 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. It differs from informed consent for adults 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.

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 ethical knowledge and values at a time and place separate from a specific patient. Ideally, this preparation will ease the stress when an actual decision needs to be made.

A. Develop an educational program to prepare NICU caregivers to address difficult decisions regarding patient care. Focus on the process (who, when, where) as well as on the substance (how). Identifying areas of frequent consensus and disagreement within a NICU and outlining a general approach to those situations can provide helpful guidance. The educational program 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.

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 decision making should be explored with them in open and honest discussions. The ethical and legal presumption is that they will make decisions that are in the best interests of their child (best interest standard) and within the context of accepted legal and social boundaries. If the health care providers believe that the parental choice is not in the child's best interest, then they have an obligation as the infant advocate to override the parental decision. 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. 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.

E. Identify available resources. Determine the roles of social service, chaplain, hospital attorney, 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 above. 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.

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. 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. Current technology allows some of these infants to survive but with a great risk of substantial neurodevelopmental impairment. Parents may ask that neonatologists pursue aggressive therapies despite poor prognoses. Neonatologists are concerned that instituting those therapies may not be the most appropriate course of action. 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. 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 the outcome. In making these decisions and recommendations, clinicians should take into account the specifics of each pregnancy as well as the local outcomes data (see National Institute of Child Health and Human Development perinatal outcome calculator: http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm). In India, the threshold of viability has not been defined by national law/national organizations; decisions must be guided based on local resources and data; family must be given a choice to choose referral to another unit, if their outcomes are better.

IV. 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 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 futile. In India, in 2017, the Indian Academy of Pediatrics (IAP) formulated guidelines on do not resuscitate (DNR) and end-of-life care. In addition to the key areas mentioned by the AAP, their recommendations include the following: (i) DNR or end-of-life care should not be initiated till consensus is achieved between the health care team and the family members (next of kin); (ii) treating doctors should have all the facts of the case including investigations available with them before discussion; (iii) DNR orders should be reviewed in the event of unexpected improvement or on request of next of kin; and (iv) DNR orders remain valid during transport.

One model to consider emphasizes an objective, interdisciplinary approach to determine the best course of action.

A. The goal of the process is to 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. Shared decision making should be guided by evidence. Caregivers should explore every reasonable avenue to maximize best evidence 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.

C. 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.

D. 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.

E. 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 parents and staff should not feel remorse in withdrawing those treatments if they no longer, or never did, improve the infant's condition and therefore serve his or her best interests. 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 on Medical Ethics argues that withdrawal of life-sustaining treatment after having shown no efficacy may be more justifiable than presuming futility and thus withholding treatment. 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 and Neglect 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. 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. In Asia, many countries have not addressed specific situations where medical treatment is considered futile. However, care is guided by moral principles similar to those described in the AAP statement with adaptation to social norms and cultural practices. Substantial conflict can arise if the caregivers and parents disagree about the goals of care. Health care professionals could experience moral distress when, due to demands of family, they provide infants with continued intensive care that they feel is not beneficial. The NICU team must be prepared to anticipate and deal with these circumstances in a timely manner.

F. 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. It can often ease tensions between parents and caregivers, allowing for a resolution to the dilemma.

Suggested Readings

Amendments to Child Abuse Prevention and Treatment Act (CAPTA), 42 USC §5101; 1984.

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20 Management of Neonatal End-of-Life Care and Bereavement Follow-Up

Caryn E. Douma and Patrick Jones

KEY POINTS

- Neonatal deaths are more common than in any other time in childhood; some follow a decision to withdraw life-sustaining treatment.
- 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. Providing compassionate, family-centered, end-of-life care in the neonatal intensive care unit (NICU) environment is challenging for caregivers. The care team must balance the medical needs of the infant with those of the parents and family. Parents are profoundly affected by the compassion and treatment they receive from health care providers during end-of-life care. 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 effectively cope with their loss.

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 NICU. Perinatal hospice 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.

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 intensive care unit. 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 families

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 obstetric care team and other consultants when appropriate.

c. Encourage sibling visitation and extended family support.

d. Encourage incorporation of cultural and spiritual customs.

e. Provide an environment that allows parents to develop a relationship with their infant, visiting and holding as often as medically appropriate.

2. Parents want to be given information in a clear, concise manner and value honesty and transparency.

3. 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.

4. Most neonatal deaths occur following a decision to remove life-sustaining treatment.

5. 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 goals of care and identify the needs of the patient and family.

6. Address conflicts within the team early in the process, utilizing available professional supports, such as ethical or spiritual consultants.

7. It is essential for the team to reach agreement prior to meeting with the family.

8. One spokesperson (usually the attending physician) is recommended to maintain the continuity of communication.

In a multicultural, multireligious environment, it is important for the health care team to have an understanding of the various processes that relate to events around deaths. Some believe that there will be rebirth while others

may not. In Hinduism, infants are buried unlike adults who are cremated and even these practices may vary across regions. It is essential that health care staff be aware of these concepts and beliefs to ensure that feelings are not hurt inadvertently.

B. Patient- and family-centered decision making

1. 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. In Asian countries, especially in rural settings, decisions are often made by the extended family such as elder brother or grandfather and sometimes in tribal settings by village chiefs. The medical team must ensure that all relevant stakeholders are involved in decision making with the consent of parents.
2. The parents need to feel supported regardless of the decision that is made.
3. 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.
4. Shared decision making involves the support and participation of the entire team.
5. 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 support will be withdrawn and determine their desired level of participation.

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 and private, and will accommodate everyone the family wishes to include.
2. Staffing should be arranged so that one nurse and one physician will be readily available to the family at all times.
3. Allow parents ample time to create memories and become a family. Allow them to hold, photograph, bathe, and dress their infant before, during, or after withdrawing mechanical ventilation or other life support.
4. Discuss the entire process with parents, including endotracheal tube removal and pain 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 baptism and spiritual support if desired; incorporate spiritual and cultural customs into the plan of care if desired. Many times, parent wish to have their spiritual guru pay a visit to the newborn either in person or via digital means. Often prayers may be recited, and imagery of family gods be placed in the neonatal bed and holy water sprinkled. Allowance needs to be made for these practices as they help the grieving process for 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 relaxation before extubation. The goal of medication use should be to ensure that the infant is as comfortable as possible.
7. When the infant is extubated, discontinue all unnecessary intravenous catheters and equipment.
8. Allow parents to hold their infant for as long as they desire after withdrawing life support. The nurse and attending physician should be nearby to assist the family and assess heart rate 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. Autopsy should be discussed before or after death at the discretion of the attending physician.
11. 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. Parents often change their minds later and are grateful that these items have been retained.
12. 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 utilizes volunteer professional photographers and is available in many communities.
13. "Code Krishna" is a practice that has been initiated in rural Gujarat, India, and may be emulated as per local custom. In Code Krishna, the clinical team shows its respect to the departed soul in the intensive care unit after death has occurred. The ICU team and patient's relatives offer floral tributes, sing/play a prayer appropriate to the religious faith, and follow it up with meditative silence. Code Krishna ensures a calm silence space amidst the hustle of the ICU.

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 or cremation 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 or 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 the 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 ensure that 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 1-year 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.

Suggested Readings

Balaguer A, Martín-Ancel A, Ortigoza-Escobar D, et al. The model of palliative care in the perinatal setting: a review of the literature. *BMC Pediatr* 2012;12:25.

Koopmans L, Wilson T, Cacciatore J, et al. Support for mothers, fathers and families after perinatal death. *Cochrane Database Syst Rev* 2013;(6):CD000452.

Vaishnav B, Nimbalkar S, Desai S, Vaishnav S. *Code Krishna: an innovative practice respecting death, dying and beyond*. *Indian J Med Ethics* 2017;2(4):289–292.

Online Resources/Websites

British Association of Perinatal Medicine Working Group Report. *Palliative care (supportive and end of life care): a framework for clinical practice in perinatal medicine*. http://nebula.wsimg.com/c84cb7310f1d226b1072c40c0c7754ac?AccessKeyId=BE16207C-1CC3A18A9A3A&disposition=0&alloworigin=1. Accessed August 1, 2015.

Gundersen Health System. *Resolve through sharing: bereavement services home*. http://www.gundersenhealth.org/resolve-through-sharing. Accessed August 1, 2015.

Texas Pediatric Society. *Palliative care toolkit*. https://txpeds.org/palliative-care-toolkit. Accessed August 1, 2015.

21 Nutrition

Diane M. Anderson, Brenda B. Poindexter, and Camilia R. Martin

KEY POINTS

- Optimal nutrition is essential for physiological accretion of preterm babies.
- Early nutrition influences childhood growth and neurodevelopment.
- Growth assessment is essential to ensure optimal nutrition.

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 an increased risk for nutritional compromise. These infants are born with limited nutrient accretion and reserves due to their shorter *in utero* life, have immature digestion and metabolic pathways, and have increased nutrient demands due to illnesses. In addition, medical and surgical conditions commonly associated with prematurity have the potential to alter nutrient requirements and complicate adequate nutrient delivery. Early enteral nutrition and parenteral nutrition (PN) 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 the gestational age at birth and birth weight.

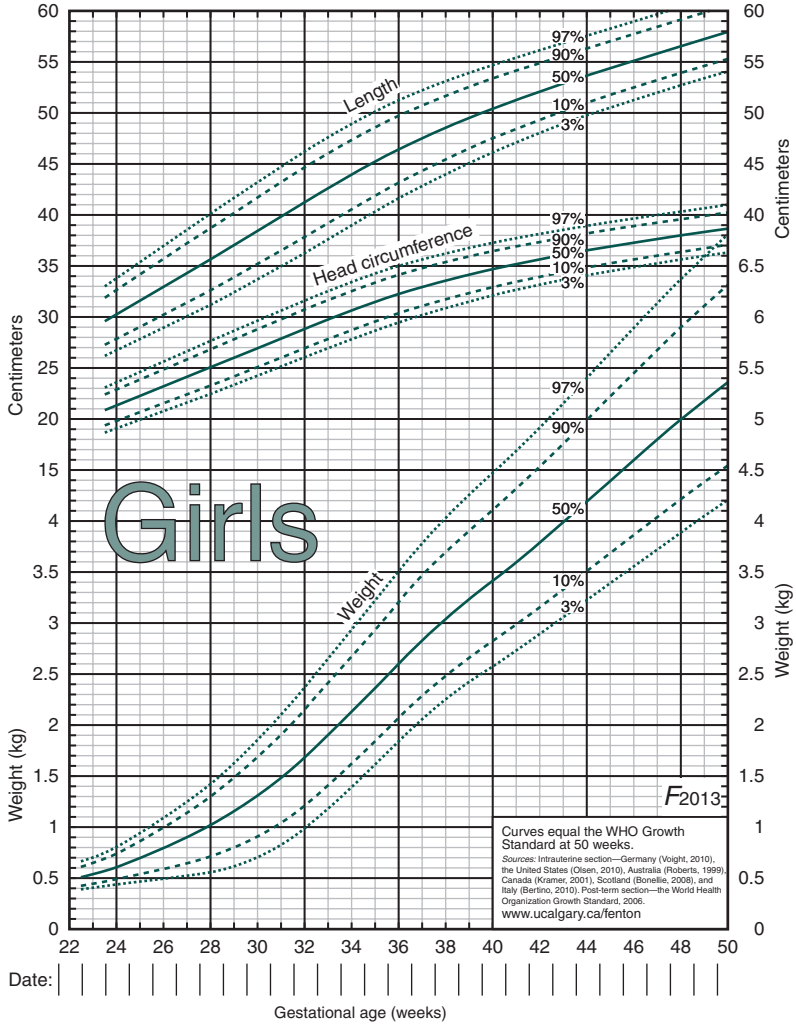
B. Postnatal growth varies from intrauterine growth in that it begins with a period of weight loss, primarily through the loss of extracellular fluid. The typical postnatal weight loss in the term infant is 5% to 10% of birth weight. Historically, in preterm infants, this postnatal weight loss can be as much as 15% of birth weight, with the nadir by 4 to 6 postnatal days and a regain to birth weight by 14 to

21 days. 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 facilitate regain of birth weight within 7 to 10 postnatal days.

C. After achieving birth weight, intrauterine growth and nutrient accretion rates are targeted. Goals for weight gain are 15 to 20 g/kg/day for infants <2 kg and 20 to 30 g/day for larger infants. Approximately 1 cm/week in length and 1 cm/week in head circumference are used as a goal for growth in these parameters. 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 and enteral nutrition.

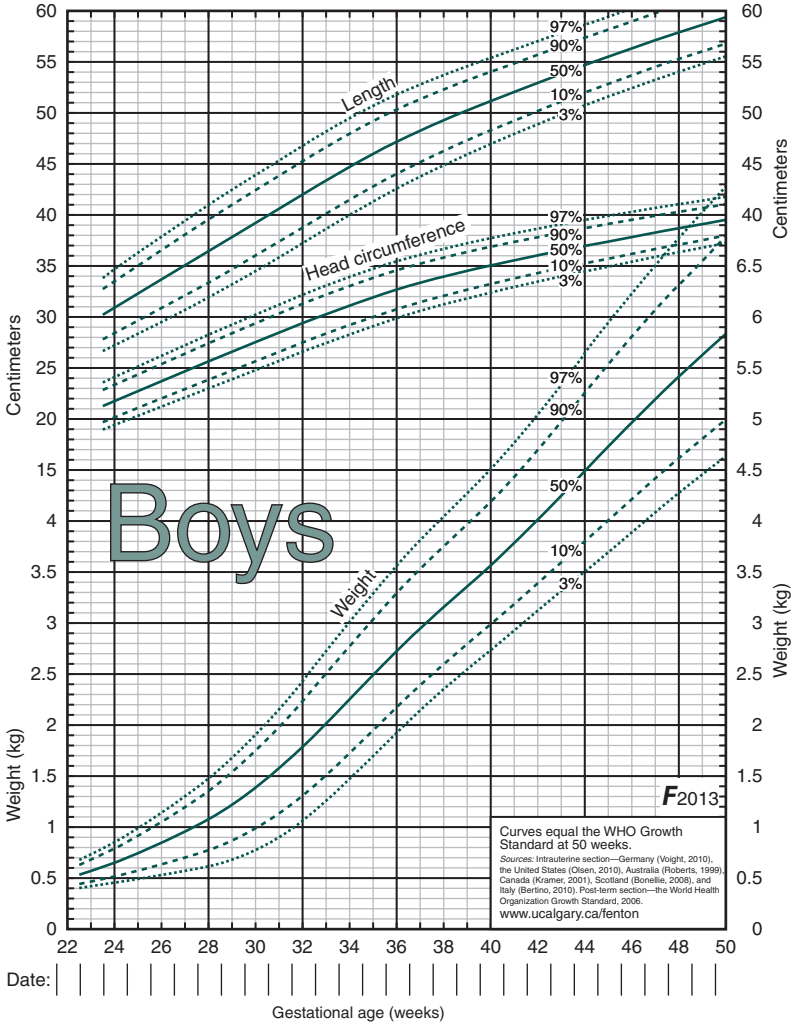
D. Serial measurements of weight, head circumference, and length plotted on growth curves provide valuable information in the nutritional assessment of the preterm infant. Gender-specific growth charts are available based on intrauterine growth curves for weights, lengths, and head circumferences. The revised Fenton growth charts combine intrauterine growth chart 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 (Fig. 21.1A and B). The Olsen growth curves are drawn from a large, contemporary, racially diverse U.S. sample (Fig. 21.2A–D). Infants can be plotted from 23 to 42 weeks' PMA on gender-specific weight, length, and head circumference curves. Olsen growth curves are good to determine whether the baby is born large for gestational age (LGA), appropriate for gestational age (AGA), or small for gestational age (SGA). Postnatal growth curves follow the same infants over time (i.e., longitudinal growth curves) and are available from the National Institute of Child Health and Human Development (NICHD) multicenter study (2000). These curves, however, show *actual*, not ideal, growth. The INTERGROWTH-21 postnatal growth standards are specifically constructed for monitoring the postnatal growth of preterm infants. The data were derived from preterm infants from early pregnancy to 2 years of age, who were assessed by serial ultrasound scan in a longitudinal study, and were selected because they were at low risk of adverse clinical outcomes and had no evidence of intrauterine growth restriction. Intrauterine growth remains the gold standard for comparison. Postnatal growth chart is preferred because it is a more realistic representation of the true postnatal growth and takes into consideration the initial weight loss in first 2 weeks.

E. After a preterm infant reaches full term (estimated term age [ETA]). The Centers for Disease Control and Prevention (CDC) recommends the WHO Child Growth Standards 2006 be used for monitoring of growth. Infants' growth should be plotted by age corrected for prematurity. The charts can be downloaded from http://www.cdc.gov/growthcharts/who_charts.htm.



A

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. (*Continued*)



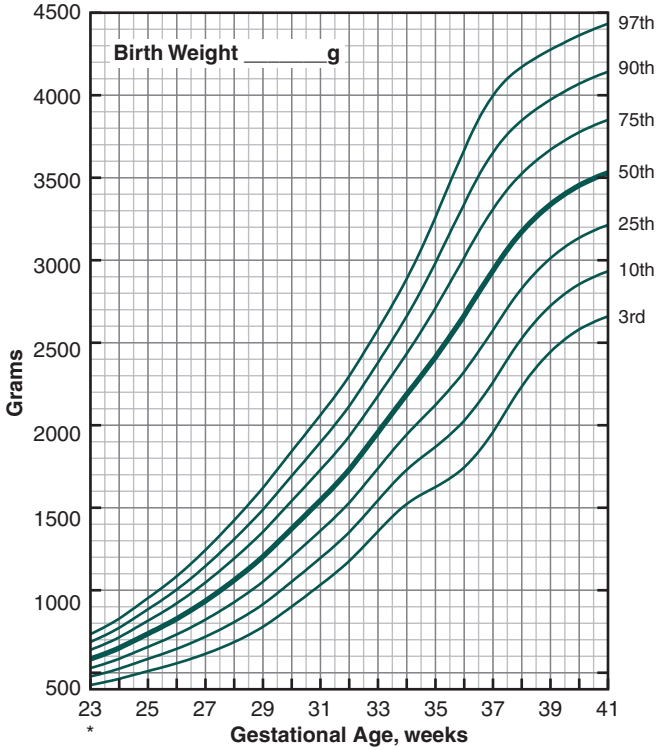
B

Figure 21.1. (*Continued*) **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.

A

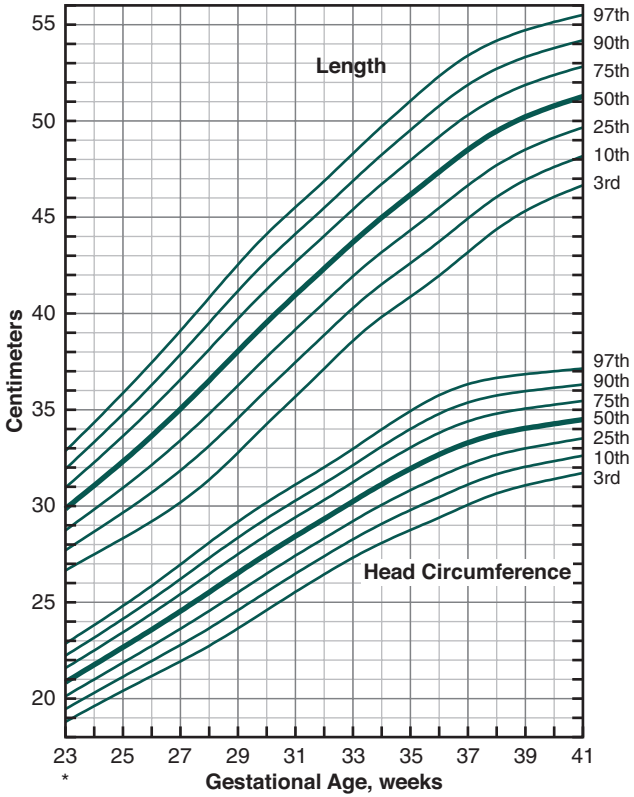
Figure 21.2. A: Olsen weight chart for girls. (Reproduced with permission from Olsen IE, Groveman S, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125: e214–e224. Copyright 2010 by the American Academy of Pediatrics. *Data source:* Pediatrix Medical Group.) (*Continued*)

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.

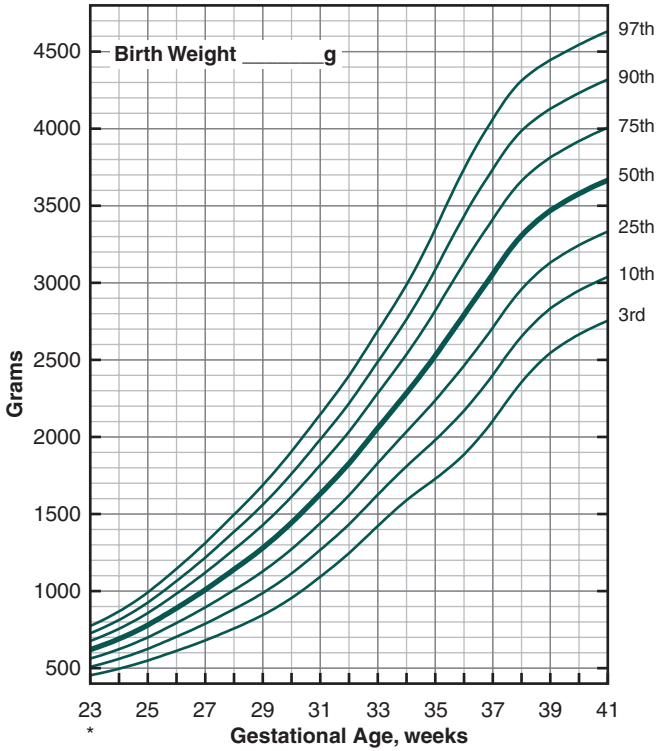
B

Figure 21.2. (*Continued*) **B:** Olsen length and head circumference chart for girls. (Reproduced with permission from Olsen IE, Groveman S, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125:e214–e224. Copyright 2010 by the American Academy of Pediatrics. *Data source:* Pediatrix Medical Group.) (*Continued*)

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.

C

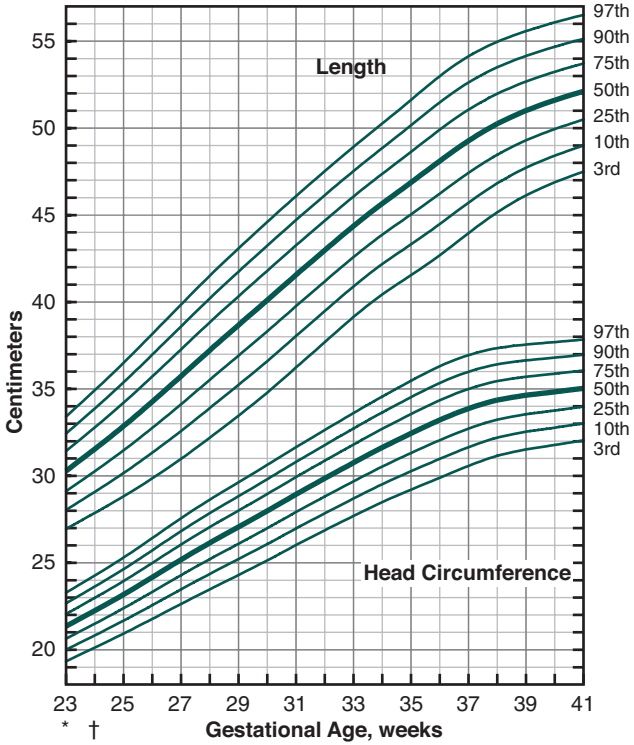
Figure 21.2. (*Continued*) **C:** Olsen weight chart for boys. (Reproduced with permission from Olsen IE, Groveman S, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125:e214–e224. Copyright 2010 by the American Academy of Pediatrics. *Data source:* Pediatrix Medical Group.) (*Continued*)

Page 2

Name _____

Record # _____

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.

D

Figure 21.2. (*Continued*) **D:** Olsen length and head circumference chart for boys. (Reproduced with permission from Olsen IE, Groveman S, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125:e214–e224. Copyright 2010 by the American Academy of Pediatrics. *Data source:* Pediatrix Medical Group.)

III. NUTRIENT RECOMMENDATIONS

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 the textbook *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines* (Table 21.1). These recommendations are based on (i) the intrauterine accretion rate data, (ii) the nutrient content of human milk (HM), (iii) the assumed decreased nutrient stores and higher nutritional needs in preterm infants, and (iv) the available data on biochemical measures reflecting adequate intake. However, due to the limitations of the currently available data, the goals for nutrient intake for preterm infants are considered to be recommendations only.

Table 21.1. Comparison of Enteral Intake Recommendations for Preterm and Nutrients in Mature Human Milk.

Nutrient	Unit	Enteral Intake Recommendations for Preterm Infants[†]	Mature Human Milk[‡]
Protein[‡]	g/kg/day	3.5–4.5	1.4
Carbohydrate	g/kg/day	10–14	12
Fat	g/kg/day	5–7	5.3
Docosahexaenoic acid	mg/kg/day	18–60	
Arachidonic acid	mg/kg/day	18–45	
Vitamin A	IU/kg/day	400–1,500	240
Vitamin D	IU/day	200–400[§]	2
Vitamin E	IU/kg/day	2.2–12	0.9
Vitamin K	μg/kg/day	4.4–28	0.4
Thiamine	μg/kg/day	140–300	30
Riboflavin	μg/kg/day	200–400	75
Vitamin B_6	μg/kg/day	50–300	30
Vitamin B_{12}	μg/kg/day	0.1–0.8	0.11
Niacin	mg/kg/day	1–5.5	0.6
Folate	μg/kg/day	25–100	16.5
Pantothenic acid	mg/kg/day	1.2–1.7	0.34

(*Continued*)

Table 21.1. Comparison of Enteral Intake Recommendations for Preterm and Nutrients in Mature Human Milk. *(continued)*

Nutrient	Unit	Enteral Intake Recommendations for Preterm Infants†	Mature Human Milk‡
Biotin	µg/kg/day	3.6–6	1.1
Vitamin C	mg/kg/day	18–25	15
Choline	mg/kg/day	8–35	
Inositol	mg/kg/day	4.4–81	
Taurine	mg/kg/day	4.5–9	
Carnitine	mg/kg/day	~2.9	
Calcium	mg/kg/day	100–220	35
Phosphorus	mg/kg/day	60–140	20
Magnesium	mg/kg/day	7.9–15	5
Iron	mg/kg/day	2–4	0.09
Zinc	µg/kg/day	1,000–3,000	300
Manganese	µg/kg/day	0.7–7.5	0.5
Copper	µg/kg/day	120–230	45
Iodine	µg/kg/day	10–60	23
Selenium	µg/kg/day	1.3–10	3
Sodium	mEq/kg/day	3–5	1.2
Potassium	mEq/kg/day	2–5	1.8
Chloride	mEq/kg/day	3–7	1.8

*Calculated intakes of human milk feedings and formulas are based on an intake of 150 mL/kg/day.
†The American Academy of Pediatrics suggests that the estimated requirements based on the fetal accretion rate of protein are 3.5 to 4 g/kg/day. The current recommendations from Koletzko et al. and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee are 3.5 to 4.5 g/kg/day to provide catch-up growth for extremely low-birth-weight infants.
‡Denotes mature milk post 2 weeks of lactation of mothers who deliver term infants.
§Aim for 400 IU/day.
HMF, human milk fortifier.

B. Fluid (see Chapter 23). The initial step in nutritional support is to determine an infant's fluid requirement, which is dependent on the gestational age, postnatal age, and environmental conditions. Generally, baseline fluid needs are inversely related to the 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

Table 21.2. 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: American Academy of Pediatrics Committee on Nutrition. *Pediatric Nutrition Handbook*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014.

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. Conversely, restriction of fluid intake is often utilized for the prevention and/or treatment of patent ductus arteriosus, renal insufficiency, and bronchopulmonary dysplasia (BPD). Fluid requirements in the first few postnatal weeks are, therefore, continually reassessed.

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 21.2). The three sources, the AAP, the ESPGHAN-CON, and Koletzko et al., recommend a range of 105 to 135 kcal/kg/day, after the initial days of acute illness is over, and growth starts. Infants with severe and/or prolonged illness frequently require a little more, range of 130 to 150 kcal/kg/day. Lesser intakes (85 to 100 kcal/kg/day) may sustain intrauterine growth rates, when PN is used.

IV. PARENTERAL NUTRITION

A. Nutrient goals. The goal of PN in the initial days is to provide adequate calories and amino acids to prevent negative energy and nitrogen balance. Goals thereafter include the promotion of appropriate weight gain and growth while awaiting the attainment of adequate enteral intake.

B. Indications for initiating parenteral nutrition. PN is started on the first postnatal day (within hours of birth) for infants who are <1,500 g birth weight and/or <31 weeks' gestational age. PN is important for term and preterm babies with

congenital/acquired gut disorder or critical illness when significant enteral feeding is not possible for 3 to 5 days.

C. Peripheral versus central parenteral nutrition

1. Parenteral solutions may be infused through a peripheral or central vein. Historically, the AAP has recommended that peripheral solutions maintain an osmolarity between 300 and 900 mOsm/L. Because of this limitation, peripheral solutions often cannot adequately support growth in extremely low-birth-weight (ELBW) infants. Central PN not only allows for the use of more hypertonic solutions but also incurs greater risks, particularly catheter-related sepsis. Umbilical venous catheters are commonly used for parenteral administration.
2. Central PN is considered to be warranted under the following conditions:
   a. Nutritional needs exceed the capabilities of peripheral PN.
   b. An extended period (e.g., >7 days) of inability to take enteral feedings, such as in infants with necrotizing enterocolitis (NEC) and in some postoperative infants
   c. Imminent lack of peripheral venous access
3. Peripheral PN is considered only in the following situations:
   a. While waiting for central venous access, to avoid delay in starting PN
   b. Inability to establish central venous access

D. Carbohydrate. Dextrose (D-glucose) is the carbohydrate source in intravenous (IV) solutions (see Chapter 24).

1. The caloric value of dextrose is 3.4 kcal/g.
2. 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 infused through central venous catheters. Infants with renal failure and those receiving extracorporeal membrane oxygenation (ECMO) therapy may require as high as 50% dextrose due to fluid restriction. The use of ultrafiltration with ECMO allows for an increase in fluid administration and a decrease in dextrose to 25% to meet the infant's glucose needs.
3. Dextrose infusions are typically referred to in terms of the milligrams of glucose per kilogram per minute delivered, which expresses the total glucose load and accounts for infusion rate, dextrose concentration, and the patient's weight (Fig. 21.3).
4. 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.
5. Preterm infants usually require higher rates of glucose because they have a higher brain-to-body weight ratio and higher total energy needs. Initial infusion rates of 4 to 8 mg/kg/minute may be required to maintain euglycemia.
6. Initial rates may be advanced, as tolerated, by 1 to 2 mg/kg/minute daily to a goal of 11 to 12 mg/kg/minute (to achieve higher calorie needs). This may be accomplished by increasing dextrose concentration, by increasing infusion

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. (From Chowning R, Adamkin DH. Table to quickly calculate glucose infusion rates in neonates. *J Perinatol* 2015;35:463.)

rate, or by a combination of both. Infusion rates above 11 to 12 mg/kg/minute are generally not recommended

7. The quantity of dextrose that an infant can tolerate will vary with the gestational and postnatal age. Signs of glucose intolerance include hyperglycemia and secondary glucosuria with osmotic diuresis.

E. Protein. Crystalline amino acid solutions provide the nitrogen source in PN.

1. The caloric value of amino acids is 4 kcal/g.
2. Aminoven Infant (Fresenius Kabi) is available in Asian subcontinent. In theory, these products are better adapted to the needs of newborns than are 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.
3. 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.
4. Infants with a birth weight <1,500 g are provided with 2 to 3 g/kg/day of amino acids shortly after birth.
5. Protein infusion rates are increased to a target of 3.5 to 4 g/kg/day

F. Lipid. The IV fat emulsion used in neonates is a soybean oil–based lipid emulsion with egg phospholipids (Intralipid 20). The soybean oil is a good source of essential fatty acids (EFAs; linoleic acid and linolenic acid) but it also contains phytosterols, which have been associated with the development of PN-associated cholestasis (PNAC). For preterm and term babies with PNAC, consider giving

composite lipid emulsion rather than pure soy-based lipid emulsion. SMOF lipid 20% (Fresenius Kabi), a combination of soy, medium-chain triglycerides (MCTs), and olive and fish oils (Omegaven), has been tried, but there is no definite decrease in PNAC. SMOF has replaced Intralipid in India.

1. The caloric value of 20% lipid emulsions is 2 kcal/mL (~10 kcal/g). The use of 20% emulsions is preferred over that of 10% emulsions because the higher ratio of phospholipids to triglyceride (TG) in the 10% emulsion interferes with plasma TG clearance. Twenty percent emulsions also provide a more concentrated source of calories. For these reasons, only 20% lipid emulsions are used.
2. Current data suggest that preterm infants are at risk for EFA deficiency that is evident within 72 hours after birth, if an exogenous fat source is not delivered. This deficiency state can be avoided by the administration of lipid emulsion, starting from the first day.
3. The optimal initiation and advancement rates for lipid emulsions have not been well studied and have not been defined. A recent recommendation suggests that lipid be given at 1 to 2 g/kg/day during the first 4 days of life and then increased by 0.5 to 1 g/kg/day to a maintenance range of 3 to 4 g/kg/day.
4. Decreased tolerance to IV lipids is frequently seen in infants <1,000 g birth weight, <27 weeks' gestation, with intrauterine growth restriction, and with sepsis. IV lipids may need to be advanced more slowly for these infants. Monitoring of blood TGs may be considered; however, the acceptable range of TG levels balancing safety and nutritional needs for preterm infants has not been determined.
5. No benefit has been found, in the practice of giving a rest period of 4 hours, by withholding the lipid infusion. Therefore, lipid emulsions are infused over 24 hours for optimal clearance.

G. Electrolytes

1. Electrolytes are not added to PN during the first 2 to 3 days of life, as there are negligible renal losses; adding early sodium is associated with BPD and early potassium with hyperkalemia. Sodium is started after serum sodium falls to 130 and potassium is started after serum potassium falls to 4, and urine output is established.
2. 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.

H. Vitamins. The current pediatric vitamin formulations do not maintain blood levels of all vitamins within an acceptable range for preterm infants. Suggested vitamin intake recommendations are listed in Table 21.3. However, there are no products currently available that are specifically designed for preterm infants. Vitamin A is the most difficult to provide in adequate amounts to the VLBW infant, without providing excess amounts of the other vitamins. Vitamin A is subject to losses through photodegradation and absorption to plastic tubing and solution-containing bags. B vitamins may also 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. No pediatric vitamin is available in India. Adult multivitamin (MVI) dose of 0.5 to 1 mL/kg is used.

Table 21.3. Suggested Intakes of Parenteral Vitamins in Infants

Vitamins	Estimated Needs	
	Term Infants (≥2.5 kg) (dose/day)	Preterm Infants (≤2.5 kg) (dose/kg)*
Lipid soluble		
A (μg)†	700	280
D (IU)†	400	160
E (mg)†	7	2.8
K (μg)	200	80
Water soluble		
Thiamine (mg)	1.2	0.48
Riboflavin (mg)	1.4	0.56
Niacin (mg)	17	6.8
Pantothenate (mg)	5	2
Pyridoxine (mg)	1	0.4
Biotin (μg)	20	8
Vitamin B_{12} (μg)	1	0.4
Ascorbic acid (mg)	80	32
Folic acid (μg)	140	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.

I. Minerals. The amount of calcium and phosphorus that can be administered through IV is limited by the precipitation of calcium phosphate. 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.

Calcium-to-phosphorus ratios of approximately 1.3:1 to 1.7:1 by weight (1:1 to 1.3:1 M) are suggested. However, despite efforts to optimize mineral intake, preterm infants receiving prolonged PN remain at an increased risk for metabolic bone disease (see Chapter 59).

J. Trace elements

1. 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.

2. As copper and manganese are excreted in bile, these trace elements are routinely reduced or omitted if impaired biliary excretion and/or cholestatic liver disease is present. Trace minerals may be provided on Monday, Wednesday, and Friday to limit intakes of these nutrients. Zinc may be provided as a separate supplement on the remaining days.
3. Infants with ostomy outputs lose excessive zinc and copper. Additional supplementation may be indicated.

K. Other additives

1. **Carnitine** facilitates the transport of long-chain fatty acids into the mitochondria for oxidation. However, this nutrient is not routinely added to PN solutions. 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 HM and/or carnitine-containing infant formula. 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.
2. **Cysteine** is not a component of current crystalline amino acid solutions because it is unstable over time and will form a precipitate. It is ordinarily synthesized from methionine and provides a substrate for taurine. However, this may be considered an essential amino acid for preterm infants due to low activity of the enzyme hepatic cystathionase, which converts methionine to cysteine. 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.
3. **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 acid solutions. Studies to date have not proven its addition to PN as helpful for the neonate.
4. **Insulin** is not routinely added to PN. Its use must be weighed against the risk of wide swings in blood glucose levels as well as the concerns surrounding the overall effects of the increased uptake of glucose. When hyperglycemia is severe or persistent, an insulin infusion may be useful (see Chapter 24).
5. **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. Studies have suggested that vitamin A supplementation can reduce the risk of BPD. In some units, infants weighing <1,000 g at birth are supplemented with 5,000 IU vitamin A intramuscularly three times per week for the first 4 postnatal weeks, beginning in the first 72 hours (see Chapter 34).

L. Metabolic monitoring for infants receiving PN. Infants receiving PN are typically monitored according to the schedule indicated in Table 21.4.

Table 21.4. Schedule for Nutrition Laboratory Monitoring

	Parenteral Nutrition	Enteral Nutrition
Electrolytes	Daily, till 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 aminotransferase (ALT), direct bilirubin	After 14 days of PN and as clinically indicated	Not indicated

PN, parenteral nutrition.

M. Potential complications associated with PN

1. **Cholestasis** may be seen and is more often transient than progressive. Risk factors include the duration of PN and more so the duration of fasting (lack of enteral feeding also produces bile inspissation and cholestasis). Recommended prevention is to avoid fasting; even minimal enteral feedings may stimulate bile secretion. Omegaven made from fish oil and SMOF have been evaluated for PNAC. However, the meta-analysis did not find any benefit. It is important to screen neonates for other causes of cholestasis. Send urine culture, thyroid function test, and transaminase level initially. Evaluate as per neonatal cholestasis protocol.
2. **Metabolic bone disease** (see Chapter 59). 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.
3. **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.
4. **Metabolic abnormalities related to lipid emulsions**
   a. **Hyperlipidemia/hypertriglyceridemia.** The incidence tends to be inversely related to the gestational age at birth and postnatal age. A short-term decrease in the lipid infusion rate usually is sufficient to normalize

serum lipid levels. The AAP suggests serum TG concentrations be maintained below 200 mg/dL.

b. Indirect hyperbilirubinemia. Because free fatty acids can theoretically displace bilirubin from albumin-binding sites, the use of lipid emulsions during periods of severe hyperbilirubinemia has been questioned. Research, however, suggests that infusion of lipid, at rates up to 3 g/kg/day, is unlikely to displace bilirubin. However, during periods of extreme hyperbilirubinemia (e.g., requiring exchange transfusion), rates <3 g/kg/day are typically provided.

c. Sepsis has been associated with decreased lipoprotein lipase activity and impaired TG clearance. Therefore, during a sepsis episode, it may be necessary to temporarily reduce and/or limit the lipid infusion to avoid hypertriglyceridemia.

d. Due to the concern about toxic products of lipid peroxidation, protecting lipid emulsions from both ambient and phototherapy lights may also be considered.

V. ENTERAL NUTRITION

A. Early enteral feeding

1. The structural and functional integrity of the gastrointestinal (GI) 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 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 non-nutritive use of very small volumes of HM or formula, for the intended purpose of preservation of gut maturation rather than nutrient delivery. Definitive conclusions cannot be drawn as to what constitutes the optimal volume for minimal enteral nutrition.

2. Benefits associated with minimal enteral nutrition include the following:

a. Improved levels of gut hormones

b. Less feeding intolerance

c. Earlier progression to full enteral feedings

d. Improved weight gain

e. Improved calcium and phosphorus retention

f. Fewer days on PN

3. The following are guidelines for the use of gut priming in preterm infants:

a. Begin as soon after birth as possible, ideally by postnatal day 1 itself. A standardized feeding protocol will help to accomplish this goal.

b. 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 4 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 infants <1,250 g birth weight).

c. 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.

d. 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.

B. Strategies to improve HM availability in NICU

1. Counseling regarding benefits of breast milk. There should be a provision of scientific information to mothers explaining the importance and benefit of HM. Monitoring HM volume and setting goals can serve as positive stimuli.

2. Free availability of breast pump (BP) in unit and personal electric BP

3. Access to NICU-specific lactation support to ensure support to tackle worries related to inadequate milk supply, difficulties in expressing, and early initiation of expression of milk

4. The mother should be allowed to visit her newborn baby as often as she can, and kangaroo mother care should be encouraged.

5. Family-centered care significantly improves the breastfeeding rate.

6. Galactagogues such as domperidone may be used at 1 to 2 weeks of life, if above-mentioned measures do not improve breast milk output.

C. Fortification of human milk. Fortified HM allows benefits of mother's own milk and opportunity to bridge the gaps in nutrients—such as proteins, calories, sodium, calcium, phosphorus, and iron—and vitamins such as A and D. The use of HM offers many nutritional and non-nutritional 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.

1. Preterm HM does contain higher amounts of protein, sodium, chloride, and magnesium than term milk. However, the levels of these nutrients remain below preterm requirements; also the higher content persists only for approximately the first 21 days of lactation.

2. For these reasons, HM for preterm infants is routinely supplemented with human milk fortifier (HMF). The use of HMF is recommended for infants <1,500 g birth weight and may also be considered for infants with birth weights up to 1,800 to 2,000 g and <34 weeks' gestation. Bovine milk–based HMF (powder and liquid) as well as human milk-based HMF (prepared from donor human milk) are available. Liquid HMF are not freely available in Asian subcontinent. Lactodex-HMF, HIJAM-HMF, and PreNAN HMF are bovine-based HMF and Neolact MMF and Neolact MMF plus are donor HM-based fortifiers available in India. All aseptic precautions have to be taken while adding powder to HM. The addition of bovine milk–based HMF to HM increases energy, protein, vitamin, and mineral contents to levels more appropriate for preterm infants. Iron supplementation is indicated for the low iron bovine milk–based HMF. The donor HM-based fortifier increases energy,

protein, and mineral intake. However, as vitamin content of the feeding is not appreciably increased with the use of this product, a multi-vitamin and iron supplement is typically administered daily.

3. Studies are ongoing to determine the optimal timing for introducing HMF; most units start adding HMF once the baby is on 100 mL/kg feeds (or earlier). The various fortification strategies include standard HM fortification and individualized fortification. In standard fortification, a fixed amount of fortifier is added to HM. This is the most common practice. The individualized fortification includes adjustable fortification and targeted fortification. In targeted fortification, more protein intake is added so as to maintain blood urea nitrogen in target range of 9 to 14 mg/dL. In adjustable fortification, HM is analyzed each day and the nutrients (fortifier) added planned accordingly. This process is labor intensive. Studies have shown better weight gain and head circumference with individualized fortification.

D. Donor human milk. When maternal milk is unavailable, PDHM may be offered to infants who are considered to be at the highest risk for feeding intolerance and NEC. Most typically, this includes ELBW newborns. 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 low in calories, babies demonstrate poor weight gain while on PDHM. If mother's own milk is not available, and the first week of life has passed (greatest risk of intolerance to formula), one must consider using a preterm formula.

E. Preterm formulas are designed to meet the nutritional and physiologic needs of preterm infants and have some common features:

1. Whey-predominant, taurine-supplemented protein source, which is better tolerated and produces a more normal plasma amino acid profile than casein-predominant protein
2. Carbohydrate mixtures of 40% to 50% lactose and 50% to 60% glucose polymers to compensate for preterm infants' relative lactase deficiency
3. Fat mixtures containing approximately 40% to 50% MCTs, to compensate for limited pancreatic lipase secretion and small bile acid pools, as well as 50% to 60% long-chain TGs to provide a source of EFAs
4. Higher concentrations of protein, vitamins, minerals, and electrolytes to meet the increased needs associated with rapid growth

F. Feeding advancement. When attempting to determine how best to advance a preterm infant to full enteral nutrition, there are very limited data to support any one method as optimal. The following guidelines reflect the current practice:

1. Meta-analyses of 10 randomized controlled trials (RCT) found that faster increments in enteral feeding at 30 to 35 mL/kg/day when compared to slower increments at 15 to 20 mL/kg/day did not show effects on the risk of NEC. The slower advancement group took longer time to regain birth weight and 1 to 5 days more to reach full enteral feeds. Enteral feeding can be safely advanced at the rate of 15 to 20 mL/kg/day in stable ELBW neonates and at 30 to 35 mL/kg/day in stable neonates >1,000 g or >28 weeks gestational age.
2. As enteral volumes are increased, the rate of any IV fluid is adjusted.

3. Even in preterm neonates with abnormal Dopplers (absent reverse end-diastolic flow [AREDF]), no difference in the incidence of NEC was found between early initiation of enteral feeding (24 to 48 hours of age) and late initiation (day 6).

G. Term formulas. The Infant Formula Act provides specific guidelines for the composition of infant formulas so that term infant formulas approximate term HM in general composition.

H. 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 21.5.

Table 21.5. Indications for Use of Specialized 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	Semielemental, 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	Semielemental 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	Semielemental 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 semielemental formula, if indicated	Impaired digestion

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

I. Caloric/energy-enhanced feedings. Many ill term and preterm infants require increased energy/nutrient intakes in order to achieve optimal rates of growth.

Many different strategies are currently utilized to maximize the energy content to achieve the recommended postnatal growth. Practice should be individualized to the infant, and the general goal is to maximize all macronutrients. Principles to guide increasing caloric/energy content of enteral feedings include the following:

a. HMF

i. Bovine milk–based HMF can provide additional 2 to 4 kcal/oz.

ii. For infants receiving a **liquid donor HM-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 HM cream supplement is available to increase the energy intake when protein needs have been met by the donor HM-based HMF.

b. 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.

c. Maximize total feed daily volume delivered as tolerated (180 mL/kg/day; some Indian studies have reported as high as 250 mL/kg/day).

d. The use of vegetable oils and powdered products should be avoided, if possible.

J. Feeding method. These should be individualized based on the gestational age, clinical condition, and feeding tolerance.

Nasogastric/orogastric feedings. Nasogastric tube feedings are preferred in some units because orogastric tubes tend to be more difficult to secure.

Indications for naso/orogastric feeding include

1. Infants <34 weeks' gestation, as most do not have the ability to coordinate suck–swallow–breathe patterns

2. Infants with impaired suck/swallow coordination due to conditions such as encephalopathy, hypotonia, and maxillofacial abnormalities

K. Transition to breast/bottle-feedings is a gradual process.

1. Non-nutritive attempts at the breast should be encouraged, if tolerated. Early, non-nutritive sucking facilitates milk production and increases the likelihood that the infant is still breastfeeding at the time of hospital discharge. Non-nutritive sucking has been tried in infants as young as 29 weeks and 1,100 g. In a meta-analysis on nonnutritive sucking, time to full feed, transition to oral feeding, and hospital discharge were shortened by a few days. Babies were offered a pacifier/emptied breast before and during orogastric feeding.

2. 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.

Oral feeding attempts at the breast should precede oral feeding attempts with the bottle.

L. Unusually persistent feed intolerance scenarios

1. Bolus versus continuous. Feedings are usually initiated as bolus, divided every 2 to 3 hours. Rarely, if difficulties persist, the feed may be infused slowly via a syringe pump over 30 to 120 minutes.

2. **Transpyloric feedings**
   a. Rarely done these days. These tubes are routinely placed under guided fluoroscopy. Transpyloric feedings should be delivered continuously because the small intestine does not have the same capacity for expansion as does the stomach. There is an increased risk of fat malabsorption, because lingual and gastric lipase secretions are bypassed.
   b. There are only a few indications for transpyloric feedings. Severe gastric retention or regurgitation/anatomic abnormalities of the GI tract such as microgastria.
3. **Gastrostomy feedings**
   a. Infants with neurologic impairment and/or those who are unable to take sufficient volumes through breast/bottle-feeding to maintain adequate growth/hydration status

M. Micronutrients

1. **Iron.** Noncompensated phlebotomy losses result from strict transfusion practices, resulting in iron deficiency in sick preterm babies. Growing preterm infants should receive iron, at 2 to 4 mg/kg/day, starting at 2 to 4 weeks. Preterm infants on iron-fortified preterm formula (15 mg/L) do not need additional iron. Iron supplementation is recommended until the infant is 12 months of age.
2. **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.

N. Research in nutrition

1. 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.
2. Specific immunonutrients have been shown to be involved with lung development and the protection from lung injury. Providing immunonutrients to premature infants may aid in the prevention and treatment of BPD. Selected immunonutrients include vitamin A, vitamin D, inositol, and long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexaenoic acid and arachidonic acid.

   Animal and limited human research suggests improved lung growth and development with the use of immunonutrients such as vitamin D, inositol, and LCPUFA. More research in timing, dosing, and delivery is indicated with these immunonutrients before clinical use can occur for the preterm infant.

VI. SPECIAL CONSIDERATIONS

A. Gastroesophageal reflux (GER). Episodes of physiological reflux are common in both preterm and full-term infants and do not cause any clinical compromise.

1. What is not gastroesophageal reflux disease (GERD)?

Episodes of feed intolerance (reflux/vomiting) are common during the *introduction and advancement of enteral feedings* in preterm infants. 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.

These episodes are most commonly related to intestinal dysmotility secondary to prematurity and will respond to modifications of the feeding regimen.

Temporary reductions in the feeding volume, spacing the feeds to 3 hourly instead of 2 hourly, *lengthening the duration of the feeding* (sometimes to the point of using continuous feeding), *removal of nutritional additives* (HMF), positioning the infant to elevate the head and upper body, in either a prone or a right-side-down position, and temporary cessation of enteral feedings are all possible strategies depending on the clinical course of the infant.

2. Which feed intolerance should be investigated?

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 partial atresia. 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).

Thickening of feeds and short-term acid suppressive therapy can be considered in case of persistent feeding difficulties and distress behavior; this is required very rarely.

B. NEC (see Chapter 27). Nutritional support of the patient with NEC focuses around providing 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.

1. 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.

2. Initiation of feedings. If the patient is clinically stable after a minimum of 5 to 14 days of bowel rest, feedings are generally introduced at approximately 10 to 20 mL/kg/day, preferably with maternal milk or PDHM, although a standard formula appropriate for the gestational age of the patient may also be used (i.e., preterm formula for the typical NICU infant). More specialized formulas containing elemental proteins are rarely indicated.

3. Feeding advancement. If low-volume feedings (10 to 20 mL/kg/day) are tolerated for 24 to 48 hours, gradual advancement is continued at approximately 10 mL/kg every 12 to 24 hours for the next 2 to 3 days. Supplemental PN is continued until enteral feedings are providing approximately 100 to 120 mL/kg/day volume.

4. Feeding intolerance. Signs of feeding intolerance include emesis, abdominal distension, and increased numbers of apnea episodes. Reduction of feeding volume or cessation of feeding is usually 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 intestinal strictures. Gastric residuals alone in the absence of other physical signs and symptoms of feeding intolerance are not reasons to withhold/decrease feed volumes.

5. **Feeding after surgical treatment of NEC.** After surgical therapy for NEC, 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. **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 higher caloric requirements due to their increased metabolic expenditure and, at the same time, are managed on restricted fluids (see Chapter 34).

Fluid restriction. Total fluid intake is typically restricted from the usual 150 mL/kg/day. 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. Infants may require up to 30 kcal/oz feedings in order to achieve the desired growth targets.

VII. NUTRITIONAL CONSIDERATIONS IN DISCHARGE PLANNING.

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. Human milk. Transition to full breastfeeding and need for enhanced caloric density feedings (fortification) poses a unique challenge. 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 postdischarge formula. This method allows the infant to nurse and receive nutrient-dense feedings. Another approach is to continue the use of HMF post discharge, but this does not allow benefits of direct breastfeeding. Infant formula powder is not sterile and does present the risk of *Cronobacter* spp. contamination for the immunocompromised infant. Hygiene in preparing formula milk is critical; the powder and milk must be mixed just before the feed is planned; one must not mix them for later use (not even 1 to 2 hours). Growth monitoring (on preterm growth chart) must continue into follow-up clinics till the ETA, and move to WHO charts for term babies after that. Fenton's charts and INTERGROWTH charts allow growth monitoring for a few weeks after ETA.

B. Formula choices

1. **Nutrient-enriched postdischarge formulas.** The growth benefits of special postdischarge formula are not notable at the age of 18 months. A meta-analysis of RCTs concluded that postdischarge formulas have limited benefits for growth and development at 18 months after term when compared with standard infant formulas. In some of the trials, infants on standard formula at higher volume intake compensated for additional nutrient needs. The

ESPGHAN suggested that preterm infants who demonstrate subnormal weight for age at discharge should be fed with fortified HM or special formula fortified with high contents of protein (preterm formula), minerals, and trace elements as well as LCPUFAs until at least 40 weeks' PMA but possibly for another 3 months thereafter. Preterm formulas are used either as an additive to HM or as a sole formula choice, if no breast milk is available.

2. **Term formulas** may also be utilized; however, careful monitoring of growth after discharge should continue.

C. Vitamin and iron supplementation

1. The AAP recommends 400 IU vitamin D per day for all infants. Unless they are consuming at least 1,000 mL/day of vitamin D–fortified formula, they will not meet this goal. Some guidelines recommend higher vitamin D supplements (800 IU) for preterm infants.
2. Preterm infants who are HM–fed are supplemented daily with 1 mL pediatric multivitamin (MVI) and with ferrous sulfate drops administered separately.
3. Preterm infants who are fed a combination of HM and formula are supplemented with vitamin D drops to provide 400 IU/day. Ferrous sulfate drops are administered separately, as needed. The upper limit of vitamin D intake for infants is 1,000 IU/day.
4. Preterm infants who are formula-fed are supplemented with 200 IU vitamin D/day supplement (+200 IU/day from the formula). Ferrous sulfate drops are administered separately, if needed.
5. Term infants, who are exclusively HM-fed, are supplemented daily with 400 IU/mL vitamin D drops, once feedings have been established. Iron supplementation is not indicated until 4 months of age. Low-birth-weight infants should receive 2 mg/kg of iron.
6. Term infants who are fed iron-fortified infant formula do not require vitamin D or iron supplements.

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22 Breastfeeding and Maternal Medications

Nancy Hurst and Karen M. Puopolo

KEY POINTS

- Breast milk provides the optimal nutritional and other bio-protective elements for baby and mother
- Hospital policies should include strategies to promote nonseparation of mothers and babies and promote exclusive breastfeeding.
- All birthing facilities must have personnel dedicated to assess and support mothers to initiate and establish lactation, and to help in special situations.
- All breastfeeding infants should be seen by their primary health provider at 3 to 5 days of age to ensure adequacy of milk intake.
- Preterm babies benefit in many ways by breast milk feeding, especially mother's own milk (MOM); there must be clear support to the mother for expression and storage of MOM, and efforts should be taken to maximize MOM.
- Most medications are safe in lactating mothers, and rarely should breastfeeding be stopped. It is the duty of the prescribing physician and the pediatrician to review safety through a standard resource, inform the family, and document a clear decision on continuing/withholding breastfeeding; consider an alternative medication, if safety in lactation is doubtful.

I. RATIONALE FOR BREASTFEEDING. Breastfeeding enhances maternal involvement, interaction, and bonding; provides species-specific nutrients to support normal infant growth; provides non-nutrient growth factors, immune factors, hormones, and other bioactive components that can act as biological 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 increases maternal metabolism; has maternal contraceptive effects with exclusive, frequent breastfeeding; is associated with decreased incidence of maternal premenopausal breast cancer and osteoporosis; and imparts community benefits by decreasing health care costs and economic savings related to commercial infant formula expenses.

II. RECOMMENDATIONS ON BREASTFEEDING FOR HEALTHY TERM INFANTS. These include the following general principles:

A. Promote hospital policies that support exclusive breastfeeding and nonseparation of the mother and the infant during hospital stay, beginning with immediate skin-to-skin contact after birth with a minimum duration of 1 hour.

B. Early initiation of breastfeeding within 1 hour of life aids in mitigation of subsequent breastfeeding difficulties. Mothers need to be encouraged to put their infants to breast as early as possible. The newborn when placed on the mother's abdomen soon after birth has the ability to find the mother's breast and decide when to take the first feed.

C. Encourage frequent feeding (8 to 12 feeds per 24 hours) in response to early infant cues.

D. When direct breastfeeding is not possible, instruct the mother to hand express and/or pump to promote milk production.

E. Supplements to breast milk (i.e., water or formula) should not be given unless medically indicated.

F. Mothers who are motivated to breastfeed their infants should be allowed to take their own decisions regarding pacifier use. There seems to be no negative impact on breastfeeding duration or nipple confusion.

G. Complementary foods should be introduced around 6 months with continued breastfeeding up to and beyond the 2 years.

H. Oral vitamin D drops (400 IU daily) should be given to the infant beginning within the first few days of age.

I. Supplemental fluoride should not be provided during the first 6 months of age.

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
3. Identification and appropriate treatment of breast and nipple problems

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. LATCH score, which allows objective evaluation of breastfeeding—latching, audible swallow, type of nipple, comfort, and hold
3. General breastfeeding information about the following:
   - **a.** Basic positioning of the infant to allow correct infant attachment at the breast
   - **b.** Minimum anticipated feeding frequency (eight times per 24-hour period)
   - **c.** Expected physiologically appropriate small colostrum intakes (about 15 to 20 mL in the 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

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 (~3/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. At 3 to 5 days postdelivery, the mother should experience some breast fullness and notice some dripping of milk from the opposite breast during breastfeeding, demonstrate ability to latch the infant to the breast, understand infant signs of hunger and satiety, and understand expectations and treatment of minor breast/nipple conditions.

2. 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 during the first month.

3. 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 the infant to transfer milk at the breast can be measured by weighing the infant before and after feeding using the following guidelines:

i. Weigh the diapered infant before and immediately after the feeding (without changing the diaper).

ii. One gram infant weight gain equals 1 mL milk intake.

4. If milk transfer is inadequate, supplementation (preferably with expressed breast milk) may be indicated.

5. Instructing the mother to express her milk with a mechanical breast pump following or in place of a feeding will 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, most likely a result of hormonal changes and increased friction caused by the infant's sucking action. A common description of this soreness includes an intense onset at 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, cracks). Nipple discomfort associated with breastfeeding that does not follow the scenario described previously requires immediate attention to determine cause and develop appropriate treatment modalities. Possible causes include ineffective, poor latch-on to the breast; improper infant sucking technique; removing infant from the breast without first breaking suction; and underlying nipple condition or infection (i.e.,

eczema, bacterial, fungal infection). Management includes the following: (i) Assess infant positioning and latch-on with correction of improper techniques. Ensure that the mother can duplicate positioning technique and experiences relief with adjusted latch-on. (ii) Diagnose any underlying nipple condition and prescribe appropriate treatment. (iii) In cases of severely traumatized nipples, temporary cessation of breastfeeding may be indicated to allow for healing. It is important to instruct the mother to maintain lactation with mechanical/hand expression until direct breastfeeding is resumed. Examine the baby for tongue tie.

C. Engorgement is a severe form of increased breast fullness that usually presents on day 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 the following: (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 the areola to facilitate infant attachment to the breast; (iii) gentle massage of the breast during feeding and/or milk expression; and (iv) mild analgesic (acetaminophen) or anti-inflammatory (naproxen) for pain relief and/or reduction of inflammation.

D. Plugged ducts usually present as a palpable lump or area of the breast that does not soften during a feeding or pumping session. It may be the result of an ill-fitting bra, tight, constricting clothing, or a missed or delayed feeding/pumping. Treatment includes the following: (i) frequent feedings/pumpings beginning with the affected breast, (ii) application of moist heat and breast massage before and during feeding, and (iii) positioning the 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. Treatment includes the following: (i) continued breastfeeding on the 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 the breast).

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 that the infant is breastfeeding effectively in order to enhance gut motility and facilitate bilirubin excretion. In **rare** instances of severe hyperbilirubinemia, while waiting for decision on exchange

transfusion after intense phototherapy, breastfeeding may be interrupted for 3 to 4 hours. However, the benefits of breastfeeding mandate that exclusive breastfeeding resumes at the earliest.

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 (i.e., obturator, nipple shield) may be utilized to achieve an effective latch.
   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. Frenulotomy is often the treatment of choice.
3. **Premature infants** receive profound benefits from breastfeeding and the receipt of mother's own milk (MOM). Mothers should be encouraged to express their milk (see breast milk collection and storage in the subsequent text)—even if they do not plan on direct breastfeeding—in order to provide their infant with the special nutritional and non-nutritional human milk components.

   Although MOM imparts the greatest benefit to preterm and high-risk infants, pasteurized donor breast milk may be an alternative when MOM is not available. When considering donor milk feeding, the product should be obtained from milk banks that adhere to the guidelines established by the Human Milk Banking Association of North America (HMBANA)/National Human Milk Banking Guidelines—Infant and Young Child Feeding (IYCF). These guidelines ensure safe handling and maintenance of the maximum amount of active human milk components. We obtain 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 the following: (i) mechanical milk expression concurrent with breastfeeding until the infant is breastfeeding effectively, (ii) systematic assessment (and documentation) of breastfeeding by a trainer observer, and (iii) weighing the infant periodically over a few days to evaluate adequacy of milk intake and determine need for supplementation.
   b. For premature infants <35 weeks, mothers should be encouraged to practice early and frequent skin-to-skin holding and suckling at the breast to facilitate early nipple stimulation to enhance milk volume and enable infant oral feeding assessment.

B. Maternal conditions

1. **Endocrine diseases** have the potential to affect lactation and milk production.
   a. 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 is recommended due to a well-documented delay (1 to 2 days) in the secretory phase of lactogenesis.

b. 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.

c. Gestational ovarian theca lutein cysts and retained placental fragments are conditions that prevent the secretory phase of lactogenesis.

2. Women with a **history of breast or chest surgery** should be 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) utilized in order to evaluate the level of follow-up indicated in the early postpartum period to monitor the progress of breastfeeding and adequacy of milk production and infant growth.

VI. CARE AND HANDLING OF EXPRESSED BREAST MILK. When possible, direct breastfeeding provides the greatest benefit for the mother and infant, especially in terms of provision of specific human milk components and maternal–infant interaction. However, when direct breastfeeding is not possible, expressed breast milk should be encouraged with special attention to milk expression and storage techniques. Mothers separated from their infants immediately following delivery due to infant prematurity or illness must initiate lactation by mechanical milk expression. Milk expression and storage techniques can affect the composition and bacterial content of MOM. 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 the following: (i) breast stimulation with a hospital-grade electric breast pump combined with hand expression/breast massage initiated within the first few hours following delivery; (ii) frequent pumping/hand expression (8 to 12 times daily) during the first 2 weeks following birth theoretically stimulates mammary alveolar growth and maximizes potential milk yield; (iii) pumping 10 to 15 minutes per session during the first few days until the onset of increased milk flow at which time pumping time per session can be modified to continue 1 to 2 minutes beyond a steady 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.

B. Guidelines for breast milk collection include the following: (i) instructing the mother to wash hands prior to each milk expression; (ii) all milk collection equipment coming in contact with the breast and breast milk should be thoroughly cleaned prior to and following each use; (iii) sterilizing milk collection equipment once a day (HMBANA/IYCF); (iv) collecting milk in sterile glass or hard plastic or stainless steel (IYCF) containers—plastic bags are not recommended for milk

storage for preterm infants; and (v) label each milk container with the infant's identifying information, date, and time of milk expression.

C. Guidelines for breast milk storage include the following: (based on HMBANA/ADA/IYCF recommendations for the hospitalized preterm infant with CDC recommendations for healthy term infants included in parentheses): (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 the infant is not being fed or the mother is unable to deliver the milk to the hospital within 24 hours of expression; (iv) in the event that frozen milk partially thaws, either complete the 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.

VII. CONTRAINDICATIONS AND CONDITIONS NOT CONTRAINDICATED TO BREASTFEEDING.

There are a 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 subclinical.

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** need not be isolated from her newborn for initial treatment. Antitubercular treatment needs to be initiated as soon as possible for the mother. In case of sputum positivity, the infant needs to be initiated on isoniazid prophylaxis. Only instances of multidrug-resistant (MDR) tuberculosis or noncompliance to antitubercular treatment requires isolation of the mother and baby.
3. The CDC recommends that **women who test positive for HIV in the United States** should not breastfeed. However, in developing countries, breastfeeding is recommended as the benefits of breastfeeding outweigh the risk. Affordable, feasible, accessible, sustainable, and safe to feed formula milk (**AFASS**) has been used in helping parents choose the best form of nutrition for their infant.
4. Varicella in the mother 5 days prior to delivery or 2 days after will require separation of the mother–infant dyad. However, expressed breast milk can be given and breastfeeding may be initiated once the lesions are crusted.
5. **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 hepatitis B surface antigen positive. Infants should receive hepatitis B immune globulin and hepatitis B vaccine to eliminate the risk of transmission.

2. Although hepatitis C virus has been found in breast milk, transmission through breastfeeding has not been shown (see Chapter 48).
3. In full-term infants, the benefits of breastfeeding appear to outweigh the risk of transmission from cytomegalovirus (CMV)–positive mothers. The extremely preterm infant is at an increased risk for perinatal CMV acquisition. Although freezing or pasteurizing MOM may reduce the risk of transmission, there is no evidence that such approaches will benefit very low-birth-weight (VLBW) infants.
4. Mothers who have symptoms of or confirmed coronavirus disease (COVID)-19 can continue breastfeeding and need to be counseled about the use of precautionary measures such as hand hygiene and use of face mask. When using breast pump, the mother should be educated on cleaning and sanitization of the same.
5. Mothers who are febrile can breastfeed
6. Mothers exposed to low-level environmental chemical agents can continue to breastfeed
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.

VIII. MATERNAL MEDICATIONS AND BREASTFEEDING. Questions commonly arise regarding the safety of maternal medication use during breastfeeding. A combination of the biological and chemical properties of the drug and the physiology of the mother and infant determines 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 biological effect of the drug on the infant.

A. Drug properties that affect entry into breast milk. Molecular size, pH, pK_a, 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).

IX. DETERMINATION OF DRUG SAFETY DURING BREASTFEEDING.

A number of available resources evaluate the risk of individual medications to the breastfed infant. Ideally, direct measurements of the entry of a drug into breast milk and the level and persistence of the drug in the breastfed infant, as well as experience with exposure of infants to the drug, are all used to make a judgment regarding drug safety. 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 judgment of a particular drug. Information about some medications (especially newer ones) is in flux, and safety judgments may change over a relatively short period of time. 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 judgment about relative safety of the drug.

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 exposure to breast milk substitutes. Consultation with the **Breastfeeding and Human Lactation Study Center** at the University of Rochester can aid the clinician in making specific clinical judgments.

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/?report=classic. 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. 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 T. *Medications and Mother's Milk.* 16th ed. Amarillo, TX: Hale Publishing; 2014. 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, Freeman RK, eds. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.* 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2015. 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 take calls only from health care professionals (not parents). It 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 address above.

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23 Fluid and Electrolyte Management

Elizabeth G. Doherty

KEY POINTS

- Enteral feeding is superior to intravenous fluids (IVF), IVF must be prescribed only if indicated.
- Extreme caution is required in IVF volume prescription during first few days of life, too much or too little cannot be handled by babies, especially preterm.
- Water load cannot be easily excreted by newborn babies (low GFR), especially preterm on first days of life.
- Tubular function immaturity limits the concentrating ability of preterm babies, they may pass more urine even if dehydrated
- Skin of extreme preterm babies allows huge insensible water losses (IWL), they must be nursed in humidified incubators to prevent IWL.
- Respiratory mucosa has a very large surface area, dry (inadequately humidified) gases can result in significant fluid losses in ventilated babies.
- On the first day(s) of life, no electrolytes must be added to IVF till urine output is established; in term babies, no electrolytes are required on day 1 and in preterm babies no electrolytes are needed for first few days.
- Preterm babies have immature renal function, they can develop hyperkalemia, hyponatremia, and metabolic acidosis (due to bicarbonate losses).
- Exclude hypoxia and hypoperfusion before interpreting high lactate (wide anion gap acidosis).

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 the 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 a 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.

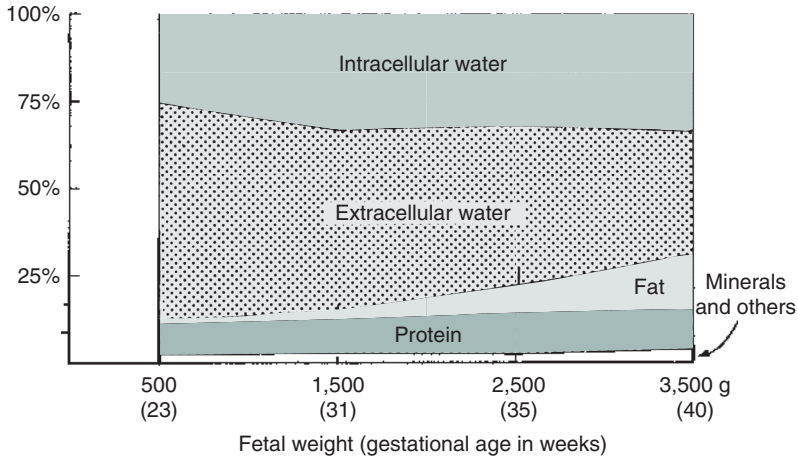


Figure 23.1. Body composition in relation to fetal weight and gestational age. (From Dweck HS. Feeding the prematurely born infant. Fluids, calories, and methods of feeding during the period of extrauterine growth retardation. *Clin Perinatol* 1975;2:183. Data from Widdowson EM. Growth and composition of the fetus and newborn. In: Assali NS, ed. *Biology of Gestation*. Vol. 2. New York, NY: Academic Press; 1968.)

B. Body water in term versus preterm

Water constitutes 70% to 80% of body weight in term born and > 90% in extreme preterm babies (Fig. 23.1). This difference is due to relatively lesser cells, glycogen, and fat in preterm.

The body water is distributed in intracellular fluid (ICF) and extracellular fluid (ECF) compartments. As baby matures, ICF increases (as cells are added) and relative amount of water in ECF decreases (Fig. 23.1).

C. Physiological postnatal changes in body water

Early postnatal period is characterized by rapid changes in water content of the body. Soon after birth, there is a rapid weight loss (decrease in total body water), this weight loss in the first few days of life of a newborn happens due to water loss from extracellular extravascular compartment (interstitial fluid). It does not compromise the cell health and tissue perfusion. This physiological contraction of ECF is achieved by physiologic diuresis, insensible water loss (IWL), and shift of fluid to intravascular compartment.

IWL is the amount of body water lost, that is not easy to measure, in immediate postnatal period, this is due to loss of water through skin and lungs. IWL is most in extreme preterm babies due to immature skin. IWL rapidly decreases after the first week of postnatal life, as the skin matures. Serial weights maybe used to estimate the IWL

$$\text{IWL} = \text{fluid intake} - (\text{urine output} + \text{weight loss})$$

In term babies, the maximal weight loss (MWL) in the first postnatal days is 5% to 7% of birth weight. Traditionally it was believed that preterm babies may lose more (10% to 15%) of their body weight. This was considered physiological and attributed to immature skin and kidneys. With advent of early use of parenteral nutrition, even preterm babies must have a MWL of 5% to 7%.

The lack of physiologic weight loss in sick neonates on fluid therapy may indicate inadvertent excess fluid administration. This excess fluid therapy is associated with increased incidence of patent ductus arteriosus (PDA) and broncho pulmonary dysplasia (BPD).

D. Water handling in term and preterm babies

1. **Glomerular filtration rate (GFR)**
   In term born babies, immediately after birth the renal blood flow increases rapidly and GFR rapidly increases over the first 2 weeks. Before this happens the newborn, in first week of life, cannot excrete a fluid load. This is the reason for a smaller saline bolus (10 mL/kg) in neonates when compared to 20 to 60 mL/kg in sick children. The very low GFR (almost similar to end stage renal failure of adult) is the reason to administer electrolyte-free (no sodium or potassium) fluids on the first few days, till diuresis happens (urine output increases from 1 to 2 voids/day on first 2 days to 2 to 3 mL/kg/h after day 3).

   In preterm babies, the GFR increase is much slower, and may take several weeks. Fluid bolus may be avoided, unless there is obvious fluid loss. Electrolytes (sodium and potassium) may be added to fluids administered, only after diuresis starts and serum sodium falls to 130 and potassium to 4 mEq/L.

2. **Renal tubular function** is very immature in preterm babies. This results in polyuria and excess sodium loss after the first 2 weeks of life (after GFR improves). The preterm baby loses water and sodium even if there is a deficiency of either. A good urine output in a preterm baby does not exclude dehydration. Preterm babies after 2 weeks of life are at risk of hyponatremia and may need as much as 10 mEq/kg/day (in contrast to 2 to 3 mEq/kg/day in term babies).

   On the first few days, extreme preterm babies are at risk of severe hyperkalemia due to renal tubular immaturity, urine output may not be less (nonoliguric hyperkalemia). This is the reason that electrolyte (Na and K) monitoring must be started at 18 hours of life in the extreme preterm babies.

3. **Skin immaturity** plays a major role in water homeostasis. In extreme preterm the skin has fewer layers, IWL can be very large and variable (depending on the use of radiant warmer, incubator, and ambient humidity). Fluid (water) planning can be very challenging, the IWL can range from 50 to 200 mL/kg/day. Use of humidified incubators is the best solution till the skin matures (first week of life).

4. **Water loss from respiratory mucosa.**
   The respiratory mucosa surface area is larger than the skin surface area. Babies with large minute ventilation due to respiratory distress can lose a lot of water, and this again is difficult to estimate. Use of humidified gases for respiratory care significantly improves water homeostasis.

5. **Water for growth (metabolism).**
   Water (and electrolytes) is necessary for cell growth. This requirement is not there on the first few days of a sick baby in NICU; in the catabolic phase of illness, no growth is happening. In fact, weight gain is not good, it indicates unhealthy excess fluid administration.

6. **Stool losses.**
   As enteral feeding increases over first 2 weeks, one has to provide for water lost through stools. This amount is insignificant in the first few days.

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. It 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 et al. (1972); and Okken et al. (1979).

7. **Renal losses.** Renal function matures with increasing GA. Immature Na and water homeostasis is common in the preterm infant after few weeks of life. Contributing factors leading to urinary water and electrolyte losses include the following:
   - **a.** Increasing glomerular filtration rate (GFR)
   - **b.** Reduced proximal and distal tubule Na reabsorption
   - **c.** Decreased capacity to concentrate or dilute urine
8. **Extrarenal 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 GA 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 ventriculo tomy or serial lumbar punctures), and nasogastric tube or thoracostomy tube drainage.

   Incubators are recommended for nursing VLBW neonates, the humidity inside the incubator decreases the IWL to a negligible level.

II. ASSESSMENT OF FLUID AND ELECTROLYTE STATUS

A. History

1. **Maternal.** Excessive use of oxytocin and hyponatremic intravenous (IV) fluid can lead to maternal and fetal hyponatremia. Antenatal steroids may increase skin maturation, subsequently decreasing IWL.
2. **Fetal/perinatal.** The presence of oligohydramnios may be associated with congenital renal dysfunction, including renal agenesis, autosomal recessive polycystic kidney disease (ARPKD), 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. Weight should be measured at least daily, and maybe twice a day in ELBW infants and babies with heart failure, renal failure, or severe skin loss (collodion). Weight loss in excess of 4% to 5% of birth weight per day may indicate dehydration. Weight gain in the first week or "not losing weight" may indicate excess TBW. The compartment affected will depend on the 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!

2. **Skin and mucosal manifestations.** Altered skin turgor, sunken anterior fontanelle, and dry mucous membranes are not sensitive indicators of hydration status in neonates.

3. **Cardiovascular.** Tachycardia can result from ECF excess (e.g., heart failure) or hypovolemia. Capillary refill time can be prolonged with reduced cardiac output or peripheral vasoconstriction, and hepatomegaly can occur with increased ECF volume. Blood pressure changes occur late in the sequence of responses to reduced cardiac output.

4. **Urine output (UO).** In term born babies (> 34 weeks) with no evident renal injury, the urine output is a good measure of hydration. UO of 1 to 3 mL/kg/h is normal. Less than 0.5 to 1 mL/kg/h must be evaluated. Polyuria (>4 mL/kg/h) is common in preterm babies after second week of life. Babies recovering from AKI (asphyxia, sepsis) may have polyuria due to renal tubular dysfunction.

   UO is measured by periodic diaper weights and urine collecting bag (or test tube in males). Catheterization becomes necessary if severe oliguria has not responded to fluid challenge and dialysis is being considered. Catheterization is accurate but associated with trauma, hematuria, and risk of infection.

5. **Edema.** Edema may be noted on sides of the chest wall, skin, and as puffiness of eyelids. In severe cases, the whole body appears bloated. Although edema indicates fluid overload most often, capillary leaks can result in edema and low intravascular volume. In this setting restricting the fluid can worsen perfusion and renal function.

C. Laboratory studies

1. **Serum electrolytes and plasma osmolarity** reflect the composition and tonicity of the ECF. Frequent monitoring, every 12 to 24 hours, should be done in infants at risk - ELBW, perinatal asphyxia, and shock. A serum sodium >150 is indicative of dehydration and <130 of overhydration (provided baby is not receiving excess sodium/diuretics. Plasma osmolarity is not measured directly, it is calculated by most machines from component values (sodium, urea, and glucose).

2. **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. It is of limited utility in planning fluid therapy. Neither urine electrolytes nor SG is very helpful when infant is on diuretics.

3. **Fractional excretion of Na (FENa)** reflects the balance between glomerular filtration and tubular reabsorption of Na.

$$\text{FENa} = \frac{\text{urine Na} \times \text{plasma creatinine}}{\text{plasma Na} \times \text{urine creatinine}} \times 100$$

There is limited utility in neonates because of glomerular and tubular maturity.

4. **Blood urea nitrogen (BUN) and serum creatinine (Cr)** values provide indirect information about ECF volume and GFR. Values in the early postnatal period reflect placental clearance. Cr should fall in the first week of life, as GFR improves.
5. **Arterial pH, arterial pH and lactate levels** determinations can provide indirect evidence of intravascular volume depletion because poor tissue perfusion leads to high anion gap metabolic acidosis (lactic acidosis).

III. MANAGEMENT OF FLUIDS AND ELECTROLYTES. Enteral nutrition with breast milk, donor human milk or formula milk (if breast milk is not available) is better than intravenous fluids (IVF) at all times. IVF are associated with risk of infections, metabolic imbalances, and lack nutrients like protein and fat when compared to milk (even parenteral nutrition is inferior to human milk). Hence, one must prescribe IVF only if absolutely indicated. Following situations may require IVF

- Hypoglycemia
- Very preterm who cannot be on full enteral feeds on first few days
- Congenital anomalies of gastro-intestinal tract (GIT)
- Acquired problems of GIT like necrotizing enterocolitis
- Severe perinatal asphyxia with GIT injury
- Suspected inborn errors of metabolism

In most of the situations, small amount of breast milk may be safely given. Feeds must be increased as quickly as feasible and period of IVF minimized.

The goal of early fluid.

The goal of early fluid management (in sick babies) is to allow initial ECF loss over the first 5 to 6 days as reflected by weight loss, while maintaining normal tonicity and intravascular volume as reflected by blood pressure, heart rate, urine output, serum electrolyte levels, and pH.

Table 23.2 gives some scenarios in managing fluids and electrolytes in babies.

Subsequent fluid management (in growing babies) should include requirements for body growth.

A. The term infant. Body weight decreases by 1% to 3%/day over the first 5 to 6 days. Fluids should be planned, allowing this weight loss. Small-for-GA term infants may not lose as much weight. Decisions on fluid volume should not be based on weight alone; clinical status should be monitored for maldistribution of water (e.g., edema). Na supplementation is not usually required in the first 24 hours.

B. The premature infant. A 5% to15% weight loss may happen, especially in the extreme preterm, babies on parenteral nutrition may lose only 5% to 7% weight. Fluids should be planned, allowing this weight loss. Table 23.2 gives a few examples of managing fluid therapy. Frequently assess response to fluid and electrolyte

Table 23.2. Illustrative Examples of Fluid Management in NICU.

Weight	Urine Output	Serum Na	Inference	Expected Action
Increased	Low	Low	Water retention	Reduce fluid intake
Increased	Low/normal	High	Salt and water retention	Reduce fluid and sodium intake
Decreased	Low/normal	High	Pure water loss—usually insensible loss from skin	Check humidity Replace water loss
Decreased	Low	Low	Salt and water loss—usually from the kidneys	Rehydrate with sodium and water

therapy during the first 2 days of life. **Physical examination and serum electrolyte determinations may be required initially as frequently as every 12 to 24 hours in infants <1,000 g** (see section VIII.A).

Water loss through the 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 2 to 5 days in extreme preterm babies (start supplementing sodium after it falls to 130 and urine output is established) (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. Hyponatremic disorders (see Table 23.3).

1. Hyponatremia with water loss

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 necrotizing enterocolitis [NEC]).

b. Diagnosis. Decreased weight, poor skin turgor, tachycardia, rising BUN, and metabolic acidosis are frequently observed.

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 water excess

a. Predisposing factors include excess fluid administration and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Factors that cause SIADH include pain, opiate administration, IVH, asphyxia, meningitis, pneumothorax, and positive-pressure ventilation.

Table 23.3. Hyponatremic Disorders

Clinical Diagnosis	Etiology	Therapy
ECF volume normal	Syndrome of inappropriate antidiuretic hormone (SIADH)	Restrict water intake
	Excess intravenous fluids	
ECF volume deficit	Diuretics	Increase Na intake
	Late-onset hyponatremia of prematurity	
	Congenital adrenal hyperplasia	
	Renal tubular acidosis	
	Gastrointestinal losses	
	Necrotizing enterocolitis (third-space loss)	
ECF volume excess	Heart failure	Restrict water intake
	Neuromuscular blockade (e.g., pancuronium)	

ECF, extracellular fluid.

b. Diagnosis of SIADH. Weight gain usually occurs even 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**. Antidiuretic hormone (ADH) production is not in response to volume loss such as reduced cardiac output or abnormal renal, adrenal, or thyroid function.

c. Therapy. Restriction of water intake must be done, giving more sodium in response to hyponatremia will worsen the condition. Sodium supplementation is not required despite low sodium except if (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, furosemide 1 mg/kg IV q6h can be initiated while replacing urinary Na excretion with hypertonic NaCl (3%) (1 to 3 mL/kg initial dose). Fluid restriction alone can be utilized 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.

B. Hypernatremic disorders

1. Hypernatremia with water loss

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. In tropical climates during summer months, hypernatremic dehydration is common in neonates.

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. As the cause of hypernatremia is excess free water loss, the therapy is replacement of water lost (the excess weight loss is a rough guide). Avoid too rapid correction of serum sodium (not faster than 1 mEq/kg/hour).

2. Hypernatremia with water excess

a. Predisposing factors include excessive sodium containing fluid (sodabicarb infusion, normal saline for arterial line etc.) 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.

C. Isonatremic disorders

1. Dehydration

a. Predisposing factors include equivalent losses of Na and water (preterm baby with immature renal tubular function, 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 dehydration and hypovolemia despite normal or low serum sodium.

b. Diagnosis. Dehydration is usually manifested by weight loss, decreased urine output, hypernatremia, and increased urine SG. However, infants of <32 weeks' gestation may not demonstrate oliguria in response to dehydration, and serum sodium may be normal or low. 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' GA.

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 fluid administration, heart failure, sepsis (capillary leak), 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.

V. OLIGURIA. UO less than 0.5 to 1 mL/kg/h. There can be many limitations in assessment of UO in neonates who are not catheterized. Spillage of urine is common. Baby may have urine in the urinary bladder; this urine is not measured and false judgment of oliguria can be made. Ultrasound will confirm a full/empty bladder. Catheterization may be necessary in a sick neonate with low urine output. Low urine output (one or two voids) in a healthy infant is not of concern until 24 hours after birth. But in sick babies on IV fluids, urine output should be assessed every 8 to 12 hours by weighing diapers or using urine collection bag; rarely urethral catheterization is indicated. Diminished urine output may reflect abnormal prerenal, renal parenchymal, or postrenal factors (Table 23.4). The most common causes of neonatal acute kidney injury (AKI) are asphyxia, sepsis, and severe respiratory illness. It is important to exclude other potentially treatable etiologies (see Chapter 28).

A. History and physical examination. These include maternal and infant history for oligohydramnios (Potter's syndrome), birth asphyxia, and maternal diabetes (renal vein thrombosis in the neonate). 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 (kidneys/bladder), or ascites; and the presence of any congenital anomalies associated with renal abnormalities (e.g., Potter's syndrome, epispadias).

B. Diagnosis

1. **Initial laboratory examination** should include urinalysis, BUN, Cr, and sometimes FENa determinations. These aid in diagnosis and provide baseline values for further management.
2. **Fluid challenge**,. Normal saline 10 mL/kg over 30 minutes, second bolus may be tried in term born babies with no underlying heart disease, especially if excess weight loss has happened. Decreased cardiac output not responsive to ECF expansion may require the institution of inotropic/chronotropic pressor agents. Dopamine at a dose of 1 to 5 μg/kg/minute may increase renal blood flow and a dose of 2 to 15 μg/kg/minute may increase total cardiac output. These effects may augment GFR and urine output (see Chapter 40).

Table 23.4. Etiologies of Oliguria

Prerenal	Renal Parenchymal	Postrenal
Cardiac dysfunction	Ischemia (hypoxia, hypovolemia)	Posterior urethral valves
Dehydration	Renal artery or vein thrombosis	Neurogenic bladder
	Nephrotoxin	Prune belly syndrome
	ARPKD	
	Agenesis	
	Dysplasia	

3. If no response to fluid challenge occurs, one may induce diuresis with furosemide 1 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.

C. Management. **Prerenal** oliguria should respond to fluid challenge. **Postrenal** obstruction requires urologic consultation, with possible urinary diversion and surgical correction. If parenchymal **ARI** is suspected, minimize excessive ECF expansion and withhold electrolytes in the fluid (potassium and sodium). 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. Metabolic acidosis results from excessive loss of buffer or from an increase of volatile or nonvolatile acid in the extracellular space. 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 the 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 the 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. Metabolic acidosis is seen most commonly due to hypoxia and ischemia at cellular level (asphyxia), cellular dysfunction (sepis), severe cardiac dysfunction (ductus dependent left sided obstructive lesion), and poor oxygen delivery due to severe anemia or poor venous return due to overdistension of lungs resulting from inappropriately high ventilator pressures.

Acidosis is physiological immediately after birth (pH is closer to 7.2) as it reflects maternal acidosis due to labor. In the absence of shock or hypoxia, high anion gap (lactate, other organic acids) points to inborn errors of metabolism. One should address common and correctible conditions of hypoxia and ischemia before considering rare diseases (do not even test anion gap if shock and hypoxia are not corrected).

1. **Anion gap.** Metabolic acidosis can result from the accumulation of acid or loss of buffering equivalents. Anion gap determination will suggest the

mechanism. Na, Cl, and bicarbonate are the primary ions of the extracellular space and exist in an approximately electroneutral balance. The **anion gap**, calculated as the difference between the Na concentration and the 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. Anion gap in healthy neonates is higher (5-15 mEq/L) than that of adults.

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, and toxin exposure. Lactic acidosis results from diminished tissue perfusion and resultant anaerobic metabolism in infants with asphyxia or severe cardiorespiratory disease.

3. **Metabolic acidosis associated with a normal anion gap (<15 mEq/L)** results from buffer loss through the renal or gastrointestinal system (see Table 23.5). Premature infants <32 weeks' gestation frequently behave like proximal or distal renal tubular acidosis (RTA). Urine pH persistently >7 in an infant with metabolic acidosis suggests a distal RTA. Urinary pH <5 documents normal distal tubule hydrogen ion secretion, but proximal tubular bicarbonate resorption could still be inadequate (proximal RTA). Preterm babies have bicarbonate losses due to renal tubular immaturity.

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. The premature infant's acid–base status can change rapidly, and frequent monitoring is warranted. The infant's ability to

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
Toxins (e.g., benzyl alcohol)	Renal dysplasia
	Gastrointestinal bicarbonate loss
	Diarrhea
	Cholestyramine
	Small bowel drainage
	Dilutional acidosis
	Hyperalimentation acidosis

Table 23.6. Metabolic Alkalosis

Low Urinary Cl (<10 mEq/L)	High Urinary Cl (>20 mEq/L)
Diuretic therapy (late)	Bartter's syndrome with mineralocorticoid excess
Acute correction of chronically compensated respiratory acidosis	Alkali administration
Nasogastric suction	Massive blood product transfusion
Severe vomiting (congenital hypertrophic pyloric stenosis)	Diuretic therapy (early)
Secretory diarrhea	Hypokalemia

Cl, chloride.

tolerate an increased Na load and to metabolize acetate is an important variable that influences the acid–base status during treatment.

C. Metabolic 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 intake (normally 1 to 2 mEq/kg/day) and excretion through urine, through the gastrointestinal tract, and by shift between intracellular and extracellular compartments.

A. Hypokalemia can lead to arrhythmias, ileus, renal concentrating defects, and obtundation in the newborn.

1. **Predisposing factors** include respiratory depression, apnea, nasogastric or ileostomy drainage, chronic diuretic use, and renal tubular defects.
2. **Diagnosis.** Obtain serum and urine electrolytes, pH, and an electrocardiogram (ECG) to detect possible conduction defects (prolonged QT interval and U waves).
3. **Therapy.** In neonates, rapid potassium corrections are avoided. Correction is done by increasing fluid potassium concentrations in a graded fashion from 20 meq/L upto 60 meq/L.

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. In extreme preterms, the potassium levels are as high as 6.5 mEq/L in the first week of life.

1. **Predisposing factors.** Hyperkalemia can occur unexpectedly in any patient but should be anticipated and screened for in the following scenarios:

a. Decreased K clearance due to renal failure, oliguria, hyponatremia, and congenital adrenal hyperplasia

b. 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).

c. The most common cause of sudden unexpected hyperkalemia in the neonatal intensive care unit (NICU) is medication error.

d. Increased K release secondary to tissue destruction, trauma, cephalhematoma, hypothermia, bleeding, intravascular or extravascular hemolysis, asphyxia/ischemia, and IVH

e. Miscellaneous associations including dehydration, birth weight <1,500 g (see section VIII.A.2), blood transfusion, inadvertent excess (KCl) administration, chronic liver disease with KCl supplementation, and exchange transfusion

2. Diagnosis. 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).

Once hyperkalemia is diagnosed, **remove all sources of exogenous K (change all IV solutions and oral sources with K content)**, rehydrate the patient if necessary, and eliminate arrhythmia-promoting factors. The pharmacologic therapy of neonatal hyperkalemia consists of three components and depends on the clinical severity:

a. Goal 1: stabilization of conducting tissues. If there are hemodynamic instability, arrhythmia, and ECG changes, Ca gluconate (10%) is given carefully at 1 to 2 mL/kg IV (over 0.5 to 1 hour). If the patient is both hyperkalemic and hyponatremic, NS infusion may be beneficial. Use of antiarrhythmic agents such as lidocaine and bretylium should be considered for refractory ventricular tachycardia (see Chapter 41).

b. Goal 2: dilution and intracellular shifting of K. If there is hyperkalemia, but the neonate has no hemodynamic instability or rhythm abnormality. Alkalemia will promote intracellular K-for-hydrogen-ion exchange. Na bicarbonate 1 to 2 mEq/kg/hour IV may be used. In order to reduce the risk of IVH, avoid rapid Na bicarbonate administration, especially in infants born before 34 weeks' gestation and younger than 3 days. Respiratory alkalosis may be produced in an intubated infant by hyperventilation, although the risk of hypocarbia-diminishing cerebral perfusion may make this option more suited to emergency situations. Theoretically, every 0.1 pH unit increase leads to a decrease of 0.6 mEq/L in serum K.

Insulin enhances intracellular K uptake by direct stimulation of the membrane-bound Na–K-ATPase. Insulin infusion with concomitant

glucose administration to maintain normal blood glucose concentration is relatively safe as long as serum or blood glucose levels are frequently monitored. This therapy may begin with a bolus of insulin and glucose (0.05 unit/kg of human regular insulin with 2 mL/kg of dextrose 10% in water [$D_{10}W$]) followed by continuous infusion of $D_{10}W$ at 2 to 4 mL/kg/hour and human regular insulin (10 units/100 mL) at 1 mL/kg/hour. To minimize the effect of binding to IV tubing, insulin diluted in $D_{10}W$ 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).

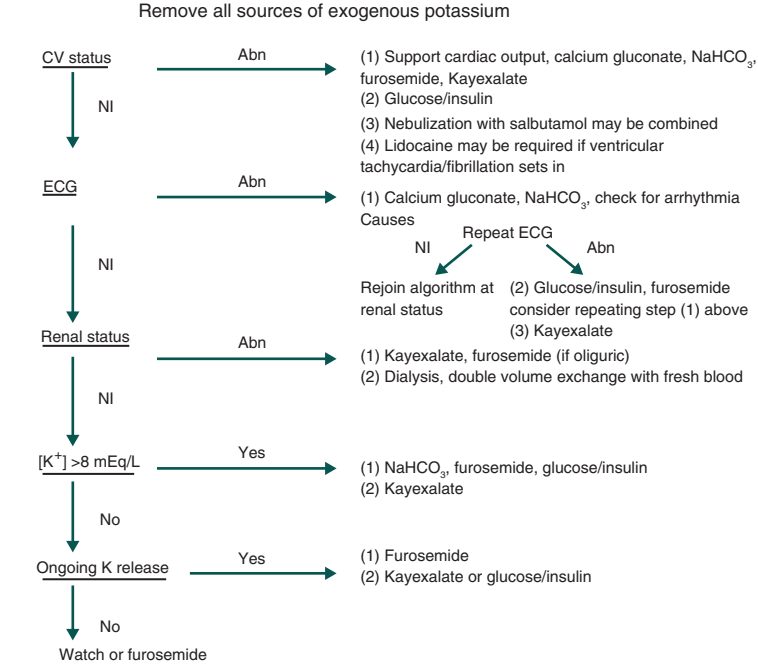
β_2-Adrenergic stimulation enhances K uptake, probably through stimulation of the Na–K-ATPase. The immaturity of the β-receptor response in preterm infants may contribute to nonoliguric hyperkalemia (NOHK) in these patients (see section VIII.A.2). To date, β stimulation is not the primary therapy for hyperkalemia in the pediatric population. However, if cardiac dysfunction and hypotension are present, use of dopamine or other adrenergic agents could, through β_2 stimulation, lower serum K.

c. **Goal 3: enhanced K excretion.** Diuretic therapy (e.g., furosemide 1 mg/kg IV) may increase K excretion by increasing flow and Na delivery to the distal tubules. In the clinical setting of inadequate urine output and reversible renal disease (e.g., indomethacin-induced oliguria), peritoneal dialysis and double volume exchange transfusion are potentially lifesaving options. Peritoneal dialysis can be successful in infants weighing <1,000 g and should be considered if the patient's clinical status and etiology of hyperkalemia suggest a reasonable chance for good long-term outcome. Use fresh whole blood (<24 hours old) or deglycerolized red blood cells reconstituted with fresh frozen plasma for double volume exchange transfusion. Aged, banked blood may have K levels as high as 10 to 12 mEq/L; aged, washed packed red blood cells will have low K levels (see Chapter 42).

Enhanced K excretion using cation exchange resins such as Na or Ca polystyrene sulfonate has been studied primarily in adults. The resins can be administered orally per gavage (PG) or rectally (after suspension in distilled water). A possible complication of resins is bowel obstruction secondary to bezoar or plug formation.

The reported experience with resin use in neonates covers those born at 25 to 40 weeks' gestation. PG administration of Kayexalate is not recommended in preterm infants because they are prone to hypomotility and are at risk for NEC. Rectal administration of Kayexalate (1 g/kg at 0.5 g/mL of NS) with a minimum retention time of 30 minutes should be effective in lowering serum K levels by approximately 1 mEq/L. The enema should be inserted 1 to 3 cm using a thin silastic feeding tube. Published evidence supports the efficacy of this treatment in infants. Kayexalate prepared in water or NS (eliminating sorbitol as a solubilizing agent) and delivered rectally should be a therapeutic agent with an acceptable risk–benefit ratio.

The clinical condition, ECG, and actual serum K level all affect the choice of therapy for hyperkalemia. Figure 23.2 contains guidelines for the treatment of hyperkalemia.



In general, if $[K^+]$ acceptable for 6 hours, cease therapy but continue monitoring

Drug doses:		
	Calcium gluconate	1–2 mL/kg IV
	$NaHCO_3$	1–2 mEq/kg IV
	Furosemide	1 mg/kg IV
	Glucose/insulin	Bolus: $D_{10}W$ 2 mL/kg Humulin 0.05 unit/kg
		Infusion: $D_{10}W$ 2–4 mL/kg/hours Humulin, 10 units/100 mL $D_{10}W$ or 5% albumin, 1 mL/kg/hour
	Kayexalate	1 g/kg PR, used cautiously in the setting of an immature ischemic GI tract

Figure 23.2. Treatment of hyperkalemia. 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). Abn, abnormal; CV, cardiovascular; D10W, dextrose in 10% water; ECG, electrocardiogram; GI, gastrointestinal; IV, intravenous; Nl, normal.

VIII. COMMON CLINICAL SITUATIONS

A. VLBW infant

1. **VLBW infants evolve through three phases of fluid and electrolyte homeostasis:** prediuretic (first day of life), diuretic (second to third days of life), and postdiuretic (fourth to fifth days of life). Increased free water loss through the skin can result in hypernatremia in the first few days of life. Marked diuresis can occur during the diuretic phase leading to hyponatremia and the need for increased rates of parenteral fluid administration. 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 situation

frequently leads to administration of reduced dextrose concentrations (<5%) in parenteral solutions. Avoid the infusion of parenteral solutions containing <200 mOsmol/L, to minimize local osmotic hemolysis.

2. **VLBW infants often develop a NOHK** in the first 2 days of life. This is caused by a relatively low GFR combined with an intracellular to extracellular K shift due to decreased Na–K-ATPase activity. Monitoring for high potassium must start by 18 hours of life. Insulin infusion to treat hyperkalemia may be necessary but elevates the risk of iatrogenic hypoglycemia. Potassium binding resins need to be used with utmost caution in VLBW neonates due to the risk of necrotizing enterocolitis. A combination of insulin glucose is preferred over potassium binding resins.
3. **Late-onset hyponatremia of prematurity** often occurs 3 to 4 weeks postnatally in the growing ELBW infant. Failure of the immature renal tubules to reabsorb filtered Na in a rapidly growing infant often causes this condition. Other contributing factors include the low Na content in breast milk, human milk fortifier, and diuretic therapy for CLD. Infants at risk should be monitored with periodic electrolyte measurements and if affected, treated with simple Na supplementation (start with 2 mEq/kg/day). A recent observational study recommends 2-weekly testing of urinary sodium to titrate supplementation. This was associated with better weight gain and no increase in respiratory morbidity.

B. Severe chronic lung disease (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). 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).

C. Surgical newborn

Enterostomy (especially distal bowel, ileostomy) can result in severe dehydration and metabolic losses (loss of water, sodium and bicarbonate)

Investigation of bowel obstruction with gastrograffin enema can cause shock due to massive fluid shift into lumen, more fluids must be prescribed in anticipation.

Persistent vomiting due to congenital pyloric stenosis is associated with dehydration, hypokalemia, and alkalosis. Correction with normal saline or N/2saline with potassium may be needed for at least a day before considering surgery

Continuous drainage from Ryle's tube aspiration, chylothorax, ventriculostomy can result in loss water and electrolytes.

Lower urinary tract obstruction can be associated with severe polyuria and electrolyte loss after catheterization and relief of obstruction. Fluids may be increased in anticipation. Electrolytes may be monitored 8 to 12 hourly.

D. Hypernatremic dehydration

Babies with severe lactation problems, especially late preterm can have weight loss exceeding 500 grams and hypernatremia exceeding 160 mEq/L at the end

of few days. Treat with milk (breast milk/formula). Extreme preterm babies nursed under radiant warmer or phototherapy can lose large amount of water and present with severe hypernatremia. Treatment of hypernatremic dehydration centers around replacement of lost water. Ensure adequate feeds in late preterm, if ELBW and also if dehydration is severe IV free water (5% to 10 % dextrose) may be required.

E. PDA with congestive heart failure

Treat with restricted fluids, only if heart failure is asociated with PDA. Restriction of fluid is not recommended as prophylactic.

F. Capillary leaks - asphyxia, severe sepsis

Babies present with signs of poor perfusion and shock, but there is severe edema due to capillary leak. Intravascular volume must be restored by adequate fluid intake to avoid poor perfusion to brain and kidneys.

G. Renal tubular dysfuction

Pseudohypoaldosteronism (PHA) may present with severe hyponatremia, hyperkalemia, dehydration, and metabolic acidosis from day 1. Babies may lose 200 to 500 grams in a day. The age of presentation contrasts with true salt losing congenital adrenal hyperplasia that presents in the same way. PHA is associated with severe polyhydramnios, often resulting in very preterm birth.

H. Collodion baby/other severe skin loss conditions

Free water losses can be massive, one must try enteral feeding as a first choice due to difficult venous access and high risk of serious infections.

Suggested Readings

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24 Hypoglycemia and Hyperglycemia

Heather H. Burris

KEY POINTS

- Symptomatic and prolonged hypoglycemia is associated with a high risk of neurodisability.
- *Plasma* glucose is the gold standard, and whole blood glucose (often measured at bedside) may be approximately 15% lower than plasma levels.
- "Normal" levels of blood sugar may be different among term and preterm, and also vary with the day of life.
- In newborn babies, target (treatment decisions) glucose levels are based on following factors: symptoms and risk setting (gestation, birth weight, age in hours after birth and other predisposition to persistent hypoglycemia) in addition to the glucose values. For purpose of urgent bedside care, one may target blood sugar levels measured by point-of-care device of 45 gm/dL (approximately 50 mg/dL plasma glucose measured in lab), irrespective of symptoms.
- After 48 to 82 hours of life, safe levels of plasma glucose levels of newly born babies should be similar to older children and adults (*the corresponding blood glucose levels are approximately 50 mg/dL*)
- Hyperglycemia (blood glucose > 145 mg/dL) is commoner in very low birth weight (VLBW) infants, most babies are managed with adjusting the glucose infusions.
- Asymptomatic at-risk infants (preterm, small for gestational age [SGA], large for gestational age [LGA], and infants of diabetic mothers [IDMs]) should be screened for hypoglycemia and promptly treated.
- The traditional 200 mg/kg dextrose "mini-bolus" for the treatment of neonatal hypoglycemia may not be necessary in asymptomatic newborns.
- Infants who fail to maintain preprandial blood sugar levels at normal levels for age or require intravenous fluids are at risk for persistent hypoglycemia, they must be investigated for a cause.
- Hyperglycemia is commoner 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 sick babies and well babies at-risk of hypoglycemia. Managing hypoglycemia requires interpretation of blood glucose values within the clinical context. Blood glucose levels in the first hours of life are typically lower than the normal values in older children or adults. In healthy infants, blood glucose levels can often be maintained in the appropriate range by initiating breastfeeding soon after birth. Most cases of neonatal hypoglycemia are transient, respond

readily to treatment, and are associated with an excellent prognosis. Symptomatic hypoglycemia is associated with high risk of severe neurodisability. Babies with persistent low sugars must be investigated for underlying causes (hyperinsulinemia is commonest).

Hyperglycemia is very uncommon 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. Maternal hepatic glucose production increases by 16% to 30% through gestation to supply the fetus with energy.

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, gluconeogenesis, and utilizing exogenous nutrients from feeding to maintain adequate glucose levels. During this normal transition, 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 in Well Babies (GLOW), trial published in 2020, is the first accurate study on Transitional Neonatal Hypoglycemia (TNH). Glucose levels (lab standard) were accurately measured twice a day, starting from birth. They found that TNH may last for 4 days, so one must observe babies at-risk of hypoglycemia for this period. Also, investigation for causes of persistent hypoglycemia may be preferably planned after this period. The "normal values" in healthy babies varied significantly, as many as 40% babies had one value of blood sugar less than 47 mg/dL in the 4 days. Management and prognosis of hypoglycemia should therefore not be based on just the number, clinical context is as important.

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 in order to interpret the glucose level and diagnose hypoglycemia. A recent prospective study of infants at risk for hypoglycemia (defined as a blood glucose <2.6 mOsm [<46.8 mg/dL]) found 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 has low blood sugar levels. In South Asia, more than 40% of the babies are low birth weight (either SGA, preterm, or both.) These SGA neonates have altered insulin metabolism, this necessitates close monitoring for hypoglycemia.

B. Definition. In a prospective study on healthy infants (GLOW trial), 39% healthy babies with no risk factors of hypoglycemia had at least one value <47 mg/dL. These babies are different from at-risk babies who cannot utilize alternate fuels easily. In 2011, the American Academy of Pediatrics (AAP) published a practical guideline for screening and management of neonatal hypoglycemia. In the absence of consensus in the literature on exact definitions of hypoglycemia (glucose values or duration of low blood sugar levels), 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 also released hypoglycemia guidelines in 2015 which specify that infants >48 hours

of age should have higher glucose levels and be evaluated for hypoglycemia with higher thresholds (plasma glucose <60 mg/dL), *the corresponding blood glucose levels are approximately 50 mg/dL*. The thresholds for treating hypoglycemia depend on the presence of symptoms, the age of the infant in hours, risk setting (infant of diabetic mother, large for gestation, small for gestation, preterm, sick baby), 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 the first hours after birth), infants 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 Pediatric Endocrine Society, by **48 to 72 hours** of life, glucose control should be similar to that of older children and adults. *The corresponding blood glucose levels are approximately 50 mg/dL* (most glucometers measure blood glucose). 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 utilizing 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). Women are screened for gestational diabetes during pregnancy and blood sugar levels are optimized by diet or medications. Yet, some women either have mild glucose intolerance that is subthreshold for diagnosis or develop

late-onset glucose intolerance; their infants may be LGA and at risk of hypoglycemia.

b. Congenital hyperinsulinism. 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. Perinatal 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)

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. Fetal growth restriction (**FGR**) or **SGA**. Among 152 SGA infants in a New Zealand study, 52% were hypoglycemic.

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. Post-resuscitation

b. Reactive hypoglycemia after exchange transfusion 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 **beta-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. Infants at risk of persistent hypoglycemia (and must be investigated) include
   - Severe hypoglycemia (symptomatic or required treatment with intravenous dextrose)
   - Inability consistently to maintain preprandial plasma glucose >50 mg/dL for up to 48 hours of age and >60 mg/dL after 48 hours of age
   - Family history of a genetic form of hypoglycemia
   - Congenital syndromes (e.g., Beckwith-Wiedemann), abnormal physical features (e.g., midline facial malformation, microphallus).
3. **Reagent strips with reflectance meter.** Although in widespread use as a 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. 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).
   d. 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.
   e. New point-of-care devices are available to allow for the accurate and rapid determination of glucose levels on small-volume samples. Glucose analyzers that use specific glucose cartridges are more accurate, but they are expensive and require more blood.
4. **Laboratory diagnosis**
   a. The laboratory sample 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/hour in a blood sample that awaits analysis.
5. **Subcutaneous (SC) continuous glucose monitors** have been shown to be accurate but have primarily been used in research settings.
6. **Additional evaluation** for persistent hypoglycemia. Most hypoglycemia will resolve in 2 to 3 days. A requirement 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. Beta-hydroxybutyrate and free fatty acid levels. Measurement of plasma beta-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 indicated as follows 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). 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. It is recommended that breastfeeding should be initiated within the first hour of birth; preferably the baby should be put to the breast as soon as the mother and the baby are stable.

Breastfed infants have lower glucose levels. The use of alternate fuels may be an adaptive mechanism during the first days of life. Lactate, ketone bodies, pyruvate, amino acids, free fatty acids, and glycerol are the first mechanism to prevent neuronal injury. These alternative energy fuels are transported across the blood-brain barrier by monocarboxylate glycoprotein transporters (MCT 1 and 2), ketone bodies are low until milk feeds are established. Early breastfeeding enhances gluconeogenesis and increases the production of gluconeogenic precursors. Some infants will have difficulty in adapting to breastfeeding, and hypoglycemia has been reported to develop in breastfed infants with lactation problems 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. The traditional practices of giving prelacteal feeds (sugar water, honey, animal milk diluted) and discarding first breast milk should be strictly discouraged.

2. Dextrose gel. In 2013, the Sugar Babies study demonstrated that the administration of 40% dextrose gel to infants at risk for hypoglycemia decreased NICU admissions for hypoglycemia and led to lower formula feeding rates at 2 weeks of life. Some units are incorporating dextrose gel into their hypoglycemia protocols.

3. IV therapy

a. Indications

i. Inability to tolerate oral feeding

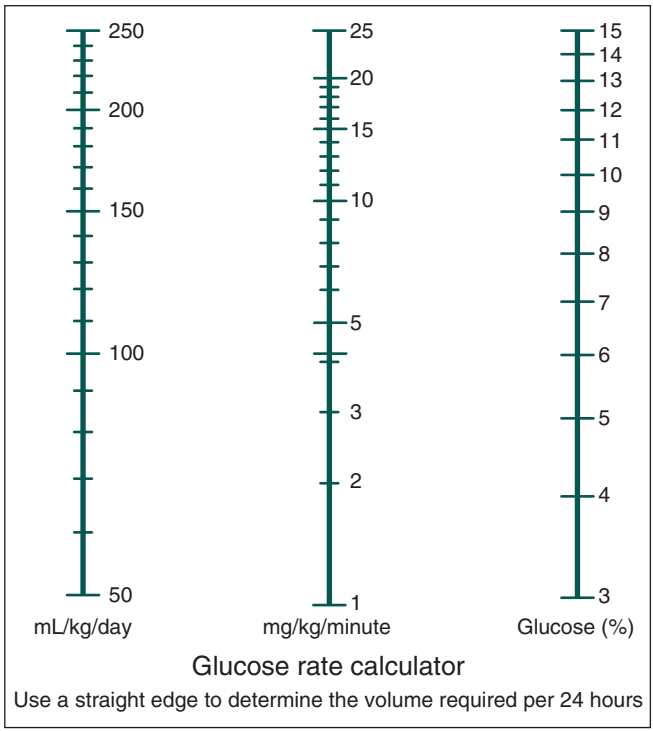

Figure 24.1. Interconversion of glucose infusion units. (From Klaus MH, Faranoff AA, eds. *Care of the High-Risk Neonate*. 2nd ed. Philadelphia, PA: WB Saunders; 1979:430.)

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. Mini bolus. The traditional 200 mg/kg dextrose "mini-bolus" given before instituting a continuous dextrose infusion for the treatment of neonatal hypoglycemia may not be necessary in asymptomatic hypoglycemic newborns. Two hundred milligrams per kilogram of glucose over 1 minute, to be followed by continuing therapy given 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 (see Fig. 24.1)

ii. Glucose infusion rate (GIR) may be calculated using the following formula:

$$\text{GIR (mg/kg/minute)} = \frac{\text{dextrose \% concentration} \times \text{mL/kg/day}}{144}$$

For example, in an infant receiving $D_{10}W$ at 80 mL/kg/day, the GIR would be

$$\frac{10 \times 80}{144} = 5.6 \text{ mg/kg/minute}$$

Another way to calculate the GIR can be easily remembered as follows (as it rhymes):

$$\frac{\text{D} \times \text{rate}}{6 \times \text{weight}}$$

This is equivalent to (dextrose % concentration × mL/hour on the pump)/(6 × 3 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 the total fluid goal and dextrose concentration.

iii. Recheck glucose level 20 to 30 minutes after IV bolus and then hourly until stable, to determine whether 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 FGR 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 adequate glucose ($D_{15}W$ 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.

4. Historically, providers have administered **hydrocortisone**, 10 mg/kg/day intravenously in two to three 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. It 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.
5. **Diazoxide** (8 to 15 mg/kg/day in divided doses every 8 to 12 hours) may be given orally to infants who are persistently hyperinsulinemic. 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, and coadministration with a diuretic such as hydrochlorothiazide may be considered.
6. **Octreotide** (5 to 20 μg/kg/day subcutaneously or intravenously divided every 6 to 8 hours). It is a long-acting somatostatin analog that inhibits insulin secretion. It can be used when diazoxide does not successfully control the glucose level. Tachyphylaxis can develop.
7. **Glucagon** (0.2 mg/kg intramuscularly, SC, or IV, 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, consider a ^{18}F-fluoro-L-DOPA positron emission tomography (PET) scan 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. Long-term follow-up and evaluation. Newborn babies exposed to hypoglycemia must be followed into late childhood. Recent systematic review showed no differences in neurodevelopmental impairment in early childhood, but significant problems were noted in midchildhood. Infants and children had visuo-motor problems, poor executive function, low literacy, and numeracy. Infants with hypoglycemia have been reported to exhibit a typical pattern of CNS injury particularly in the parieto-occipital cortex and subcortical white matter. However, it is often difficult clinically to separate isolated hypoglycemia from hypoxic-ischemic encephalopathy plus hypoglycemia. Some clinicians believe that 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. It is usually defined as a whole blood glucose level higher than 125 mg/dL or plasma glucose values higher than 145 mg/dL. This problem is not only commonly encountered in low-birth-weight preterm infants receiving parenteral

glucose but also seen in other sick infants. 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 more than 450 to 720 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 intracranial hemorrhage.

Although rarely seen in the first months of life, diabetes mellitus can present with severe clinical symptoms including polyuria, dehydration, and ketoacidosis that require prompt treatment. The genetic basis of neonatal diabetes is beginning to be understood and has implications for its treatment (see the following discussion).

A. Etiology

1. **Iatrogenic.** Exogenous parenteral glucose administration of more than 4 to 5 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 steroids, caffeine, theophylline, phenytoin, and diazoxide.
3. **Extremely low-birth-weight infants** (<1,000 g), possibly due to variable insulin response, persistent endogenous hepatic glucose production despite significant elevations in plasma insulin, or 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 associated with increased glucose levels.
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, infants present with significant hyperglycemia that requires insulin treatment in the first months of life. They characteristically are SGA term infants, without gender predilection, and one-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. Minor degrees of hyperglycemia are well tolerated.
Operational thresholds, at which treatment should be initiated.
Any blood glucose measurement of ≥20 mmol/L
Persistent blood glucose values of ≥15 mmol/L
Persistent blood glucose values of > 12 mmol/L with glycosuria ≥ 3+ on urinary dipstick testing

1. Measure glucose levels in preterm infants or infants with abnormal symptoms.
2. Extremely low-birth-weight preterm infants (<1,000 g) should start with a GIR of at least 4 to 6 mg/kg/minute. 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 under 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 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** therapy 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 VLBWs reported that prophylactic insulin use was associated with a 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 insulin available in India is 40 U/mL. Dilution with 40 mL of dextrose (or normal saline) makes the preparation as 0.1 U/ mL. Standard dilution is 15 units regular human insulin (0.15 mL) added to 29.85 mL normal saline for a concentration of 0.5 unit/mL.
      ii. Prior to starting the infusion, purge the IV tubing with a minimum of two 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 unit/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.
         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 unit/kg/hour (usual starting dose is 0.05 unit/kg/hour).

$$\text{Flow rate (mL/hour)} = \frac{\text{Dose (units/kg/hour)} \times \text{weight (kg)}}{\text{Concentration (units/mL)}}$$

For example, if the planned starting dose is 0.05 unit/kg/hour, and the infant weighs 600 g (0.6 kg).
Then at 0.05 units/kg/hour × 0.6 kg the baby needs 0.03 units/hour. If the available concentration on insulin is 0.5 units/mL, then the infusion rate will be:
Concentration is 0.5 unit/mL.
Infusion rate is:

$$\frac{0.03 \text{ unit/hour}}{0.5 \text{ mL}} = 0.06 \text{ mL/hour}$$

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, insulin shifts potassium into the cell resulting in hypokalemia.

f) Monitor for rebound hyperglycemia.

b. SC 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.

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25 Abnormalities of Serum Calcium and Magnesium

Steven A. Abrams

KEY POINTS

- In very preterm babies (<32 weeks) ionized calcium values of 0.8 to 1 mmol/L are common and not usually associated with clinical symptoms.
- In infants of >32 weeks' gestation, symptoms of hypocalcemia may occur more with an ionized calcium concentration of <1 mmol/L.
- 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 common, especially in extremely small preterm infants, and requires adjustment of calcium intake when severe in the first days of life.

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. In larger infants, and in infants of >32 weeks' gestation, symptoms may more readily occur with an ionized calcium concentration of <1 mmol/L.

2. **Pathophysiology**

   a. Calcium ions (Ca^{2+}) in cellular and extracellular fluid (ECF) are essential for many biochemical processes. Regulation of serum and ECF-ionized calcium concentration within a narrow range is critical for blood coagulation, neuromuscular excitability, cell membrane function, and cellular enzymatic and secretory activity.

   b. **Hormonal regulation of calcium homeostasis.**
   The principal calcium-regulating hormones are parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D ($1,25(OH)^2D$, also referred to as calcitriol).

      i. **PTH.** 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.

ii. **Vitamin D.** Vitamin D is synthesized from provitamin D in the skin after exposure to sunlight and is also ingested in the diet. It is transported to the liver, where it is converted to 25(OH)D (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)^{2}D (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 of diabetes is poor. Hypercalcitoninemia, hypoparathyroidism, abnormal vitamin D metabolism, and hyperphosphatemia have all been implicated, but the etiology remains uncertain.

c. **Perinatal asphyxia.** Severe perinatal asphyxia is frequently associated with hypocalcemia, hypomagnesemia, and hyperphosphatemia. Decreased calcium intake and increased endogenous phosphate load are the likely causes.

d. **Congenital.** Parathyroid glands 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 or CATCH-22 syndrome, an acronym for cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia caused by chromosome 22q11 deletion.

e. **Pseudohypoparathyroidism.** Pseudohypoparathyroidism is associated with resistance to the PTH hormone. It can be caused by GANS1 mutation. Serum calcium levels are low, phosphate levels are high, despite high PTH levels. This is due to resistance of end organs to PTH.

f. **Maternal hyperparathyroidism.** Unrecognized maternal hyperparthyroidism causes maternal hypercalcemia, this results in fetal hypercalcemia, which in turn suppresses parathyroid activity in the fetus and later impaired parathyroid responsiveness to hypocalcemia after birth.

g. **Magnesium deficiency.** Normal serum levels of magnesium (Mg) are 1.6 to 2.8 mg/dL. Mg deficiency may be congenital (magnesium transport disorder) or more commonly seen in premature infants, infants of magnesium-deficient mothers, and infants with intrauterine growth retardation.

h. **Vitamin D deficiency**

Babies born to mothers with low serum vitamin D levels will also have low vitamin D levels.

i. **Alkalosis - Metabolic and respiratory**

Alkali therapy is rarely used in NICU these days but when bicarbonate is infused, there is a risk of significant fall in calcium and potassium levels.

j. **Massive transfusion.** Rapid infusion of citrate-buffered blood (exchange transfusion) chelates ionized calcium and causes hypocalcemia.

k. **Shock and sepsis**

l. **Phototherapy.** Phototherapy may be associated with hypocalcemia by decreasing melatonin secretion and increasing uptake of calcium into the bone.

m. **Late-onset hypocalcemia.** High phosphate intakes (high phosphate–containing formula milk) lead to excess phosphorus and decreased serum calcium. This had happened in the past when the formula milk supplied had high phosphate levels.

B. Diagnosis

1. Clinical presentation

a. Hypocalcemia increases 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 hypocalcemia, in contrast, frequently present as seizures. Often, they must be differentiated from other causes of newborn seizures, including "fifth-day" fits.

2. History

For late-onset presentation, mothers may report partial breastfeeding *but rarely, if ever, exclusive breastfeeding*. Abnormal movements and lethargy may precede obvious seizure activity. Rarely, the use of goat's milk or whole milk of cow may be reported. Symptoms are usually described beginning from the third to fifth days of life.

3. Laboratory studies

Inonized calcium. 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. 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. Calcium concentration may be reported as milligrams per deciliter or as molar units (10 mg/dL converts to 2.5 mmol/L).

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.

Phosphorus. Serum phosphorus levels must be measured along with serum calcium levels. In most cases of early hypocalcemia, ionized calcium levels will be low and phosphorus levels moderate to severely elevated. This hypocalcemia is a result of poor PTH activity.

In metabolic bone disease (usually 4 weeks and beyond) in extreme preterm babies, the serum calcium and phosphorus levels are both decreased. This hypocalcemia is primarily due to renal tubular losses of phosphorus (due to immaturity) with added nutritional component. Urinary phosphorus is high. Rarely MBD may be worsened by vitamin D deficiency as well.

Vitamin D. Although an association with vitamin D deficiency is uncommon, an assessment of both maternal and neonatal serum 25(OH)D levels may be warranted. Values <10 ng/mL are suggestive of severe deficiency that may not be the reason for hypocalcemia in most infants.

Magnesium. Hypomagnesemia is often seen in association with late-onset hypocalcemia, and must be measured.

4. **Monitoring**
   - **a.** Suggested schedule for monitoring calcium levels in infants such as VLBW, IDM, and birth depression who are at risk for developing hypocalcemia is as follows:
     - **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 usually needed unless neonatal hypocalcemia does not readily resolve with calcium therapy. Measurement of $1,25(OH)_2D$ is rarely needed in neonates.
     - **iv.** A prolonged electrocardiographic QTc interval is a traditional indicator of low ionized calcium; it has been found to have poor specificity in the newborn period.

5. **Imaging**

   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 *CATCH-22* or *DiGeorge sequence*. Genetic consultation and evaluation may be of value if this is suspected.

C. Treatment

1. **Intravenous calcium**
   - **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 only for the 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.
   - **g.** Calcium gluconate 10% solution is preferred for intravenous use.
     - **i.** If the ionized calcium level drops to 1 mmol/L or less (>1,500 g) or 0.8 mmol/L or less (<1,500 g), a continuous intravenous calcium

infusion may be commenced. For infants with early hypocalcemia, this may be done through the parenteral nutrition (PN). A dose of 40 to 50 mg/kg/day of elemental calcium is necessary.

ii. It may be desirable to prevent hypocalcemia in 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).

iii. 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.

h. Monitor heart rate and rhythm and the infusion site throughout the infusion.

i. Repeat the dose in 10 to 20 minutes if there is no clinical response.

j. Following the initial dose(s), maintenance calcium should be given through continuous intravenous infusion.

2. **Correction of associated hypomagnesemia.** Give 50% magnesium sulfate solution (500 mg or 4 mEq/mL)—25 to 50 mg/kg or 0.2 to 0.4 mEq/kg per dose—every 12 hours, IV over at least 2 hours or intramuscular (IM).

   a. Aim for serum magnesium concentration greater than 1.5 mg/dL (0.62 mmol/L).

   b. Rapid IV infusions must be avoided due to risk of arrhythmias.

3. **Hypocalcemia associated with hyperphosphatemia**

   a. The goal of initial therapy is to reduce phosphate intake while increasing calcium intake. Reduce phosphate intake by feeding the infant preferably human milk or a low-phosphorus formula.

   b. Avoid the use of preterm formulas, lactose-free or other special formulas, or transitional formulas. These have high levels of phosphorus or may be limited in calcium bioavailability.

   c. Increase the oral calcium intake using supplements.

   d. Phosphate binders are generally not necessary and may not be safe for use, especially in premature infants.

   e. Gradually wean calcium supplements over 2 to 4 weeks. Monitor serum calcium and phosphorus levels one to two times weekly.

4. **Vitamin D.** The use of vitamin D or active vitamin D (1,25-dihydroxyvitamin D) is not usually necessary. If a serum 25(OH)D level is obtained and is 10 ng/mL, then 2,000 IU of vitamin D should be given daily, and the value rechecked in 14 to 21 days. Rarely should higher doses of vitamin D be given to neonates.

5. **Rare defects in vitamin D metabolism** are treated with vitamin D analogs, for example, dihydrotachysterol and calcitriol (Rocaltrol). The rapid onset of action and short half-life of these drugs reduces the risk of rebound hypercalcemia.

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) is common and does not require any intervention at all.

2. Etiology

a. Excess intake (usually iatrogenic) or imbalance of calcium intake

b. Clinical adjustment of PN by completely removing the phosphorus 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 PN mineral intakes. Values up to 2.2 mmol/L of ionized calcium occur. This is likely due to inability to utilize calcium in these infants and may or may not be associated with a high serum phosphorus.

d. Hyperparathyroidism

i. Transient hyperparathyroidism associated with maternal hypoparathyroidism usually resolves over several weeks.

ii. Neonatal severe primary hyperparathyroidism (NSPHP). The parathyroid glands 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 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.

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 PN

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 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 utilize 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/PN are not apparent. Measurement of $1,25(OH)^2D$ is rarely indicated unless hypercalcemia persists in infants >1,000 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 the 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)

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.

2. Inorganic phosphate may lower serum calcium levels in hypophosphatemic patients by inhibiting bone resorption and promoting bone mineral accretion.

3. 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.

4. Low-calcium, low-vitamin D diets are an effective adjunctive therapy for subcutaneous fat necrosis and Williams' syndrome.

5. 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.

6. Parathyroidectomy with autologous reimplantation may be indicated for severe persistent neonatal hyperparathyroidism.

7. Early supplementation of phosphorus is imperative in PN for better mineral accretion along with calcium supplementation. Phosphorus supplementation is in the form of sodium or potassium phosphate in PN or early use of breast milk (with Ca:P ratio of 1:2), or fortified human milk or preterm formula is essential.

III. DISORDERS OF MAGNESIUM: HYPOMAGNESEMIA AND HYPERMAGNESEMIA.

In newborns, average magnesium (Mg) levels at birth are similar to that of mothers during pregnancy (0.74 mmol/L), but increased during the first week of life (0.91 mmol/L) before returning to adult levels (confidence intervals omitted). The Mg levels are higher in babies born to mothers with Mg supplementation during pregnancy, average 1.29 mmol/L at birth and 1.44 mmol/L during the first week of life. Determinants of neonatal Mg include prenatal Mg supplementation, gestational age, birth weight, renal maturity/function, and postnatal Mg intake.

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 PN

2. Hypomagnesemia

Mg deficiency may be noted in infants of magnesium-deficient mothers and intrauterine growth retardation babies.

Hypomagnesemia is not uncommon with excessive dietary calcium, phosphorus, or protein intake in relation to dietary magnesium, especially during periods of excess demand associated with rapid growth.

Low Mg may be due to low magnesium supplementation in parenteral nutrition. Other reasons can be the use of magnesium-wasting drugs, gastrointestinal or renal losses, or increased needs during postsurgical healing.

B. Diagnosis

1. Elevated serum magnesium level (>3 mg/dL) suggests hypermagnesemia, although symptoms are uncommon with serum values <4 to 5 mg/dL. 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. Mg levels may be low in asphyxiated babies, and may be further low during therapeutic hypothermia.

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 or intramuscularly given over 1 to 2 hours. When administering intravenously, infuse slowly and monitor the 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. In symptomatic babies with hypermagnesemia, begin feedings only after suck and intestinal motility are established. Rarely, respiratory support may be needed.

Suggested Readings

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26 Neonatal Hyperbilirubinemia

Ann R. Stark and Vinod K. Bhutani

KEY POINTS

- Severe neonatal jaundice (SNJ) is an important cause of preventable neurodisability: cerebral palsy and deafness.
- SNJ is far more common in low- and middle-income countries, steps need to be urgently taken to improve health care systems to decrease the associated neurodisability.
- Visual inspection is **not** a reliable measure of bilirubin level.
- Jaundice identified prior to age 24 hours is a medical emergency and may result from excessive bilirubin production.
- Bilirubin measurement and identification of risk factors before discharge of healthy term and late preterm infants predicts the need for phototherapy and guides the timing of follow-up.
- Prevention of bilirubin induced neurological dysfunction (BIND) requires quality improvements at all levels: processes, manpower training, improvement of equipment, and infrastructure. All levels of health care manage babies with neonatal hyperbilirubinemia, necessitating changes even at primary health care.
- Evaluation of cholestasis in infants with jaundice at 2 weeks of age ensures prompt therapy of treatable disorders.

I. BACKGROUND. Physiologic jaundice is very common; most babies look yellow for a few days and recover with no intervention (or with perception of success following exposure to sunlight or even phototherapy). A few babies may develop severe neonatal jaundice (SNJ) that can result in irreversible neurodisability or death if not managed timely and appropriately. It is important for a pediatrician to assess jaundice in the hospital at birth admission and educate about timely follow-up. Objective assessment of bilirubin (not just visual estimation), recognizing babies at a higher risk of SNJ, and if necessary, treatment in the form of phototherapy or exchange transfusion (ET) must be initiated without delay; the babies must be followed up for development and hearing.

A. Physiologic jaundice. Approximately 85% of all term newborns and most preterm infants develop clinical jaundice. Also, 6.1% of well term newborns have a peak total bilirubin (TB) level >12.9 mg/dL. A TB level >15 mg/dL is found in 3% of normal term infants.

B. Severe Neonatal Jaundice. SNJ is defined as jaundice related to any one of the clinical outcomes including acute bilirubin encephalopathy (ABE), kernicterus,

ET, or jaundice-related death. SNJ is not evenly distributed across the world, the low- and middle-income countries are most affected. A systematic review of population-based studies showed extremely high incidence in the South East Asian region, 251 (132 to 473)/10,000 births in sharp contrast to 4.4 (1.8 to 10.5) and 3.7 (1.7 to 8.0) in America and Europe, respectively. The incidence of ET was 107 in the South East Asian region as compared to 0.38 in Europe and America. SNJ is probably the commonest cause of preventable neurodisability; it is associated with cerebral palsy, deafness, and language problems. The lack of equity calls for identifying gaps in health care and capacity building in resource-limited regions. Even from developed world (Sweden), audits of population-based registry showed association between severe hyperbilirubinemia and neurodisability. In 85% of the children, preventable factors in health care were noted: lack of predischarge bilirubin evaluation, incorrect estimate of bilirubin, and delay in phototherapy/ET.

II. BILIRUBIN METABOLISM.

The TB level results from the balance of bilirubin production and excretion.

A. Bilirubin production.

Bilirubin is derived from the breakdown of heme-containing proteins (metabolized 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.

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 to 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** and **carbon monoxide (CO)** (excreted from the lung); the **iron** that is released is reused. The enzyme **biliverdin reductase** 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 does not usually enter the central nervous system (CNS) and is thought to be nontoxic. Displacement of bilirubin from albumin by acidosis, by drugs, such as ceftriaxone, or by free fatty acids (FFAs) at high molar ratios of FFA:albumin may increase bilirubin toxicity.
2. **Hepatic uptake.** Nonpolar, fat-soluble 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.
3. **Conjugation.** In hepatocytes, the enzyme **uridine diphosphogluconurate glucuronosyltransferase (UGT1A1)** catalyzes the conjugation of bilirubin

with glucuronic acid, resulting in mostly bilirubin diglucuronides and some monoglucuronides that are more water-soluble than unconjugated bilirubin. Both forms of conjugated bilirubin are excreted into the bile canaliculi against a concentration gradient.

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's syndrome). Differences in these polymorphisms in individuals of different ancestry contribute to the racial 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. 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 hemolytic disease of the newborn and in fetal intestinal obstruction below the bile ducts.

III. NONPATHOLOGIC HYPERBILIRUBINEMIA. The serum TB level of most newborn infants rises in full-term infants to a peak of 6 to 8 mg/dL by 3 to 5 days of age and then falls. A rise to 12 mg/dL is in the physiologic range. In preterm infants, the peak may be 10 to 12 mg/dL on the fifth day after birth, and can rise further in the absence of treatment without any specific abnormality of bilirubin metabolism, and may not be benign based on the infant's gestational age. Levels <2 mg/dL may not be seen until 1 month of age in both full-term and preterm infants. This nonpathologic jaundice 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 days vs. 120 days) in infants compared to in adults
2. Increased ineffective erythropoiesis and increased turnover of non-hemoglobin heme proteins

B. Defective uptake of bilirubin from plasma caused by decreased ligandin and binding of ligandin by other anions

C. Decreased clearance due to decreased UGT1A1 activity. ***In term infants at 7 days of age, UGT activity is approximately 1% that of adults and reaches adult levels only by 3 months of age.***

D. Increased enterohepatic circulation caused by high levels of intestinal β-glucuronidase, preponderance of bilirubin monoglucuronide rather than of diglucuronide, decreased intestinal bacteria, and decreased gut motility with poor evacuation of bilirubin-laden meconium

IV. HYPERBILIRUBINEMIA.

It is defined as a TB >95th percentile (on the hour-specific Bhutani nomogram) (Fig. 26.1).

A. The following situations suggest severe hyperbilirubinemia and require evaluation:

1. Onset of jaundice before 24 hours of age

2. An elevation of TB that requires phototherapy (Fig. 26.2)

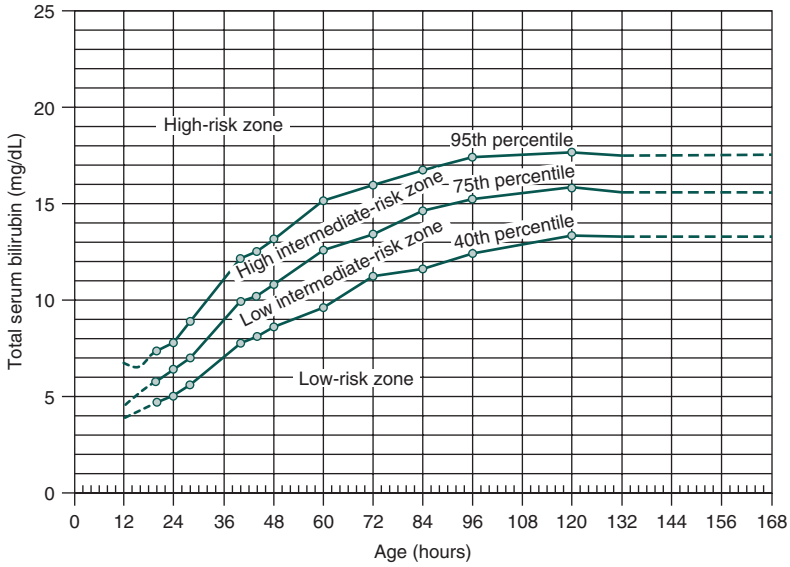

Figure 26.1. Hour-specific bilirubin nomogram. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values. The high-risk zone is designated by the 95th percentile track. The intermediate-risk zone is subdivided to upper- and lower-risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. (Dotted extensions are based on <300 TSB values/epoch). This study is based on heel-stick venous bilirubins. (Reprinted with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics* 1999;103:6–14.)

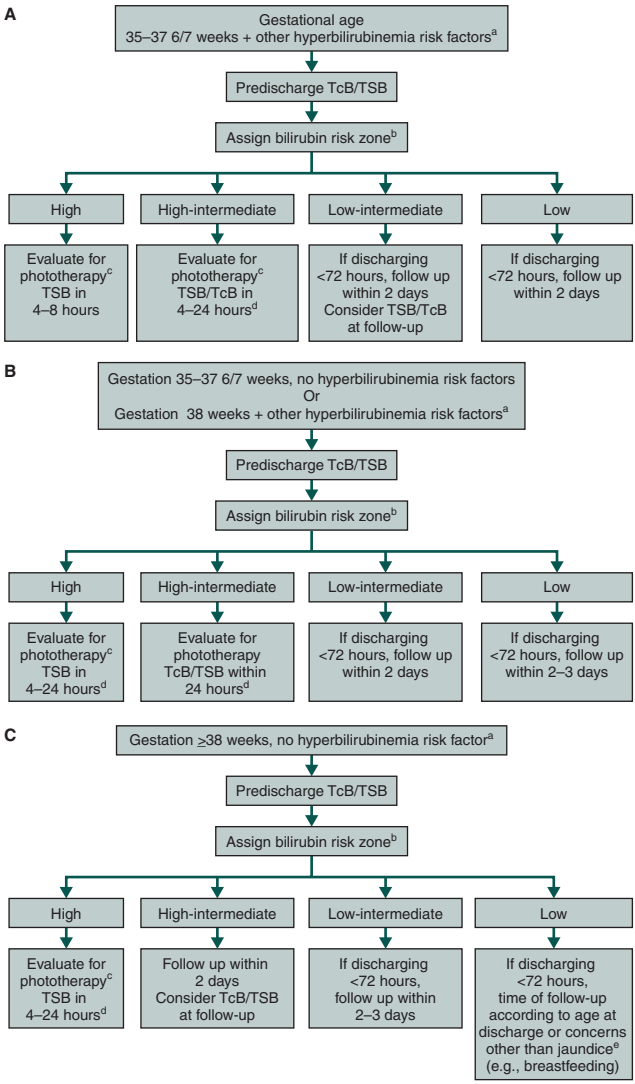

Figure 26.2. Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. • Provide lactation evaluation and support for all breastfeeding mothers. • Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile (Fig. 26.1). Higher and earlier initial TSB levels require an earlier repeat TSB measurement. • Perform standard clinical evaluation at all follow-up visits. • For evaluation of jaundice, see 2004 AAP guideline. (a) Table 26.1. (b) Fig. 26.1. (c) Fig. 26.3. (d) In hospital or as outpatient. (e) Follow-up recommendations can be modified according to level of risk for hyperbilirubinemia; depending on the circumstances in infants at low risk, later follow-up can be considered. (From Maisels MJ, Bhutani VK, Bogen D, et al. Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications. *Pediatrics* 2009;124:1193–1198.)

3. Rate of rise in total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level of >0.2 mg/dL/hour
4. Associated signs of illness such as lethargy, poor feeding, and temperature instability
5. Jaundice persisting after 14 days in a term infant, high-colored urine, and pale stools

B. Causes of severe hyperbilirubinemia (SNJ)

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, sequestered blood due to bruising or cephalohematoma, and polycythemia.
2. **Decreased bilirubin clearance**
   - **a.** Prematurity is associated with poor bilirubin conjugation and birth of babies few days before term (late preterm) increases the risk of jaundice significantly.
   - **b.** Poor feeding results in reabsorption of bilirubin due to enterohepatic recirculation.
   - **c.** Family history (previous sibling) with SNJ may be due to genetic variance in metabolism. The subsequent babies are at a higher risk.
   - **d.** Decreased clearance may occur in infants of diabetic mothers and with congenital hypothyroidism, galactosemia, and other inherited metabolic disorders.
   - **e.** Mutations in the gene that encodes UGT1A1 decrease bilirubin conjugation, reducing hepatic clearance and increasing serum TB levels.
   - **f.** Crigler–Najjar syndrome due to either absent UGT activity (type I) or reduced UGT activity (type II) results in severe hyperbilirubinemia.
   - **g.** Gilbert's syndrome results from a mutation in the promoter region of the UGT1A1 gene, reducing the 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.
   - **h.** Polymorphisms of the organic anion transporter protein OATP-2 may lead to severe hyperbilirubinemia, especially when combined with a UGT1A1 mutation.
3. **Increased enterohepatic circulation.** Pathologic conditions leading to increased enterohepatic circulation include decreased enteral intake, including breastfeeding failure; or impaired intestinal motility due to intestinal atresias, meconium ileus, or Hirschsprung's disease.
4. **Breastfeeding failure jaundice.** Breastfeeding failure jaundice typically occurs with lactation failure during the first postnatal week that leads to insufficient intake, with weight loss and sometimes hypernatremia. Hyperbilirubinemia is

attributed mainly to the decreased intake of milk that leads to slower bilirubin elimination and increased enterohepatic circulation. The risk of hyperbilirubinemia (≥20 mg/dL) is significantly increased when breast milk feeding is associated with polymorphisms in genes involved in hepatic uptake and conjugation of bilirubin. This is an example of an environmental modifier (breast milk feeding) on genetic predisposition of jaundice. Prevention or treatment of this condition involves ensuring frequent breastfeeding and lactational support. Infants who are breastfed have higher bilirubin levels on day 3 of age compared to formula-fed infants, although this never causes SNJ.

5. **"Breast milk jaundice"** (condition that may be due to genetic predisposition) **occurs in about 2.4% of all infants**. Typically, it 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 stopped, 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 thought to be associated with either Gilbert's disease or perhaps a factor in human milk, possibly β-glucuronidase, that deconjugates intestinal bilirubin and promotes its absorption. This condition generally resolves spontaneously and may rarely require phototherapy. The benefits of breast milk far outweigh the risk of hyperbilirubinemia and cessation of breastfeeding is not recommended.

V. PREVENTION OF HYPERBILIRUBINEMIA IN HEALTHY TERM AND LATE-PRETERM INFANTS.

The American Academy of Pediatrics (AAP) practice guideline for the treatment of unconjugated hyperbilirubinemia in healthy newborn infants at 35 weeks' gestation and greater is based on three general principles to reduce the occurrence of severe hyperbilirubinemia while also reducing unintended harm: **universal systematic assessment before discharge, close follow-up, and prompt intervention when indicated**.

A. Risk assessment is performed prior to discharge

of otherwise healthy infants ≥35 weeks' gestation to predict the development of severe hyperbilirubinemia that requires treatment. This is accomplished with a measurement of serum/plasma or TcB. Visual inspection is **not** a reliable measure of bilirubin level.

1. A **screening TB** collected by heel-stick sampling at the time of the metabolic screen is plotted on an hour-specific bilirubin nomogram (Fig. 26.1) and combined with clinical risk factors (see section V.B), especially lower gestational age, helps to identify infants at an increased risk for developing hyperbilirubinemia and those who require close follow-up.
2. **TcB** measurement is sometimes used to avoid blood sampling, and TcB hour-specific nomograms are available. TcB estimation is noninvasive and the device measures bilirubin levels by comparing the wavelengths of lights directed into the skin of the neonate and of those that return back. TcB measurements correlate well with TB levels in term and near-term infants and the AAP recommends the use of TcB devices for screening in infants greater than 35 weeks' gestation. The use of these devices can reduce the need for

blood sampling by 40% to 60%. However, TcB measurements are not reliable in certain circumstances such as during or after phototherapy, after sunlight exposure, or at TB levels ≥15 mg/dL. TcB can overestimate TB in darkly pigmented infants and underestimate TB in light-skinned infants. As a result, if TcB is used to screen infants, TB should be measured if TcB is above the 75th percentile on the Bhutani nomogram (Fig. 26.1) or above 95th percentile on TcB nomogram, if the TcB is ≥13 mg/dL on follow-up after discharge, or if therapy is being considered.

3. **End-tidal carbon monoxide (ETCO)**, corrected to ambient CO_2, does not improve the sensitivity or specificity of predicting severe hyperbilirubinemia over TB alone. However, it identifies infants with increased bilirubin production due to hemolytic conditions who need closer monitoring and earlier intervention. It is not used in routine clinical practice.

B. Major risk factors for the development of severe hyperbilirubinemia include the following:

1. Predischarge TB in a high-risk zone (>95th percentile for age in hours according to the Bhutani nomogram) or high intermediate-risk zone (Fig. 26.1)
2. Jaundice within the first 24 hours after birth
3. Immune or other hemolytic disease
4. Gestational age 35 to 36 weeks (even babies <38 weeks' gestation are at a higher risk)
5. Previous sibling with jaundice
6. Cephalohematoma or significant bruising
7. East Asian race

C. 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. Infants discharged before 72 hours should be seen within the next 2 days. Infants at lower gestational ages or who have other risk factors should be seen earlier (see Fig. 26.2). Suggested management and follow-up are guided by predischarge bilirubin level and risk factors including gestational age. Parents should receive written and verbal instructions about the need for follow-up.

VI. EVALUATION OF INFANT 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, α_1-antitrypsin deficiency, tyrosinosis, hypermethioninemia, Gilbert's disease, Crigler–Najjar syndrome types I and II, or cystic fibrosis.

c. Ethnic or geographic origin associated with hyperbilirubinemia (East Asian, Greek, and American Indian)

d. A sibling with jaundice or anemia may suggest blood group incompatibility or breast milk jaundice.

e. Vacuum extraction (cephalohematoma).

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), 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.

d. Delayed cord clamping may be associated with neonatal polycythemia and increased bilirubin load.

4. Infant history

a. History suggestive of encephalopathy—poor feeding, excessive sleepiness, and temperature instability increase the risk of bilirubin-induced neurologic injury and may be early signs of kernicterus. In either case, urgent ET may be critical.

b. Delayed or infrequent stooling may be caused by poor caloric intake or intestinal obstruction and lead to increased enterohepatic circulation of bilirubin.

c. Poor caloric intake may decrease bilirubin uptake by the liver.

d. Vomiting can be due to sepsis, pyloric stenosis, or galactosemia.

B. Physical examination. Jaundice results from deposition of bilirubin in the skin and subcutaneous tissues. Blanching the skin with finger pressure makes it easier to observe jaundice. However, **visual inspection is not a reliable indicator of the 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. Jaundiced infants should have a bilirubin measurement and be examined for the following contributing factors:

1. Lower gestational age

2. Small for gestational age (SGA) may be associated with polycythemia and intrauterine infections.

3. Microcephaly may be associated with congenital infections.

4. Extravascular blood—bruising, cephalohematoma, or other enclosed hemorrhage

5. **Pallor** associated with hemolytic anemia or extravascular blood loss
6. **Petechiae** may suggest congenital infection, sepsis, or erythroblastosis.
7. **Hepatosplenomegaly** may be associated with hemolytic anemia, congenital infection, or liver disease.
8. **Omphalitis** or other sign of infection
9. **Chorioretinitis** associated with congenital infection
10. Evidence of **hypothyroidism** (see Chapter 61)

C. Additional laboratory tests should be performed when serum TB is ≥95th percentile for age in hours or at or near the threshold for initiation of phototherapy.

1. **The mother's blood type, Rh, and antibody screen** should have been done during pregnancy and the antibody screen repeated at delivery.
2. **The infant's blood type, Rh, and direct Coombs' test** to assess for isoimmune hemolytic disease. Infants of Rh-negative women should have a blood type, Rh, and Coombs' test performed at birth. Routine blood typing and Coombs' testing 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. Blood typing and Coombs' testing should be considered for infants who are discharged early, especially if the mother is type O.
3. **Peripheral smear for RBC morphology and reticulocyte count** to detect causes of Coombs-negative hemolytic disease (e.g., spherocytosis). 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. According to one report, a mean corpuscular hemoglobin concentration (MCHC) of ≥36.0 g/dL has 82% sensitivity and 98% specificity for diagnosing HS.
4. **Hematocrit** or hemoglobin measurement will identify polycythemia or suggest blood loss from occult hemorrhage.
5. Identification of specific **antibody on the infant's RBCs** (if result of direct Coombs' test is positive)
6. **Direct or conjugated bilirubin** should be measured when bilirubin levels are at or above the 95th percentile or when the phototherapy threshold is approaching. Direct bilirubin should also be measured when jaundice persists beyond the first 2 weeks of age or with signs of cholestasis (light-colored stools and bilirubin in urine). If direct bilirubin is elevated, obtain urinalysis and urine culture, check state newborn screen for hypothyroidism and galactosemia, and check urine for reducing substances (see section IX).
7. With prolonged jaundice, tests for liver disease, congenital infections, sepsis, metabolic defects, or hypothyroidism are indicated.
8. **G6PD measurement** may be helpful, especially in infants of African, East Asian, Mediterranean, or Middle Eastern descent or if the TB is ≥18 mg/dL.

The incidence of G6PD deficiency among African Americans males is 11% to 13%, comprising the most affected subpopulation in the United States.

VII. MANAGEMENT OF UNCONJUGATED HYPERBILIRUBINEMIA. Management of hyperbilirubinemia is directed at prevention of encephalopathy or severe hyperbilirubinemia, defined as TB >25 g/dL in term, even in the absence of encephalopathy. Treatment thresholds are lower during the first few days of life. In late preterm infants and in preterm infants, lower values may preferably be treated. **Initiation of therapy** is directed by the hour-specific TB value, and modified by the presence of any risk factors that increase the risk of brain damage 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 (Fig. 26.3). These neurotoxicity risk factors include isoimmune hemolytic disease, G6PD deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, or albumin <3 g/dL (if measured) (Table 26.1). Lower gestational age increases the risk of toxicity. Intervention in preterm infants is guided by the gestational and postmenstrual age (Table 26.2). **Phototherapy** is the initial intervention used to treat and prevent severe hyperbilirubinemia in asymptomatic infants and should be provided to infants with signs of ABE while preparations are made for ET. TB typically begins to decline within a few hours of treatment initiation. The rate of decline is increased by increased irradiance, more exposed surface area, and a higher initial TB value.

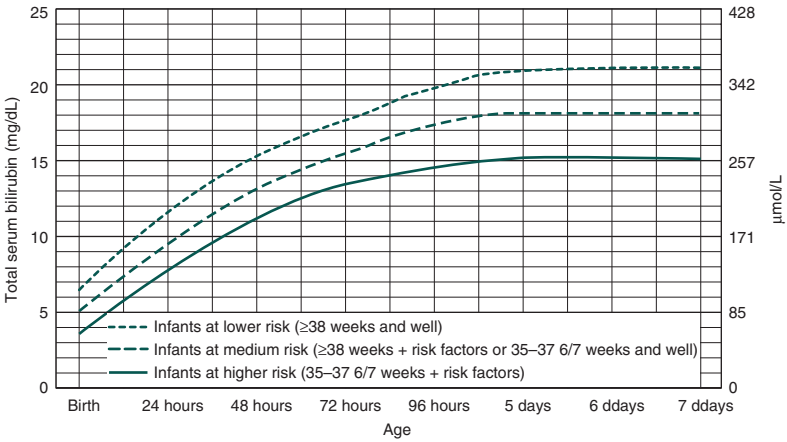

Figure 26.3. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. TSB, total serum bilirubin. • Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin. • Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured). • For well infants 35–37 6/7 weeks, can adjust TSB levels for intervention around the medium-risk line. It is an option to intervene at lower TSB levels for infants closer to 35 weeks and at higher TSB levels for those closer to 37 6/7 weeks. • It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors. (Reprinted with permission from the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297–316.)

Table 26.1. Risk Factors for Hyperbilirubinemia Neurotoxicity

Isoimmune hemolytic disease
G6PD deficiency
Asphyxia
Sepsis
Acidosis
Albumin <3.0 mg/dL

G6PD, glucose-6-phosphate dehydrogenase.
Source: From Maisels MJ, Bhutani VK, Bogen D, et al. Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications. *Pediatrics* 2009;124:1193–1198.

Table 26.2. Suggested 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: 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.

A. Mechanisms of bilirubin reduction by phototherapy

1. The main mechanism is **structural isomerization** by light that irreversibly converts bilirubin to lumirubin, a more soluble substance that can be excreted into bile and urine without conjugation.
2. **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 distinguish between the isomers, so TB levels may not change, although they may be less toxic.
3. **Photo-oxidation** is a slow process that converts bilirubin to small polar products that are excreted in the urine and is the least important mechanism of bilirubin elimination.

B. Characteristics of devices. Although multiple devices are available for phototherapy, according to an AAP Technical Report, the most effective are characterized by the following:

1. Light emission in the blue-green spectrum (460 to 490 nm), which includes the region (460 nm) where bilirubin most strongly absorbs light
2. Irradiance of at least 30 $\mu W/cm^2/nm$
3. As close to the baby as possible (older recommendation of 45 cm should not be practiced)
4. Illumination of maximal body surface area
5. Shown to decrease TB during the first 4 to 6 hours of exposure

C. Light sources

1. Blue light-emitting diodes (LEDs) provide optimal high-intensity light in the absorption spectrum of bilirubin and are available as either overhead or underneath (mattress or fiberoptic pad) devices. The LED units do not generate as much heat and can be placed closer to the infant. The light sources are durable with an average life span of 10,000 hours. Because LED units deliver high intensity light in a narrow spectrum, are power efficient and durable, they are preferred over fluorescent and halogen lights.
2. Among fluorescent light phototherapy, fluorescent special blue light F20T12/BB and TL52 tubes lower TB most effectively because they deliver light in the blue-green spectrum, providing maximal absorption and good skin penetration.
3. Halogen white lights are placed at the recommended distance from the infant because they are hot and can cause thermal injury.
4. Fiberoptic blankets or pads can be placed directly under the infant, generate little heat, and provide higher irradiance than fluorescent lights. 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.

D. Phototherapy administration

1. Parents must be educated about the need for phototherapy. Often the stress of delay in discharge from the hospital (or readmission) is compounded by separation from the mother and fear of high bilirubin.

   Exposure during phototherapy should be as extensive as possible, minimizing the area covered by a diaper.

   An opaque mask should shield the eyes, avoiding occlusion of the nose.
2. Fluorescent lights should be used with the infant in an open crib, bassinet, or warmer because the top of an incubator would prevent the lights from being close enough to the infant.
3. Encourage exclusive breastfeeding and tolerate short interruptions (of up to 30 minutes) for breastfeeding, general care, or cuddles if TB is not significantly high. Use of reflective curtains during phototherapy may result in greater decline in bilirubin and even shorter duration of hospital stay.

E. Sunlight exposure. Although sunlight exposure effectively lowers the TB level, safety concerns, including exposure to ultraviolet light, potential sunburn, and thermal effects, preclude the use of sunlight as a reliable therapeutic tool. Delay in accessing health care and treatment may happen, as parents tend to try sunlight

exposure as the first treatment. In low-resource settings, the use of appropriate filters and thermal monitoring may allow the use of sunlight for phototherapy.

F. Monitoring

1. **TB level** is measured to monitor the response to therapy. The frequency of measurement depends on the initial TB value and the baby's age at initiation. When phototherapy is started during the birth hospitalization for a rising TB, TB is measured 4 to 6 hours after initiation and then repeated in 8 to 12 hours if TB has declined. For babies readmitted after birth hospitalization with a TB value that exceeds the 95th percentile for age in hours, TB is measured 2 to 3 hours after phototherapy is begun to ensure that TB is decreasing. TB is measured 18 to 24 hours after discontinuation of phototherapy.

G. Adverse effects. Phototherapy is generally considered safe. 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 an erythematous rash, if present, is typically transient.

1. **"Bronze baby" syndrome**, a dark bronze discoloration of the skin thought to be related to impaired excretion of photoproducts of bile pigment, may occur with phototherapy in infants with direct hyperbilirubinemia (cholestatic jaundice) and usually resolves gradually within a few weeks after phototherapy is discontinued. The etiology is unknown, and whether the bronze pigments cause neurotoxicity is uncertain.
2. Due to the risk of retinal degeneration seen in animals after 24 hours of fluorescent phototherapy exposure and for reasons of infant comfort, the eyes are covered in all newborns undergoing phototherapy.
3. Risk of high-intensity phototherapy—potential oxidative stress, especially in very low-birth-weight (VLBW) babies

H. Adequate hydration and urine output should be maintained to promote urinary excretion of lumirubin. Breastfeeding should continue during phototherapy unless TB is approaching the ET level; in that case, phototherapy should not be interrupted by feeding until TB has fallen below 20 mg/dL. Breastfed infants with inadequate intake or excessive weight loss should be supplemented with expressed breast milk. Breastfeeding, if interrupted, should resume as soon as possible and mothers should be offered support to continue lactation during this period. There is no role for routine intravenous or oral fluid supplementation in neonates receiving phototherapy to hasten the fall of bilirubin levels. Intravenous fluids should not be used unless oral feeding is compromised or preparations for ET are underway.

I. Pharmacologic therapy. Intravenous immunoglobulin (IVIG) has been used in infants with hemolytic disease caused by Rh or ABO incompatibility when TB continues to rise despite continuous intensive phototherapy or is within 2 or 3 mg/dL of the threshold recommended for ET. IVIG as an adjunct to phototherapy is administered at a dose of 0.5 to 1 g/kg IVIG over 2 hours with a repeat dose after 12 hours if needed. The mechanism of action is unknown, but IVIG may act by occupying the Fc receptors on macrophages, and decreasing the removal of antibody-coated red cells from the circulation. The data on the efficacy of IVIG in reducing the need for ET are conflicting, and trials with low risk of bias

show no benefits. Hence, based on the current evidence and considering the potential adverse effects noted with IVIG, it is not recommended in severe isoimmune hemolytic jaundice. It may be considered if ET is not feasible (settings without such facilities or if the neonate has already undergone one or more ETs and access is an issue).

J. ET is used to remove bilirubin when intensive phototherapy fails to prevent a rise in bilirubin to potentially toxic levels or in infants with neurologic signs suggestive of bilirubin toxicity (Fig. 26.4). It is the most effective method for rapid removal of bilirubin. In cases of isoimmune hemolytic disease, ET also removes antibody and sensitized RBCs which are replaced with donor RBCs lacking the sensitizing antigen.

1. Immediately after a double volume ET (about 160 to 180 mL/kg), TB 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 TB levels return to approximately two-thirds of pre-exchange levels. This procedure replaces approximately 85% of the circulating RBCs.
2. We use fresh (less than 5 days old) type O 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. The volume ordered should be twice the infant's estimated blood volume (two times 80 to 90 mL/kg plus additional volume to account for

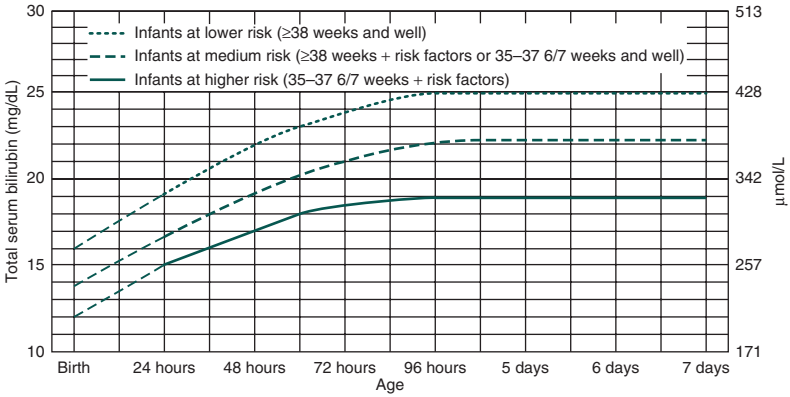

Figure 26.4. Guidelines for exchange transfusion in hospitalized infants of 35 or more weeks' gestation. TSB, total serum bilirubin; G6PD, glucose-6-phosphate dehydrogenase. • The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy. • Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is ≥5 mg/dL (85 mmol/L) above these lines. • Risk factors—isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis. • Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin. • If infant is well and 35–37 6/7 weeks (medium risk), can individualize TSB levels for exchange based on actual gestational age. (Reprinted with permission from the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297–316.)

tubing losses [~30 mL]). A blood warmer is used to maintain temperature at 37°C to avoid hypothermia. Uncontrolled warming methods such as placing under the radiant warmer or in a hot water bath or hand agitation should be avoided as they can lead to hemolysis.

3. ET 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).
4. Albumin administration before ET (albumin priming) does not consistently result in reduction in bilirubin levels or phototherapy duration post exchange and is not recommended.
5. Intensive phototherapy should be resumed after the transfusion, and TB should be monitored at 2, 4, and 6 hours after the transfusion and then at least every 12 to 24 hours until TB declines sufficiently to discontinue phototherapy. Increasing TB or recurrent neurologic signs are followed to assess the need for repeat ET.
6. Infants should be monitored for complications that are related to the procedure and use of blood products. Common complications include thrombocytopenia and coagulation abnormalities; hypoglycemia, hyperkalemia, and hypocalcemia; and acid–base abnormalities. Routine antibiotic therapy (unless infection is suspected) or calcium infusions after ET are not recommended. Less frequent complications include necrotizing enterocolitis (see Chapter 27), portal vein thrombosis, cardiac arrhythmias, and infection.
7. **Home phototherapy** is effective, cheaper than hospital phototherapy, and easy to implement with the use of fiberoptic blankets but may not have the same irradiance or surface area exposure as hospital phototherapy. The AAP recommends the use of home phototherapy only for infants with bilirubin levels in the "phototherapy optional" range (see Fig. 26.3). This is not an option in resource-limited settings.

VIII. BILIRUBIN TOXICITY

A. Brain injury by bilirubin. 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 disrupted by factors including hyperosmolarity, asphyxia, hypercarbia, and meningitis, lower values of bilirubin can be damaging. Acidosis affects bilirubin solubility and promotes its deposition into the brain tissue. The blood–brain barrier may be more vulnerable in preterm than in term infants.

B. Bilirubin deposited in the brain can result in **bilirubin-induced neurologic dysfunction (BIND)**. Severe hyperbilirubinemia (TB >25 mg/dL) is associated

with an increased risk of BIND in term infants; the levels of bilirubin that place preterm infants at risk are uncertain, but presumed to be lower. The brain regions typically affected by bilirubin toxicity include the basal ganglia, cerebellum, white matter, and brainstem nuclei for oculomotor and auditory function. MRI shows increased T1-signal intensity in the globus pallidus and subthalamic nucleus in the acute phase, and increased T2-signal intensity in the same and possibly in the substantia nigra and cerebellar dentate nucleus.

C. Assess for risk factors for neurotoxicity (ABCDE)

Acidosis, albumin level low
Blood brain barrier disruption (e.g. intracranial haemorrhage, asphyxia, sepsis)
Coombs positive
Displacers of bilirubin (e.g. FFA from intralipid, Ceftriaxone)
Encephalopathy (extreme prematurity)

D. Neurologic manifestations of bilirubin toxicity reflect the areas of the brain that are most often affected and can be reversible or permanent.

1. **ABE** is the clinical manifestation of bilirubin toxicity seen in the neonatal period. The clinical presentation consists of three phases:
   a. **Early phase.** Signs are subtle and may include lethargy, hypotonia, high-pitched cry, and poor suck.
   b. **Intermediate phase** progresses in the absence of intervention for hyperbilirubinemia and is characterized by hypertonia of extensor muscles (rigidity, opisthotonus, and retrocollis), oculogyric crisis, irritability, fever, and seizures. Some infants die in this phase. All infants who survive this phase are likely to develop chronic bilirubin encephalopathy (clinical diagnosis of kernicterus).
   c. **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.

   BIND score is a simple scoring system to objectively evaluate the neurologic dysfunction. It assigns a score of 1, 2, or 3 to mild, moderate, or severe abnormalities, respectively, in an infant's mental status, muscle tone, and cry pattern. A total score of 1 to 3 indicates mild ABE but is indistinguishable from other causes unless ancillary investigations are done. Scores of 4 to 6 and 7 to 9 indicate moderate and severe ABE, respectively. All neonates with suspected ABE should also be evaluated for other causes of encephalopathy such as asphyxia, sepsis, and meningitis as these can coexist with hyperbilirubinemia and can increase the risk of ABE. All neonates with features of BIND or high bilirubin levels in the presence of risk factors should undergo hearing evaluation with auditory brainstem response (ABR) audiometry to diagnose auditory involvement.
2. **Kernicterus** refers to the chronic and permanent sequelae of bilirubin toxicity that develop during the first year of age. Most infants who develop kernicterus have had signs of ABE in the neonatal period, although some have a history of high TB level with few or no signs of ABE. The signs of kernicterus are as follows:
   a. Choreoathetoid cerebral palsy with neuromotor impairments
   b. Sensorineural hearing loss (auditory neuropathy), characterized by abnormal brainstem auditory evoked response with normal otoacoustic emission testing

c. Limitation of upward gaze

d. Dental enamel dysplasia

Recently a new classification has been proposed called kernicterus spectrum disorders (KSD) to include a wide spectrum of neurodisability that may be due to hyperbilirubinemia.

IX. CHOLESTASIS, OR CONJUGATED HYPERBILIRUBINEMIA. It 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 by a direct or conjugated bilirubin level >1 mL/dL or >15% of the TB level. It may be 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 bilirubin level. Rapid diagnosis is important so that therapy for treatable disorders can be started promptly.

A. Many disorders cause neonatal cholestasis. A complete list is beyond the scope of this chapter.

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 is Alagille's 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 an uncommon but surgically treatable cause of cholestasis.
2. **Infectious causes** include sepsis and urinary tract infections as well as infections caused by numerous viral, bacterial, and other organisms.
3. **Metabolic disorders** include α_1-antitrypsin deficiency, cystic fibrosis, galactosemia, tyrosinemia, galactosemia, storage diseases (Gaucher, Niemann–Pick), Zellweger's 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 neonatal intensive care unit (NICU) occurs in infants unable to take enteral feeding who have prolonged courses of total parenteral nutrition (PN) including lipid. This condition typically resolves with the 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 weeks.

B. Diagnosis

1. History and findings on physical examination may support a specific diagnosis. Acholic stools suggest obstruction.
2. Laboratory studies to evaluate liver function should include total and direct or conjugated bilirubin, serum alanine aminotransferase (ALT), aspartate

aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), 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 analogs 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 is recommended to evaluate cholestatic jaundice in a guideline of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

6. If studies support a diagnosis of biliary atresia, intraoperative cholangiography is performed. If biliary obstruction is demonstrated, a hepatoportoenterostomy (Kasai's procedure) is performed.

C. Management of PN-associated cholestasis. Most cholestasis in the NICU is due to inability to tolerate enteral feeding and prolonged exposure to PN.

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 (ADEK). If cholestasis persists as enteral feedings are increased, we consider the 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 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210589Orig1s000Approv.pdf).

Suggested Readings

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27 Necrotizing Enterocolitis

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KEY POINTS

- Necrotizing enterocolitis (NEC) is 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 function, formula feeding, bacterial dysbiosis, and a hyperinflammatory 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.
- In recent years, there is a move to clearly separate entities such as spontaneous intestinal perforation and other NEC-like diseases from NEC.
- Treatment includes gastric decompression, bowel rest, and broad-spectrum antimicrobial therapy. Transfer to a surgical center may be indicated.
- Current best evidence for NEC prevention exists for antenatal steroid use, standardized enteral feeding guidelines, exclusive use of human milk, avoidance of acid-blocking drugs, and minimization of empiric antibiotic exposure.
- The routine use of probiotics remains controversial due to the lack of an–approved, pharmaceutical grade product and unclear dosing schedules.

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 few decades, the mortality and morbidity secondary to NEC remains high. Current clinical practice is directed mainly towards prompt, early diagnosis and institution of proper intensive care management.

A. Definition.

NEC is an acute inflammatory injury 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) 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. In the past 10 years or so, there is a move to define the type of NEC pathogenesis (NEC reductionism) which could help the approach to treatment, and also help differentiate these categories by the timing of the event, associated factors, and blood picture (as discussed in the subsequent text).

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% to 10% of very low-birth-weight (VLBW) infants. Mortality ranges from 20% to 40% but can approach 100% in case of NEC totalis. Overall, NEC is responsible for 12% of deaths in extreme premature infants <27 weeks' gestational age.
2. As perforation is a defining feature of advanced NEC, it is important to differentiate NEC from SIP, a less dangerous clinical entity. SIP has an early onset, is often seen in extreme preterm, much before significant feeds are given. There is higher association of SIP with PDA and its treatment. Pathology of SIP differs significantly from NEC; with sparing of mucosa, subserosal thinning, and necrosis of muscularis. In contrast, NEC has necrosis of all layers. Preventive strategies are different for NEC and SIP.
3. At least 30% of NEC cases result in surgical resection of the affected tissue. However, the timing for surgical intervention and the type of surgery remain controversial. Severe NEC that requires surgical intervention increases the average length of stay by 43 days and is associated with increased morbidity (e.g., short bowel syndrome) and mortality.
4. **Prematurity** is the single greatest risk factor. Decreasing gestational age is associated with an increased risk of NEC. The postnatal age at onset of symptoms and signs of NEC 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. This is in contrast to SIP, which typically occurs in the first 10 days or so in extreme preterm babies.
5. **Maternal risk factors** for the disease. Risk factors for the disease include chorioamnionitis, fetal growth restriction (FGR), and maternal smoking. Antenatal steroids improve the maturity of the GI tract and have been shown to reduce the incidence of NEC.
6. Prolonged empiric antimicrobial use is associated with an increased NEC occurrence. Studies have documented decreased microbial diversity and overgrowth of potential pathogenic bacteria **(dysbiosis)** prior to clinical presentation of NEC. Although bacteria are clearly involved in the pathogenesis of the disease, no single infectious organisms have been isolated, except in relative rare outbreak situations.
7. As mentioned under section I A, **NEC reductionism** is a concept used to try and define the etiopathogenesis based subtype based on the timing of the event and associated factors. The following points provide details on these subtypes.
8. **Term NEC.** Approximately 10% of infants with NEC are **termborn**. The presentation is relatively early (in the first week), and is mostly linked to mesenteric bowel ischemia. There is a link to rapid formula feeding, and 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.

9. There is a subgroup of babies who present with the features of **viral enteritis**, although often viral studies may be negative. This could be associated with epidemic presentation within a unit, and justify isolation measures. This subgroup typically is associated with lymphocytosis. Clinical management includes antibiotics and decompression measures, as viral colitis can lead to mucosal damage, gut bacterial translocation, and sepsis.

10. The next category is NEC associated with **cow's milk protein intolerance (allergic colitis)**—the timing is similar to that of classic NEC, but association with the use of formula, cow's milk–based human milk fortifier, and eosinophilia is typical. Blood in stool and pneumatosis is seen, but babies are typically less sick and respond well to elimination of milk protein in their diet. Stool microscopy usually is abnormal. Expressed breast milk (EBM) may be restarted (ensure mother is not consuming cows milk products). Human milk fortifier (cow's milk based) is also avoided. Extensively hydrolyzed or amino acid formula diet may be required, clinical response suggests the diagnosis.

11. The more benign form of NEC, *pneumatosis coli*, could be linked to this group. 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.

12. Transfusion-associated NEC (TANEC) has been described in numerous reports and although blood transfusions were independent risk factors in several retrospective studies, a causal relationship has not yet been confirmed in larger prospective trials. An association with post-transfusion eosinophil spike is noted, as well as higher association with AB blood group. It is possible that the AB epitopes expressed on enterocytes are overwhelmed by antibodies in the transfused blood (following repeated transfusion exposure) and this could trigger eosinophilia, mucosal injury, and NEC—the disease is typically more severe and has poorer outcomes. RBC factors in the transfused blood (physical factors, increased viscosity, reduced oxygen-carrying capacity in the setting of reduced gut perfusion) could contribute as well. Efforts to minimize late transfusions in the extreme preterm babies including micro-sampling techniques and clear blood transfusion criteria. Holding feeds for a few hours before, during, and after transfusion, might help, although there is not enough evidence to recommend.

13. The final clinical picture that mimics NEC includes **feed intolerance** in extreme preterm babies. Almost all infants with NEC have received enteral feedings prior to the 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 exclusively breast milk. Early initiation of feeds, use of breast milk, and standardized progression of feed volume will decrease episodes of feed intolerance and days on parenteral nutrition (PN).

14. Other NEC like conditions include gastrointestinal (GI) signs following intravenous immunoglobulin (IVIG), association with gum (thickeners used for reflux disease) and GI signs associated with gastroschisis.

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 imbalances. Because these factors affect most preterm infants, infants who develop NEC must also exhibit an especially harmful inflammatory response to intestinal antigens.

2. Genetic polymorphisms have been described in patients at a higher risk for severe NEC such as in genes encoding toll-like receptor (TLR) 4 or interleukin-18 (IL-18) signaling. Polymorphism in the secretor gene fucosyltransferase (FUT) 2 encoding low secretor status has been associated with earlier and more severe disease.

3. Intestinal immaturity plays an important role in the pathogenesis of NEC: increased permeability of the intestinal epithelium, decreased motility, a thinner mucus layer, low or absent levels of secretory IgA, and lack of regulatory adaptation of the intestinal mucosal immune system.

4. Microbes have an important role in development of NEC. In experiments on germ-free animals and also in TLR4 knock out mice (no portal for entry of microbes), NEC did not happen.

   In babies developing NEC, there is a decrease in microbial diversity and abundance of potentially pathogenic bacteria. Understanding of this abnormal pattern of bacterial species **(dysbiosis)** became possible due to sequencing bacteria by molecular methods (16S r RNA), conventional culture techniques are not enough to detect all these bacterial species.

   Role of microbes is also implicated in "outbreaks" of NEC, both bacteria and viruses have been associated.

5. An excessive and inappropriate intestinal inflammatory response appears to be the 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 $FOXP3^+$ T regulatory cells in the mucosa are examples that can explain why the poorly adapted premature intestine is prone to inflammatory injury. Prenatal factors (e.g., corticosteroids vs. chorioamnionitis) may influence the "inflammatory setup" of the preterm gut at birth.

6. Evidence supports a critical role for inflammatory mediators. **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 to those without. In animal models, exogenous administration of PAF mimics NEC-like injury and PAF antagonists limit such injury. Various other inflammatory mediators such as cyclooxygenase-2 (COX-2), reactive oxygen species, tumor necrosis factor alpha (TNF-α), and IL-18 have been implicated in NEC pathogenesis mostly in animal models. These data also point to the multifactorial etiology of the disease and underline the fact that not one but several strategies are necessary for the prevention of NEC.

7. Several retrospective studies have suggested a temporal association of packed red blood cell (PRBC) transfusions with the onset of NEC, but this link remains to be confirmed by prospective matched case–control studies. Hypothesized mechanisms include T-cell activation, and splanchnic vasoconstriction (factors in the transfused blood) associated with the transfusion. Though plausible, it still remains unclear whether blood transfusions play a causal role for NEC or are just indicators of impending or ongoing disease.
8. A large number of other factors such as low Apgar scores, timing and volumes of feeding, umbilical catheterization, hypoxic-ischemic insults, presence of a 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, and bleeding diathesis.
2. **Abdominal (enteric) signs.** Abdominal distension or tenderness, gastric aspirates (feeding residuals), 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. The latter course will vary with the rapidity of therapeutic intervention and require consistent monitoring and anticipatory evaluation (see section III).

B. Laboratory features. The diagnosis is suspected from clinical presentation but must be confirmed by diagnostic radiographs, surgery, or autopsy. No 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 consistent with ileus. Anteroposterior (AP) view and cross-table lateral or left lateral decubitus views should be included as indicated. These films may reveal bowel wall edema, a fixed-position loop on serial studies, 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 because intramural gas or pneumoperitoneum becomes the more commonly presenting feature, only 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; although in early stages of NEC there may be increase in blood flow, decreased movement of a segment or whole of the bowel. Thinning of bowel wall will be evident, before perforation happens.

2. **Blood and serum studies.** Thrombocytopenia, persistent metabolic acidosis, and severe refractory hyponatremia have been traditionally described as triad of NEC, but have not great relevance in 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. 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 Kleigman 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. **Stage I** (suspect) includes clinical signs and symptoms, including abdominal signs and nondiagnostic radiographs. These signs are nonspecific in most instances, so this stage is more a clinical guide to management, and stage 1 which does not progress is not usually included in NEC datasets.
2. **Stage II** (definite) includes clinical and laboratory signs and pneumatosis intestinalis and/or portal venous gas on radiographs (portal gas on ultrasound may be seen earlier in course than on radiograph).
   a. Mildly ill
   b. Moderately ill with systemic toxicity
3. **Stage III** (advanced) 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 frequently associated with intestinal ileus. The abdominal distension, discoloration, and tenderness characteristic of NEC should be absent, however, 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. **As discussed under section I.B, 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.

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 early NEC can be difficult. Many NICUs advocate minimal aspiration to check gut emptying if the baby is clinically stable. However, if the baby is clinically unwell with large-volume aspirates (over 30% to 40% of feed volume over a 6-hour period) and distension, 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 x-ray abdomen can sometimes help distinguish significant 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 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 end point in mind, but none have been clinically established to date. Although traditionally persistent or worsening abnormalities in 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 interpretation and to plan for further appropriate studies, which may increasingly include abdominal ultrasound with Doppler.

III. MANAGEMENT

A. Immediate medical management (Table 27.1).

Treatment should begin promptly when a diagnosis of NEC is suspected. Therapy is based on intensive care measures and the anticipation of potential problems.

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, C-reactive protein, electrolytes Blood culture Ampicillin and gentamicin ×48 hours Consider KUB q8–12h ×48 hours (can be less frequent if clinically stable) 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, C-reactive protein, electrolytes Consider KUB (AP and lateral) q6–8h ×24–48 hours (frequency based on clinical status) and then PRN Abdominal ultrasound with Doppler 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, C-reactive protein, electrolytes Consider KUB (AP and lateral) q6–8h ×24–48 hours based on clinical need and then PRN Abdominal ultrasound with Doppler Ampicillin, gentamicin, and metronidazole Surgical consultation

AP, anteroposterior; CBC, complete blood count; IV, intravenous; KUB, kidney, urethra, bladder x-ray; NPO, nothing by mouth; PRN, as needed.

1. **Respiratory function.** If the baby has signs of systemic instability like respiratory distress, hypoxia, poor respiratory effort, or recurrent apnea, early ventilation should be considered.
2. **Cardiovascular function.** Some of the clinical signs of shock may overlap with other morbidities. Tachycardia may be due to inflammation, low urine output may be due to third space losses, and poor sensorium can be due to hypoglycemia, hypercarbia and coexisting sepsis. Capillary refill time, blood pressure, and lactate must be monitored for perfusion assessment. Saline bolus may be necessary due to 3rd space loss of fluid. Inotropes can compromise gut

circulation, especially at higher doses. Steroids are a difficult choice in setting of perforation and infection.

3. **Metabolic function.** Metabolic acidosis will generally respond to volume expansion. 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 continuous passive drainage through a nasogastric or orogastric tube. The duration of withholding enteral nutrition varies between 5 and 14 days. PN is given through peripheral or central access as soon as possible, with the aim of providing 90 to 110 cal/kg/day. A central venous catheter is almost always necessary to provide adequate calories in the VLBW infant. It is preferable to place a central catheter for this purpose.
5. **Infectious disease.** Traditional culture and 16S rRNA gene sequencing from blood and peritoneal fluid of patients with NEC have identified a vast variety of aerobic and anaerobic Gram-positive 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, treatments include clindamycin, piperacillin–tazobactam, or meropenem, sometimes in combination with vancomycin (especially in babies with possible central line associated blood stream infection [CLABSI]). *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 has not been established in infants with NEC, and therefore none of these drugs or combinations are U.S. Food and Drug Administration (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. Antibiotics may be continued for 10 to 14 days in cases of definite NEC (≥Bell II). There is no evidence to support the use of enteral antibiotics.
6. **Hematologic aspects.** Watch for anemia and/or thrombocytopenia. PRBCs are often transfused to maintain the hematocrit at a level considered appropriate for the age and sickness level of the baby (avoiding overaggressive transfusion policy). It is important to consider holding feeds before and during the transfusion. The prothrombin time, partial thromboplastin time, fibrinogen, and platelet count should be evaluated for evidence of DIC. Fresh frozen plasma may be used to treat coagulation problems.
7. **Renal function.** Oliguria may be due to third space fluid loss and prerenal failure, true renal failure is not uncommon. AKI can progress to anuria, peritoneal dialysis is technically impossible in the setting of bowel perforation. Besides, babies' clinical course may be complicated by severe hyponatremia, metabolic acidosis (see Chapter 8).

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 or 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 8 to 12 hours during the first 2 to 3 days if clinical concerns) radiographs are used to assess the ongoing GI damage. 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 will allow the surgeon to become familiar with the infant and will provide 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 probably 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 point to severe NEC.
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. Paracentesis may help to identify these patients before perforation occurs, diagnostic paracentesis is not a routine and any defined indication for testing cannot be recommended.
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. To date, no randomized controlled trial has demonstrated a clear benefit for one procedure over another. 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 already before surgery. The goal is to excise complete 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 is typically not attempted.

5. In ELBW infants (<1,000 g) and extremely unstable infants, **peritoneal drainage** under local anesthesia may be a management option. In many cases, this temporizes laparotomy until the infant is more stable, and in some cases, no further operative procedure is required. Prospective studies have found no difference in mortality between laparotomy and peritoneal drainage for surgical NEC. However, approximately half of patients with peritoneal drainage eventually receive laparotomy (35% to 74%), potentially limiting the validity of the intention-to-treat analyses. The cost burden of peritoneal drainage followed by laparotomy is large compared to that of laparotomy alone, and given the absence of survival benefit and reported worse long-term neurodevelopmental outcome after peritoneal drainage, its utility is questionable.

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 their own secretions, 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 occurrence of strictures may complicate feeding plans. The incidence of recurrent NEC is 4% and appears to be independent of the type of management. 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. However, 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 (of over 50%), growth delay (delay in the growth of head circumference is of most concern), and poor neurodevelopmental outcome. 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 disease process or to the long-term NICU management often necessary to treat it. GI sequelae include 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 as a result of bowel resection during surgical treatment is seen in approximately 10% to 20% of such patients. 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. Although the outcomes for many prematurity-related illnesses have improved over the past decades, mortality and morbidity rates for NEC have remained constant.

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 by antenatal steroid therapy.
2. **Exclusive feeding of human milk–based diet.** Premature infants who are fed exclusively with expressed human milk are at a decreased risk for developing NEC. Mothers should be strongly encouraged to provide their own expressed milk (mother's own milk [MOM]) for their premature babies. **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 in growth rates or neurodevelopmental outcome after discharge.
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. However, 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 promising new approach to the prevention of NEC. Probiotics fed to preterm infants may help to normalize intestinal microflora colonization. A recent meta-analysis has shown reduced incidence of NEC by over 50% in infants fed probiotics (e.g., *Lactobacillus* GG, *Bifidobacterium breve*, *Saccharomyces boulardii*, *Lactobacillus acidophilus*) compared with in controls. However, the studies included in the meta-analysis were quite disparate in the type of probiotics and in their use. More recently, neither the large Probiotics in Preterm babies Study (PiPS) trial in the United Kingdom nor the ProPrems trial in Australia (together over 2,500 babies) demonstrated any reduction in death, sepsis, or NEC in infants *below 28 weeks*' gestational age. In addition, fatal infectious complications have been reported in association with unregulated use of live probiotic supplementation.

Although the Cochrane meta-analysis shows a positive benefit with the use of probiotics, there is still reluctance to widely implement them due to issues with FDA approval, concerns about strains available in local markets not matching the ones in the trials, lack of clarity on dosing, concern about quality control, and risk of contamination. Recently, the European Society of Pediadric Gastroenterology, Hepatology and Nutrition (ESPGHAN) position paper suggested that provided all safety issues are met, there is currently a conditional recommendation (with a low certainty of evidence) to provide either *L. rhamnosus* GG ATCC53103 or the combination of *B. infantis* Bb-02, *B. lactis* Bb-12, and *S. thermophilus* TH4 in order to reduce NEC rates. Until further evidence is available to help determine the most effective probiotic(s), their optimum dosage, and long- and short-term safety, the routine use of probiotics in the prevention and treatment of NEC cannot be universally recommended.

5. A number of nutritional **supplements** (e.g., polyunsaturated fatty acids [PUFA], L-arginine); **growth factors** such as transforming growth factor beta (TGF-β) and heparin-binding epidermal growth factor (HB-EGF); and **immune modulators** such as immunoglobulins, trefoil factors, lactoperoxidase, superoxide dismutase, PAF acetylhydrolase, alkaline phosphatase, and inhibitors of TLR4 have been explored in animal models and even clinical trials but are not ready yet for routine clinical use. One currently explored promising agent is oral bovine or human lactoferrin. **Lactoferrin** is a glycoprotein with broad-spectrum antimicrobial activity found in colostrum and milk. Current evidence suggests that oral lactoferrin with or without probiotics decreases late-onset sepsis and NEC in preterm infants without adverse events. However, these data need to be confirmed after completion of ongoing trials for dosing optimization and type of lactoferrin. Long-term outcomes of lactoferrin use are unknown. Other mostly experimental therapy options include TLR4 inhibitors and HB-EGF. Currently, the best evidence for **NEC prevention** strategies exists for antenatal steroids, standardized enteral feeding guidelines, exclusive use of human milk, avoidance of acid blockade, and minimization of empiric antibiotic exposure.

Suggested Readings

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28 Neonatal Kidney Conditions

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KEY POINTS

- Renal function in preterm and term babies evolves rapidly due to changes in renovascular resistance, renal blood flow and maturation of glomerular and tubular function.
- Glomerular filtration rate (GFR) at birth is very low in newborns and more so in premature infants.
- In term babies, GFR rises quickly, doubling by 2 weeks of age and reaching adult levels by 1 year of age.
- Preterm birth is an independent risk factor for a decrease in one's nephron endowment. A *low nephron endowment* has been linked to the development of hypertension and cardiorenal disease in adult life.
- The first 40 days of postnatal life provide a window of opportunity where extrauterine nephrogenesis may be promoted by ensuring a stress-free environment.
- Episodes of acute kidney injury (AKI) increase the risk of adverse renal outcomes in preterm and low-birth-weight infants.
- Management of infants who develop AKI should focus on treating the underlying etiology, avoiding further injury, and addressing the consequences of decreased renal function.
- Most cases of congenital anomalies of the kidney and urinary tract (CAKUT) are evident on prenatal ultrasound. Some of them present later in life as urinary infection, failure to thrive, or hypertension.

I. RENAL EMBRYOGENESIS AND FUNCTIONAL DEVELOPMENT

A. Embryogenesis. Nephrogenesis requires a fine balance of numerous factors that can be disturbed by genetic and/or epigenetic prenatal events resulting *in low nephron number at birth*.

The mature human kidney is the final product of three embryonic organs: the pronephros, the mesonephros, and the metanephros.

The transient pronephros, the first structure containing rudimentary tubules, disappears at the end of the fourth week of gestation. Despite its transient nature, the pronephros is required for normal kidney development.

The ***mesonephros*** follows and contains well-developed *nephrons* comprising vascularized glomeruli connected to proximal and distal tubules draining into a mesonephric duct. Ultimately, the mesonephros fuses with the cloaca, and contributes to the formation of the urinary bladder and in the male, the genital system.

The *metanephros* is the final developmental stage and can be identified around the fifth or sixth week of gestation. The metanephros has two components: the ureteric bud (UB) and the metanephric mesenchyme. The UB is a branching epithelial tube whose inductive signals induce mesenchymal cells; with each division of the UB, a new layer of nephrons is induced from stem cells. As development proceeds, the metanephros is located at progressively higher levels, reaching the lumbar position by 8 weeks' gestation.

The developmental history of the nephron and collecting system differs: Whereas the nephron arises from mesenchymal cells, the *tubules develop from UB branching*.

The UB branch in a highly reproducible manner with a nephron induced at each of its tips. These branches eventually form the collecting system (ducts, renal pelvis, ureter, and bladder trigone).

Multiple gene regulatory networks have been reported to act as either inducers or inhibitors. 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, lack of UB leading to renal hypoplasia, renal agenesis, abnormal ureter–bladder connections, etc.

Four stages of nephron development have been defined: stage I, in which the renal vesicle appears; stage II, in which the renal vesicle transforms 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 stage IV, the renal interstitium differentiates into the various components of cortex, medulla, etc. Disruption of any part of this sequence leads to reduced nephron numbers. 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.

Nephrogenesis is completed at 36 weeks' gestation, with 60% of nephrons being added in the last trimester. There can be a 10-fold variance in the nephron number (from approximately 200,000 to 2,000,000 per kidney) in the individuals at birth. Nephrons cannot regenerate; therefore, nephron endowment has profound implications for future chronic kidney disease (CKD) development.

Premature birth interferes with normal intrauterine nephrogenesis, putting all preterm babies at risk of poor nephron endowment. The first 40 days after birth provide a short window of opportunity where ongoing nephrogenesis is still possible if the environment of a preterm is not taxed by nephrotoxic drug exposure or hemodynamic instability.

Renal size and nephron number is 10% to 15% less in females at an early age.

Autopsy studies have shown that infants with growth restriction have fewer nephron numbers.

Post birth' recurrent AKI, obesity, and natural aging processes all negatively impact the nephron endowment.

Gene-targeting experiments have greatly improved our understanding of the kidney and urinary tract morphogenesis. The consequence of even subtle changes in the reciprocal and complex interactions between cell types has severe consequences on the ultimate development of the human kidney.

B. Functional development. An understanding of the differences in renal physiology in the neonatal period compared to those at later ages is necessary for evaluation.

1. ***Amniotic fluid volume and urine output.*** 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. Beyond 20 weeks' gestation, urine is the contributor to 80% of the amniotic fluid. Thus, oligohydramnios or polyhydramnios beyond this gestational age reflects dysfunction of the developing kidney.

   At birth, the kidneys replace the placenta as the major homeostatic organ, maintaining fluid and electrolyte balance and removing harmful waste products. This transition is facilitated by an increase in the *renal blood flow (RBF), glomerular filtration rate (GFR), and tubular functions.* Because of this postnatal transition, the prime determinants of renal function are the gestational age, mean arterial pressure, and to some extent total kidney volume (TKV).

2. ***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 because of (i) a decrease in renal vascular resistance, which is proportionally greater in the kidney compared to in the other organs; (ii) an increase in systemic blood pressure (BP); and (iii) an increase in the inner to outer cortical blood flow.

3. ***Glomerular filtration*** begins soon after the first nephrons are formed and increases in parallel with the body and kidney growth (~1 mL/minute/kg of body weight). Glomerulogenesis is completed at 36 weeks but GFR continues to increase until birth due to decreases in renal vascular resistance.

   GFR at birth is very low in the most premature infants and rises slowly after birth.

   In term babies, GFR rises quickly, doubling by 2 weeks of age and reaching adult levels by 1 year of age (Table 28.1); it takes much longer in preterm babies, as long as 8 years (Table 28.2).

   The kidneys regulate GFR by altering the angiotensin II–induced vasoconstriction at the efferent arteriole and the concurrent prostaglandin-induced vasodilatation at the afferent arteriole to maintain constant renal capillary pressure.

   This autoregulation of GFR is poor in newborns, making them *dependent on mean arterial pressure for maintaining GFR.* Thus, in the early postnatal period, prime determinants of GFR are the gestational age, mean arterial pressure, and nephron endowment which is reflected by TKV.

Table 28.1. Normal GFR Measurements for Term Neonates

Age	GFR (mL/minute/1.73 m^2)
1–3 days	21 ± 5
1–3 months	85 ± 35
1–2 years	105 ± 17

GFR, glomerular filtration rate. *Source:* Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatric Nephrol* 2007;22(11):1839–1848.

Table 28.2. Inulin Clearance Glomerular Filtration Rate in Healthy Premature Infants

Age	GFR (mL/minute/1.73 m^2)
1–3 days	14.0 ± 5
4–8 days	44.3 ± 9.3
1.5–4 months	67.4 ± 16.6
8 years	103 ± 12

GFR, glomerular filtration rate. *Source:* Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatric Nephrol* 2007;22(11):1839–1848.

4. **Tubular function**
   a. **Sodium (Na^+) handling.** The ability of the kidneys to reabsorb Na^+ is developed by 24 weeks' gestation, although tubular reabsorption of Na^+ is low until after 34 weeks' gestation. This is important when evaluating preterm infants because they will be unable to reabsorb sodium maximally and thus will have an elevated fractional excretion of sodium (FENa). 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. After 34 weeks' gestation, Na^+ reabsorption becomes more efficient so that 99% of the filtered Na^+ can be reabsorbed, resulting in an FENa of <1% if challenged with renal hypoperfusion (prerenal state). Full-term neonates can retain Na^+ when in negative Na^+ balance. Both term and premature infants have limited ability to excrete a Na^+ load because of their low GFR.
   b. **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. Although this is of little consequence in infants receiving appropriate amounts of water with physiologic 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.
   c. **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. Potassium should be accurately measured using a central blood draw (as opposed to a heel stick).

d. Acid and bicarbonate handling is limited by a low serum bicarbonate threshold in the proximal tubule (14 to 16 mEq/L in premature infants, 18 to 21 mEq/L in full-term infants) which improves as maturation of Na^+–K^+-ATPase and Na^+–H transporter occurs. Very low-birth-weight infants can develop mild metabolic acidosis during the second to fourth week after birth, which often does not require the administration of sodium bicarbonate. Essentially, *premature infants behave like having a mild proximal renal tubular acidosis (RTA) that improves with maturation.*

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.

e. Calcium and phosphorous handling in the neonate is characterized by a pattern of increased phosphate retention associated with growth. Serum phosphorus levels are higher in newborns than in older children and adults. 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 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 hormone effects, as well as a growth-related Na^+-dependent phosphate transporter, so that a positive phosphate balance for growth is maintained. Tubular reabsorption of phosphate (TRP) is also altered by the gestational age, increasing from 85% at 28 weeks to 93% at 34 weeks and 98% by 40 weeks.

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 the 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 the 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 and urinary Na^+ excretion, and inversely with plasma Ca^{2+}. Poor GFR resulting in low urine flow in tubules and use of drugs such as furosemide and dexamethasone which cause hypercalciuria coupled with alkaline urine pH predispose the neonate to the development of nephrocalcinosis (NC).

II. CLINICAL ASSESSMENT OF KIDNEY FUNCTION.

Assessment of kidney function is based on the perinatal history, physical examination, and appropriate laboratory and radiologic tests.

A. History

1. Micturition. It is natural to enquire about urination (micturition) as a first question in the evaluation of the renal problem. The first void happens in the

delivery room itself in 17% of newborns; 90% of newborns void by 24 hours, and 99% void by 48 hours. The most common cause of delayed or decreased urine production is improper recording of the initial void and less commonly inadequate perfusion of the kidneys. Even rare, delay in micturition may also be due to intrinsic obstruction of the urinary tract or intrinsic renal problems.

Although a poor urinary stream is not sensitive in the detection of lower urinary tract obstruction, seeing a normal stream in males is reassuring.

2. **Prenatal history** includes any maternal illness, drug use, or exposure to known and potential teratogens.
   - **a.** Maternal use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or indomethacin decreases glomerular capillary pressure and GFR and interferes with the normal tubular development. This results in a condition called renal tubular dysgenesis which leads to refractory oligoanuric AKI.
   - **b.** Oligohydramnios may indicate a decrease in fetal urine production. It may 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.
   - **c.** Polyhydramnios may be a result of renal tubular dysfunction with inability to fully concentrate urine.
   - **d.** Elevated serum/amniotic fluid alpha-fetoprotein and enlarged placenta are associated with congenital nephrotic syndrome.
3. **Delivery history.** Fetal distress and perinatal asphyxia may lead to ischemic or anoxic injury. Although often multiorgan, the neonatal kidneys are at a particular risk for ischemic injury due to their low baseline GFR.
4. **Family history.** The risk of renal disease is increased if there is a family history of urinary tract anomalies, PKD, consanguinity, or inherited renal tubular disorders. Familial diseases (congenital nephrotic syndrome, autosomal recessive polycystic kidney disease [ARPKD], hydronephrosis, or dysplasia) may be recognized *in utero* or remain asymptomatic until later life.

B. Physical examination. Careful examination will detect *abdominal masses* in 0.8% of neonates. Most of these masses are renal in origin. Hydronephrosis and multicystic dysplastic kidney (MCDK) are the common causes of renal mass in neonates.

1. **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 and water losses which can lead to ***dehydration***.
2. Many **congenital syndromes** may affect the kidneys; thus, a thorough evaluation is necessary in those presenting with congenital renal anomalies. Findings associated with congenital kidney anomalies include low-set ears, ambiguous genitalia, anal atresia, abdominal wall defect, vertebral anomalies, aniridia, meningomyelocele, tethered cord, pneumothorax, pulmonary hypoplasia, hemihypertrophy, persistent urachus, hypospadias, and cryptorchidism among

others. 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 Table 28.3).

1. Urine analysis

a. Protein excretion varies with gestational age. Urinary protein excretion is higher in premature infants and decreases progressively with postnatal age. In normal full-term infants, *protein excretion is minimal after the second week of life*.

b. 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.

c. Hematuria is abnormal and rare in the term newborn. It is more frequent in the premature infants and may indicate intrinsic kidney damage or result from a bleeding or clotting abnormality.

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		
Protein excretion (mg/m^2/24 hours) (mean ± 1 SD)	60 ± 96	31 ± 44		
Maximal concentration ability (mOsm/L)	500	800	900	1,200
Maximal diluting ability (mOsm/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 ++	Neg to +	Neg	Neg
Glucose	Neg to ++	Neg	Neg	Neg
Blood	Neg	Neg	Neg	Neg
Leukocytes	Neg	Neg	Neg	Neg

GFR, glomerular filtration rate; Neg, negative; SD, standard deviation; TRP, tubular reabsorption of phosphate.

d. 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 the newer absorptive diapers).

2. Method of collection

a. Suprapubic aspiration is the most reliable method to obtain an uncontaminated sample collection for urine culture. Ultrasound guidance will improve chance of success.

b. Bladder catheterization is a method that is most often used for collecting urine sample for culture in a sick-looking infant. Bladder catheterization with an indwelling catheter is also needed in cases of suspected functional or anatomic obstruction to optimize urine drainage and in cases of suspected AKI when precise urine volume needs to be measured.

c. Bag collections are adequate for most studies such as determinations of specific gravity, pH, electrolytes, protein, glucose, and sediment. However, *bag collections should never be used for sample collection for urine culture* because of very high rates of contamination. They are the preferred mode of sample collection if hematuria is suspected.

Bladder catheterization can cause trauma of the urethral mucosa; therefore, bag collection is the preferred method.

d. Diaper urine specimens are a reasonable noninvasive measure of urine weight (volume), 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 and within the first 48 hours is a reflection of the maternal kidney function rather than that of the newborn. In healthy term infants, serum creatinine levels fall from approximate values of 0.75 mg/dL at birth to 0.5 mg/dL at 7 days and reach a stable level of 0.3 mg/dL by 28 days (Table 28.4). Premature infants' serum creatinine may rise transiently for the first few days after birth secondary to reabsorption by renal tubules and then reduces 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 due to lower GFR.

Hence, the premature newborns usually have slightly absolute levels of serum creatinine than term infants and this trend persists for up to 4 weeks of age. Although creatinine may be slightly higher physiologically, high creatinine in preterm babies should not be passed off as physiologic. Small elevations in serum creatinine may be indicative of a significant kidney injury in this vulnerable population. They need a careful evaluation of urine output and monitoring of creatinine trends to rule out underlying AKI.

b. Blood urea nitrogen (BUN). Besides poor kidney function, BUN can be elevated as a result of increased production of urea nitrogen in

Table 28.4. Normal Serum Creatinine Values in Term and Preterm Infants (Mean ± SD)

Age (Days)	<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.

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, cystatin C, and beta-trace protein (BTP) (Table 28.5). Practical considerations such as frequent blood sampling, urine collection, or infusion of an exogenous substance limit their use and they are used only for research purposes. So estimating equations based on blood levels of endogenous substances (most often creatinine and cystatin C) are most often used in children. Cystatin C is considered to be a better biomarker of GFR than creatinine but huge variability in values in neonates and complex estimating equations (though more accurate) make creatinine the more popular analyte for estimating GFR and diagnosing AKI.

Table 28.5. Equations Most Suitable for Application to Infants

Creatinine and length eGFR = 0.413 × length (cm)/Cr eGFR = [0.0414 × ln(age) + 0.3018] × length (cm)/Cr
Cystatin C alone eGFR = 70.69 × $(CysC)_{-0.931}$ eGFR = 75.94 × $(CysC)_{-1.170}$
Beta-trace protein eGFR = $10^{(1.902+(\ 0.951\ 5\ x\ lo\ g10\ (1/BTP)))}$ eGFR = −35.2 + 122.74 × $(1/BTP)^{0.5}$
Combined equations eGFR = 3.98 × (length [cm]/Cr) × 0.456(1.8/CysC) × 0.418(30/BUN) × 0.079 eGFR = (43.82 × e0.003 × length [cm])/(CysC × 0.635 × Scr × 0.547)

BTP, beta-trace protein; BUN, blood urea nitrogen; Cr, creatinine; CysC, cystatin C; e, natural log (=2.7183); eGFR, estimated glomerular filtration rate; ln, natural log; $\log_{10}$, log to base 10; S Cr, serum creatinine (Abitbol et al.).

Traditionally Schwartz equation has been used that is based on length in centimeters, serum creatinine (as measured by Jaffes method), and an adjustment factor or constant k which differs in different age groups (0.33 for preterms, 0.45 for terms, 0.55 for children, 0.7 for adolescent males). With a worldwide change in the methodology of creatinine measurement from previous Jaffes method to newer, more accurate enzymatic essay, value of adjustment factor k was revised to 0.413 for children (called modified Schwartz equation). However, adjustment factors for newborns including preterm have still not been derived. Hence, Schwartz equation is no longer considered an accurate measure of GFR in a newborn. Over the last decade, a large number of estimating equations have been proposed based on novel chemical biomarkers (such as cystatin C, BTP), anatomical biomarkers (TKV, renal parenchymal area [RPA]), or combination of both.

Although the best estimating equation for calculating GFR in a neonate is still debatable, univariate equations based on cystatin C or combined equations based on both creatinine and cystatin C are considered best for preterm and term infants, respectively. It has been suggested that laboratories should directly report GFR (based on the equations) rather than merely reporting numerical values of these analytes. Recently a newer equation for estimating GFR in newborns has been derived that is based on both blood cystatin C levels and renal volumetry by 3D sonography. This involves calculating TKV (as a surrogate marker of newborn nephron endowment) and normalizing it to the body surface area.

GFR = [(Vol × TKV/BSA)/Cys C]/1.73. This is considered by experts to be a very promising approach but is yet to be validated against inulin clearance studies in newborns. Till the time pediatric nephrology community develops new equations for estimated glomerular filtration rate (eGFR) based on new creatinine assay or laboratories start reporting GFR according to cystatin C/combined cystatin and creatinine- based equations, *it seems prudent to continue to use Schwartz equation with the clear understanding of its fallacies*.

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. As prematurity is known to be associated with sodium wasting, the cutoffs of FENa to distinguish prerenal from intrinsic renal failure are different across different gestational ages. A cutoff of 2% is valid for term neonates, 3% for newborns between 31 and 38 weeks, and 6% for newborns between 29 and 30 weeks. It is unreliable in infants less than 29 weeks.

D. Radiologic studies

1. Ultrasonography is noninvasive, can be done at the bedside, and is especially useful in unstable infants. It can easily confirm the presence of gross renal abnormalities seen in the antenatal ultrasound, such as hydronephrosis or dysplastic kidney disease. Generally, the *length of the kidneys* in millimeters is approximately the gestational age in weeks.

a. Larger kidneys may suggest the presence of hydronephrosis, PKD, MCDK disease, or, rarely, congenital nephrotic syndrome or renal tumors. Smaller kidneys may suggest dysplasia or hypoplasia.

b. The *kidney cortex echogenicity* is like that of the liver or spleen in the neonate, in contrast to the hypoechoic renal cortex seen in adults and older children. Hyperechogenic 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.

c. Ultrasonography has a pivotal role in the follow-up of AKI survivors. *Static kidney sizes, loss of volume, decreased parenchymal thickness, altered echogenicity, and cortical cysts* have been the traditional markers of CKD in newborns.

d. **TKV** is a novel anatomic marker of low GFR as in Figure 28.1. This entails 3D measurements of length, width, and depth of both kidneys by use of an ellipsoid formula (volume = length × width × depth × 0.523). The volumes are then summated for the TKV and adjusted for body surface area.

It has been seen that stagnant values of TKV on follow-up, especially in the presence of abnormal chemical biomarkers, are one of the most sensitive for poor renal function. In the absence of 3D images, 2D images of renal parenchymal thickness and renal length may be used, albeit with lesser accuracy.

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.

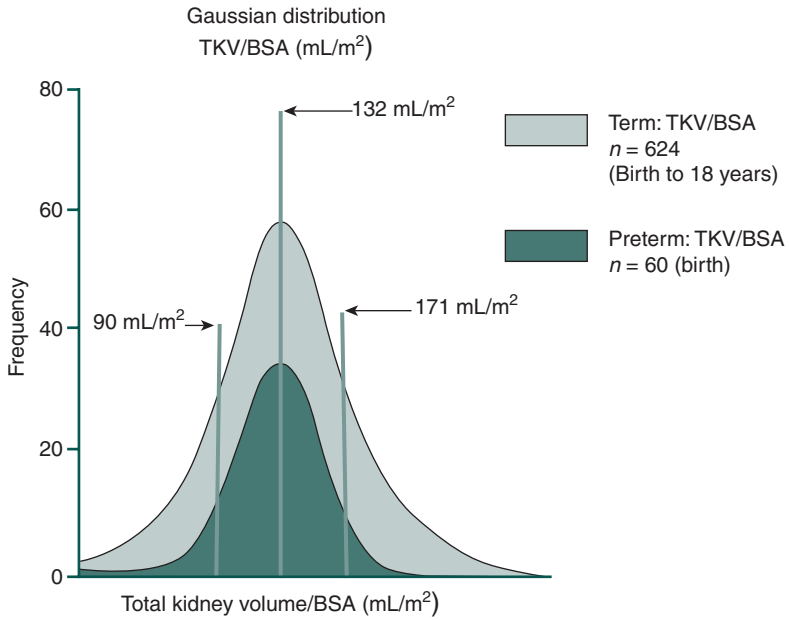

Figure 28.1. Normative values of TKV. Data of 624 healthy German children from younger than 1 month to 18 years of age. Nephron endowment closely correlated with kidney volume. An individual whose TKV/M2 falls below the 10th percentile (<90 mL/m^2) should be observed closely for the development of CKD due to nephropenia. The darker curve within is data from a cohort of 60 preterm babies. Preterm infants should be followed sequentially for kidney growth by TKV/M2.

2. **Voiding cystourethrography (VCUG)** is an excellent method to determine vesicoureteral reflux (VUR) and bladder anatomy, and define lower tract anatomy in posterior urethral valves (PUV). It involves catheterization and per urethral injection of a radiocontrast agent followed by x-rays during filling, voiding, and post void. Simultaneous fluoroscopy improves sensitivity but increases burden of radiation dose. Radiocontrast VCUG is the preferred technique for initial evaluation of obstructive uropathy. Radionuclide cystography reduces radiation exposure, but its sensitivity to pick up anatomical details is limited. So, it may be a preferred test for follow-up study of VUR.

   VCUG must be done without sedating the baby under cover of a periprocedural antibiotic.

3. ***Radionuclide scintigraphy*** involves intravenous injection of a radioisotope followed by imaging over the renal fossa by a gamma camera. As most of these nuclear techniques rely on renal filtration, they are done only when the infant is 6 weeks of age.

   A dynamic study can be done by using isotopes such as technetium-99m diethylenetriaminepentacetic acid (DTPA) or mercaptoacetyltriglycine (MAG3) which are handled by glomerular filtration. They are useful to determine RBF, GFR, and differential kidney function. Test done after intravenous furosemide helps to differentiate obstructive from nonobstructive hydronephrosis.

   A static study may be done by radioisotopes that bind to the renal tubules, such as technetium-99m dimercaptosuccinic acid (DMSA) to 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.

III. COMMON KIDNEY PROBLEMS IN NEONATES—ANTENATAL.

Congenital anomalies of the kidney and urinary tract (CAKUT) may become apparent with prenatal ultrasound, discovered at birth, or present later in life.

Common lesions are fetal hydronephrosis and dysplastic kidneys (with or without cysts). 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 contralateral kidney is viable, and 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.

A. Fetal hydronephrosis.

Ultrasound screening of the fetus for anomalies is the routine; the commonest finding is dilatation of the upper urinary tract or fetal hydronephrosis.

Initial management of a newborn with prenatally identified hydronephrosis depends on changes noted in the amniotic fluid volume (surrogate for urine output), changes in major and minor calyces, dilatation of the ureters, and thickening of the bladder wall (not just dilatation of the pelvis in millimeters).

1. **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 of life to determine the etiology (PUV, ureteropelvic junction [UPJ] obstruction, ureterovesical junction [UVJ] obstruction, prune belly syndrome, or VUR). In cases of infravesical obstruction (such as PUV), ultrasonography demonstrates a thickened trabeculated bladder wall often with concomitant dilated tortuous ureters. Altered renal cortical echogenicity, reduced parenchymal thickness, and presence of renal cortical cysts signify underlying secondary renal dysplasia which predicts a grim prognosis.

2. **Unilateral hydronephrosis** is more common and is unlikely to be associated with systemic or pulmonary complications if the contralateral kidney is normal. Postnatal ultrasonographic confirmation should be deferred till 72 hours of life to decrease false negatives secondary to physiologic oliguria. A normal USG should be followed up at 6 weeks.
   - **a.** If the renal pelvis is >10 mm or changes in major and minor calyces or dilated ureter are noted, investigations should be planned. If the lower urinary tract is obstructed (bladder thickening, bilateral hydronephrosis), consult a surgeon.
   - **b.** If the renal pelvis is 7 to 10 mm, the ureter is not visualized on ultrasound (non-dilated), and parenchyma is normal (major and minor calyces), 3- to 6-month follow-up suffices.
   - **c.** Antibiotic prophylaxis is recommended until VCUG rules out VUR. Parents are alerted to perform urgent urine analysis if the infant develops fever. A DTPA is done at 6 weeks of age. Drugs of choice are amoxicillin (10 mg/kg/day) or oral cephalexin at 10 mg/kg as a single bedtime dose. Nitrofurantoin and trimethoprim–sulfamethoxazole are not used in infants younger than 3 months of age. Nitrofurantoin can cause hemolytic anemia and sulfa can displace bilirubin from albumin with the possibility of kernicterus.
   - **d.** In the presence of VUR, long-term prophylactic antibiotics have been shown in some trials to reduce the number of symptomatic urinary tract infection (UTIs). Despite the improvement in clinical infections, there was no difference in the rate of renal scarring between children given prophylaxis and those not given prophylaxis. This finding might indicate that the underlying renal dysplasia might have set in during renal development, even before antibiotic prophylaxis is initiated. Circumcision in males is associated with a 10-fold reduction in the incidence of UTIs in infants with high-grade VUR. If DTPA (diuretic renography) shows obstructive pattern and significant differential function between kidneys, surgery may be considered.

B. Cystic disease of the kidney may result from abnormalities in development, as in case of MCDK, or from inherited genetic conditions. The principal differential diagnosis of bilateral cystic kidney disease in the newborn includes ARPKD, autosomal dominant polycystic kidney disease (ADPKD), and glomerulocystic kidney disease.

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. The clinical findings of ARPKD are variable and include bilateral smooth enlarged kidneys, varying degrees of renal insufficiency,

which usually progresses to renal failure over time, and severe renin-mediated hypertension seen in up to 60% of patients. Infants with more severe involvement may have oligohydramnios with pulmonary hypoplasia and Potter's 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. In later life, it may progress to liver failure requiring transplantation in adolescence.

In contrast, macroscopic cysts are usually detected in cases of ADPKD and glomerulocystic disease and the liver is spared. 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 include bilateral renal masses that are usually less symmetric than in ARPKD. Recent literature supports the use of aquaretics such as tolvaptan to retard cyst enlargement and delay the progression of renal dysfunction but studies in children are awaited. Neonatal use has not been reported so far.

1. ***MCDK*** is one in which no functional parenchyma is present and a lobulated "ball of grapes"–like structure is present. Infants with unilateral MCDK are usually asymptomatic, and by definition, the affected kidney has no renal function as demonstrated by DTPA renal scan. Surgical removal was practiced decades back to decrease the potential of renal cell carcinoma. But there is no evidence that surgical removal of asymptomatic MCDK improves long-term outcomes. Surgery is indicated only rarely in cases with infection or with respiratory compromise secondary to abdominal compression by the abnormal kidney. Current management is conservative which includes annual monitoring of renal functions (creatinine, microalbuminuria, BP) and sonography to ensure that the affected side is involuting slowly (by 5 to 7 years) and the healthy side is exhibiting compensatory hypertrophy.
2. 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.

C. Renal abnormalities may be associated with other congenital anomalies including neural tube defects, congenital heart lesions, intestinal obstructive lesions, abdominal wall defects, central nervous system (CNS) or spinal abnormalities, and urologic abnormalities of the lower urinary tract.

IV. COMMON KIDNEY PROBLEMS IN NEONATES—POSTNATAL

A. AKI, previously termed acute renal failure, is defined as an abrupt decrease in GFR leading to accumulation of nitrogenous wastes and dysregulation of fluid electrolyte, and acid–base homeostasis. The change in terminology has come with the recognition that renal dysfunction is a dynamic process; dysfunction is a spectrum with increasing stages from 1 to 3 indicating increasing severity and worsening prognosis. The previous definition adopting one single absolute value of serum creatinine >1.5 mg/dL to define AKI is not applicable across all gestational and postnatal ages. The previous approach led to under-recognition of AKI episodes and delayed institution of nephroprotective strategies to limit

further damage potential of compromising both acute and long-term outcomes. Currently a revised, stage-based definition is recommended that is based on changing trends of creatinine/deviation of creatinine from the baseline and a drop in urine output (Table 28.6). Neonatal RIFLE is one of the most popular creatinine- and urine output-based definition for bedside diagnosis of AKI in newborns. However, a creatinine-alone-based definition may not be the most accurate marker of GFR/AKI. Creatinine estimation is cheap, easily available, and economical, but suffers from some inherent drawbacks. Creatinine is relatively insensitive in the early stages; it crosses the placenta, is dependent on the muscle mass, and also undergoes tubular secretion so often underestimates fall in GFR. So, researchers have explored other more sensitive endogenous markers such as cystatin C (not affected by size, gender, minimal placental transfer) and BTP; newer equations are based on these markers. Studies comparing creatinine-based equations with cystatin C–based definitions have showed conflicting results with the majority in favor of cystatin C for both diagnosis of neonatal AKI and follow-up of AKI survivors.

AKI is suspected when a newborn fails to pass urine for 48 hours after birth or develops oliguria, edema, or hypertension at any time after birth. A rising trend of creatinine with at least a 0.3 mg/dL rise in 48 hours along with electrolyte and acid–base disturbance suggests AKI. Higher stages witness further increases in creatinine—doubling and tripling of the nadir value. Creatinine above 2.5 mg/dL is suggestive of end stage of failure and portends a grave prognosis especially if associated with oliguria. Exclusion of urine output from the AKI criterion is not recommended; recent studies show under-recognition of up to one-third episodes of AKI.

Table 28.6. Acute Kidney Injury Criteria in Neonates

	Serum Creatinine	Urine Output
	Neonatal KDIGO	
1.	SCr 1.5–1-9-fold baseline or ≥0.3 mg/dL increase	<0.5 mL/kg/hour for 6–12 hours
2.	SCr 2–2.9-fold baseline	<0.5 mL/kg/hour for ≥12 hours
3.	SCr threefold baseline or increase in SCr to ≥2.5 mg/dL with an acute increase of ≥0.5 mg/dL or RRT	<0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours
	AKIN	
1.	SCr 1.5-fold baseline or ≥0.3 mg/dL increase	<0.5 mL/kg/hour for ≥6 hours
2.	SCr twofold baseline	<0.5 mL/kg/hour for ≥12 hours
3.	SCr threefold baseline or increase in SCr to ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or RRT	<0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours

AKIN, acute kidney injury neonate; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine; RRT, renal replacement therapy.

Sick preterm babies on ventilation and inotropes and receiving nephrotoxic drugs are more likely to develop AKI. The challenge is in recognition of AKI in preterm newborns; their baseline creatinine values are expected to be high for many weeks after birth. In most instances, a high value of creatinine in a sick preterm baby is passed off as physiologic; recent evidence indicates that longer periods of high creatinine may be episodes of AKI with an ominous prognosis. Watching trends of creatinine, urine output, and BP may help to arrive at the correct diagnosis. Infants develop more than one episode of AKI, which besides conferring an immediate risk of mortality and longer hospital stay also compromise the long-term renal outcome. Many follow-up cohort studies show that AKI survivors have fourfold greater chance of CKD.

Perinatal asphyxia, extracorporeal membrane oxygenation, cardiac surgery, sepsis, prematurity, and nephrotoxicity. Neutrophil gelatinase-associated lipocalin (NGAL), both serum and urinary, is a useful marker for detecting asphyxiated neonates at risk of developing AKI. A single dose of prophylactic theophylline helps in the prevention of AKI/severe renal dysfunction in term neonates with severe birth asphyxia (moderate-quality evidence) without increasing the risk of complications and without affecting all-cause mortality (very low-quality evidence). Serum cystatin C, urinary NGAL, kidney injury molecule-1, and interleukin-18 are promising neonatal AKI biomarkers. Emerging biomarkers which require further study in the neonatal population include netrin-1 and EGF.

1. **Causes of AKI.** Conventionally AKI is categorized into prerenal azotemia, intrinsic AKI (tubular, glomerular, or interstitial disease), and postrenal AKI (obstructive) (Table 28.7).
   - ***Prerenal azotemia*** (80% of cases of AKI in neonatal intensive care unit [NICU]) occurs when the kidney is underperfused for a short time, so that the structural integrity of the nephron has not yet been compromised. It may be seen in infants with loss of effective blood volume, relative loss of intravascular volume from increased capillary leak, poor cardiac output, medications, or intra-abdominal compartment syndrome. These conditions can lead to intrinsic renal tubular damage if not corrected expeditiously.
   - ***Intrinsic AKI*** implies direct damage to the glomeruli, interstitium, or tubules. In neonates, tubular injury is caused mostly by prolonged or severe ischemia, nephrotoxins, or sepsis. Glomerular and primary interstitial injury is rare in neonates. Most cases of acute tubular necrosis or vasomotor nephropathy are nonoliguric.
   - ***Postrenal AKI*** results from obstruction to urinary flow through both kidneys and accounts for 3% to 5% of cases of AKI in neonates. In boys, the most common lesion is PUV, a congenital obstruction to the flow of urine; acquired obstruction (from masses, stones, or fungal balls) can also occur. After obstruction is relieved, a period of brisk diuresis is noted along with electrolyte wasting. Renal functions usually improve after surgical intervention but may remain subnormal in others who have associated renal dysplasia.
2. **Management of AKI.** Important aspects of the management of AKI are determining the underlying etiology, preventing additional nephrotoxicity by stabilizing perfusion, adjusting drug dosing, and managing complications.
3. **History in case of AKI.** Antenatal history of oligohydramnios, perinatal asphyxia, polycythemia, thrombocytosis, sepsis, or maternal drug use. Enquire for

Table 28.7 Causes of Acute Kidney Injury in the Neonatal Period

1. Prerenal
   a. Reduced effective circulatory volume
      i. Hemorrhage
      ii. Dehydration
      iii. Sepsis
      iv. Necrotizing enterocolitis
      v. Congenital heart disease
      vi. 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
   b. Ureterocele
   c. Ureteropelvic/ureterovesical obstruction
   d. Extrinsic tumors
   e. Neurogenic bladder
   f. Megacystis or megaureter syndrome

ACE, angiotensin-converting enzyme.

preceding use of nephrotoxic medications—aminoglycosides, vancomycin, 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. Recent studies indicate that over 80% of preterm babies receive an average of a 2-week course of one or more nephrotoxic drugs during hospital stay.

4. **Monitoring suspected/established AKI.** Place an indwelling urinary catheter for an accurate record of urine output and relieving obstruction in postrenal causes.
   - Evaluate for signs and symptoms of intravascular depletion (tachycardia, sunken fontanelle, poor skin turgor, dry mucous membranes).

- 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.
- A fluid challenge with normal saline 10 to 20 mL/kg over 30 minutes is diagnostic and may be therapeutic as well. Evaluation for cardiac failure is imperative prior to aggressive fluid resuscitation for renal failure.
- Renal ultrasonogram should be performed to rule out bladder obstruction and to assess for CAKUT.
- Laboratory evaluation can help determine the underlying etiology. Table 28.8 list laboratory tests that are helpful in differentiating prerenal azotemia from intrinsic and obstructive causes. Test samples should be obtained before fluid challenge if possible.

5. **Management of AKI.** It should focus on treating the underlying *etiology, avoiding further injury*, and addressing *consequences of decreased renal function.*
   - Fluid challenge is the first step in babies suspected to have AKI; response to the fluid challenge will differentiate prerenal from intrinsic cause of AKI.

     Fluid volume should be carefully planned. Overhydration (weight gain, edema, hyponatremia) is associated with increased ventilation needs and poorer prognosis. Overzealous fluid restriction can cause dehydration and add prerenal component to the AKI. 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. The inability to adequately prescribe fluids for nutrition, blood products, or medications due to fluid restriction and/or significant fluid overload is a relative indication for dialysis.
   - Avoidance of nephrotoxic medications to prevent further insult and dose adjustment of concurrent medications based on estimated renal function are critical to early recovery. A policy of antibiotic stewardship and active creatinine surveillance has shown to decrease incidence of both nephrotoxic drug exposure and related AKI.
   - 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 the patient has response to diuresis, careful monitoring of electrolytes and fluid status should be followed; hypokalemia,

Table 28.8. 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

FENa, fractional excretion of sodium.
Source: Modified from Mathew OP, Jones AS, James E, et al. Neonatal renal failure: usefulness of diagnostic indices. *Pediatrics* 1980;65:57.

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 increase urine output.
- A single dose of theophylline in the dose of 5 to 8 mg/kg is known to decrease renal damage in newborns with birth asphyxia.

6. Management of complications of AKI

- Discontinue or minimize potassium (K^+) intake. K^+-free IV fluids are used. *Treatment of hyperkalemia* (K^+ >6 mEq/L) is as follows:
  - Calcium is given as 1 to 2 mL/kg of calcium gluconate 10% over 5 to 10 minutes if there is arrhythmia or cardiac dysfunction. The electrocardiogram (ECG) should be monitored.
  - Sodium bicarbonate will shift K into the cells and can temporarily lower serum K^+. It may be used if metabolic acidosis is severe and CO_2 is normal.
  - 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 unit/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.
  - Furosemide can be given for kaliuresis as well as natriuresis. A trial of 1 mg/kg intermittently is given. Avoid volume depletion due to overdiuresis.
  - Calcium polystyrene sulfonate (K-Bind) is administered rectally in a dose of 1.0 to 1.5 g/kg (dissolved in normal saline at 0.5 g/mL saline) or orally in a dose of 1.0 g/kg (dissolved in dextrose 10% in water) as needed to decrease serum K levels. The enema tube, a thin silastic feeding tube, is inserted 1 to 3 cm rectally. If possible, K exchange resins in low-birth-weight infants due to the risk of bowel perforation. K-Bind 1 g/kg removes approximately 1 mEq/L of potassium. These exchange resins are active in the colon, so rectal doses lower potassium quicker than oral doses.
  - *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 venovenous hemoperfusion (CVVH) can be used.
  - *Sodium (Na^+)* intake is restricted and Na^+ concentration is monitored, as a measure of 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 sodium, is needed during diuretic therapy or with dialysis.
  - *Phosphorus* is restricted in AKI by using a low-phosphorus formula (preterm formula/calcium–phosphate supplements). Oral calcium carbonate or calcium acetate can be used as a phosphate-binding agent.
  - Calcium supplementation is given if ionized calcium is decreased or the patient is symptomatic.
  - *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 due to heart failure or volume loss from hemorrhage. Sodium bicarbonate is used to correct severe hyperkalemia associated with metabolic acidosis.

- *Feeds.* Infants who can take oral feeding are given a low-phosphate and low-potassium formula with a low renal solute load. Infants with AKI who are critically ill requiring parenteral nutrition should receive amino acids up to a maximum of 1.5 g/kg which can be increased by additional 1.5 g/kg for those on renal replacement therapy.

7. **Renal replacement therapy (RRT).** Dialysis is indicated when conservative management has been unsuccessful in correcting severe fluid overload, hyperkalemia, acidosis, and uremia. Inability to provide desired nutrition due to severe fluid restriction in the anuric infant is a relative indication for dialysis.
   - PD is generally considered the optimal dialysis modality for neonates. It allows for the slow removal of fluid and solutes while avoiding hemodynamic instability. It is technically simple and avoids risks of systemic anticoagulation in the critically ill neonate. Fluid removal and solute removal is accompanied by placing a hyperosmolar PD solution (composed of dextrose, sodium, chloride, lactate, magnesium, and calcium) in the peritoneum. The equipment includes either a stiff plastic PD catheter with a stylet or a soft silicone catheter (or even a 10-F Ryles' tube). A silicone catheter offers the dual advantage of less chances of abdominal trauma and lower rates of peritonitis.

     Fluid removal/ultrafiltration can be enhanced by increasing the PD dextrose concentration, the amount of fluid in the peritoneum, or the frequency of exchanges. Commercially available PD solutions have dextrose concentrations of 1.5% (1,500 mg/dL), 2.5% (2,500 mg/dL), and 4.25% (4,250 mg/dL). Options for enhancing solute removal are increasing fill volume or dwell time. PD in critical neonates is based on frequent exchanges with short dwells (30 to 40 minutes) and lower dialysate volumes (starting with 10 mL/kg and up to 25 to 30 mL/kg). Longer dwells lead to poor ultrafiltrates as most neonates are rapid transporters and hence quickly dissipate the hyperosmolar milieu from the peritoneal cavity (due to rapid glucose transfer from the abdominal cavity to the splanchnic capillaries). Larger fill volumes are best avoided as they may cause pericatheter dialysate leaks and respiratory compromise. In the presence of severe hyperkalemia or volume overload, the dwell time can be temporarily decreased to 10 minutes or even lesser. Strict asepsis, clinical monitoring, PD intake output, and overall intake output charting should be practiced. Serum electrolytes should be checked 6 to 12 hourly, and renal functions and PD cytology every 24 hours.
   - *HD/CVVH.* When using either HD or CVVH, the smaller blood volume of neonates results in a relatively large extracorporeal circuit volume. A blood prime is required for each treatment, and the infant may experience temperature instability and rapid fluid shifts.

8. **Dose modification in renal dysfunction.** Modifications of drug dose in renal disease are usually necessary only when GFR is less than 30 to 40 mL/minute/1.73 m^2. Most newborns, especially preterms, have a physiologic reduction of GFR during the initial few weeks of life. Paradoxically these are the infants who require drugs most often and become victims of drug overdosages

or run risk of therapeutic failure from underdosing. As a rule, nephrotoxic drugs are best avoided altogether. If unavoidable, doses of renally excreted drugs should be adjusted in accordance with GFR and therapeutic drug level monitoring must be done. GFR may be estimated using cystatin C or serum creatinine-based equations as described. One may use web-based software for dosing calculators.

Given the abundance of literature relating AKI with poor long-term renal and cardiovascular outcome, there is an urgent need for strict follow-up of newborns surviving an episode of AKI. Prematurity and low birth weight should be regarded as additional risk factors in such children as both conditions lead to poor nephron endowment with an associated risk of hyperfiltration and worsening GFR with time. Such newborns may exhibit enhanced salt sensitivity and high risk of hypertension, obesity, and glucose intolerance in the future life, and may benefit from lifestyle modification and pharmacologic intervention. Survivors of AKI should be on lifelong follow-up with the first visit within 3 months postdischarge or earlier. Surveillance should include estimation of GFR, using Cr- or cystatin C–based equations, detection of microalbuminuria, and monitoring of BP, preferably TKV/body surface area which is considered to be a good surrogate anatomical marker of poor nephron endowment. A scoring system may be forthcoming that incorporates the degree of prematurity, AKI, renal size, and other relevant factors to be validated for better stratification of future risk for CKD in these at-risk patients.

B. 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 renal failure in adolescence (see Chapter 44).
2. ***Renal vein thrombosis (RVT)*** has the predisposing conditions of hyperosmolarity, polycythemia, hypovolemia, and hypercoagulable states and is often associated with infants of diabetic mothers or use of umbilical venous catheters. Cases of intrauterine renal venous thrombosis have been described and present with calcification of the clot in the inferior vena cava (IVC). The classic clinical findings include gross hematuria often with clots, enlarged kidneys, hypertension, and thrombocytopenia. Other symptoms are nonspecific and include vomiting, shock, lower extremity edema, and abdominal distention. 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. The differential diagnosis includes renal masses.

The management of RVT is also controversial. Initial therapy should focus on the maintenance of circulation, fluid, and electrolyte balance while examining for underlying predisposing clinical conditions. Assessment of the coagulation status includes platelet count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and fibrin split products and, if suggested by maternal history, lupus antiphospholipid antibodies.

No consensus exists on the use of heparin. If there is unilateral involvement without evidence of disseminated intravascular coagulation (DIC), conservative management is warranted. If there is bilateral involvement and evidence of DIC, more aggressive therapy is indicated because the infant is at risk for complete loss of kidney function. Heparin therapy should be initiated with an initial bolus of 50 to 100 units/kg followed by continuous infusion at 25 to 50 units/kg to maintain PTT of 1.5 times normal.

Antithrombin III (AT III) activity should be reassessed before heparin therapy is instituted as AT III is required for the anticoagulant action of heparin. Recently, low-molecular-weight heparin has been used both as initial treatment for thrombosis and as prophylactic therapy after recanalization of the occluded vessel. In the treatment of patients with thrombosis, dosages of 200 to 300 anti-Fxa units/kg are reported to reach a therapeutic level of 0.5 to 1.0 anti-Fxa unit/mL. Reported dosages range from 45 to 100 anti-Fxa units/kg to reach prophylactic levels of 0.2 to 0.4 anti-Fxa unit/mL.

Thrombolytic therapy with streptokinase and urokinase has been used in both RAT and RVT, with variable success, but is no longer commercially available. There is limited experience with the use of thromboplastin activator (TPA). This is used in low dose (0.02 to 0.03 mg/kg) if there is evidence of bleeding and titrated to PTT value of 1.5 times normal. Plasma infusion may be necessary to provide thromboplastin activation. Protamine and epsilon-aminocaproic acid should be present at the bedside because significant bleeding can occur.

Surgical intervention should be considered if there has been an indwelling umbilical vein catheter, the thrombosis is bilateral, and it involves the main renal veins leading to renal failure. This type of thrombosis is likely to have started in the IVC rather than intrarenal and hence is more likely amenable to surgical attention (see Chapter 44).

C. Urinary tract infection. 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, or any clinical signs of sepsis after 1 week of life. UTI is uncommon in the first 48 hours of life. Late-onset conjugated hyperbilirubinemia with onset after 1 week of life may be an unusual presentation; UTI should be considered in unexplained prolonged jaundice. UTI with underlying CAKUT in infants can closely mimic congenital adrenal hyperplasia (CAH) in presentation (these infants develop a transient state of aldosterone resistance); in contrast to CAH, these infants have normal values of 17-hydroxyprogesterone and raised aldosterone levels.

UTI is confirmed by a positive urine culture obtained by suprapubic bladder aspiration or a catheterized specimen (with a colony count exceeding 1,000 colonies per milliliter). A blood culture should also be obtained prior to antibiotic

administration, in babies with suspect UTI, as 5% of cases may have associated bacteremia. Although most newborns with UTIs have leukocytes in the urine, an infection can be present in the absence of leukocyturia.

Epidemiology of UTI in term born differs from that in a preterm baby. While *Escherichia coli* is a common uropathogen in community-acquired UTI in term born babies, etiology in hospitalized or preterm babies may be *Klebsiella*, other Gram-negative organisms associated with late-onset sepsis, fungus, and even coagulase-negative *Staphylococcus*.

Evaluation of the urinary tract by ultrasonography is required to rule out hydronephrosis, obstructive uropathy, severe VUR, or neurogenic bladder (inability to empty the bladder). In cases of infravesical obstruction, besides parenteral antibiotics, drainage or relief of obstruction is necessary to control the infection. Neonates with culture-positive UTI must undergo evaluation by VCUG after demonstrating urinary sterilization to define lower tract abnormalities and to detect reflux. VUR may be present in 40% of neonates with UTI, but may not be detectable by USG. Radionuclide cortical scan—DMSA—must be done 3 to 4 months after an acute attack of UTI to detect residual scars which may develop following pyelonephritis.

The initial choice of antibiotic is based on the regional data and later 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. Circumcision is known to be beneficial in decreasing the risk of pyelonephritis many-fold in males with high-grade reflux even in the absence of a demonstrable infravesical obstruction.

D. Tubular disorders

1. **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.
   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. 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's syndrome.
   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 alkali therapy. 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.

2. **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.
Clinical and laboratory findings include the following:
   - 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.
   - Metabolic acidosis is secondary to bicarbonate wasting (proximal RTA).
   - Aminoaciduria and glycosuria do not result in significant clinical signs or symptoms.
   - These infants have polyuria and are therefore at risk for dehydration.
   - Hypokalemia, due to increased excretion by the distal tubule to compensate for the increased sodium reabsorption, is also frequent and sometimes profound.

   a. **Etiology.** The primary form of Fanconi's syndrome is rare in the neonatal period and is a diagnosis of exclusion. 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's syndrome (oculocerebrorenal syndrome), and mitochondrial disorders.

E. Nephrocalcinosis (NC). It is detected by ultrasound examinations and 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. 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, not needed 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 (BPD) with a need for long-term diuretic therapy may be helpful. Although the prospect of using a urinary solubilizer such as sodium citrate is appealing, it is not supported by the literature. Monitoring of urinary calcium excretion (urine calcium:creatinine ratio) helps in determining response to the therapy.

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.

F. Kidney tumors. These are rare in the neonatal period. These include mesoblastic nephroma and nephroblastomatosis. The differential diagnosis includes other causes of renal masses.

G. Proteinuria. It is frequent in small quantities during the first weeks of life. After the first week, persistent proteinuria >250 mg/m^2/day should be investigated.

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. No specific treatment is required for mild proteinuria. Treat the underlying disease and monitor the proteinuria until resolved.

Massive proteinuria (>1.5 g/m^2/day), hypoalbuminemia with serum albumin levels <2.5 g/dL, and edema are all components of congenital nephrotic syndrome. Prenatal clues to the diagnosis include elevated maternal/amniotic alpha-fetoprotein levels and enlarged placenta. Children with severe forms of congenital nephrotic syndrome require daily intravenous albumin and Lasix for fluid removal, high-calorie diets, replacement of thyroid, iron and vitamins due to excess losses of binding proteins, and, ultimately, bilateral nephrectomies and renal transplantation. They are at a high risk for infections and thrombosis due to immunoglobulin losses and loss of anticoagulant proteins.

H. Hematuria. It is defined as >5 red blood cells (RBCs) per high-power field. It is uncommon in newborns and should always be investigated (Table 28.9).

Hematuria has many causes including hemorrhagic disease of the newborn. 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.

Evaluation of neonatal hematuria depends on the clinical situation. One may consider performing the following tests: urinalysis with examination of the

Table 28.9. Etiology of Hematuria in the Newborn

1. Cortical necrosis
2. Vascular disease
   a. Renal vein thrombosis
   b. Renal artery thrombosis
3. Bleeding and clotting disorders
   a. Disseminated intravascular coagulation
   b. Severe thrombocytopenia
   c. Clotting factor deficiency
4. Urologic anomalies
5. Glomerulonephritis (neonatal lupus)
6. Tumors
   a. Wilms' tumor
   b. Neuroblastoma
   c. Angiomas
7. Nephrocalcinosis
8. Trauma
   a. Suprapubic bladder aspiration
   b. Urethral catheterization

sediment, urine culture, ultrasonography of the upper and lower urinary tract, evaluation of renal function (serum creatinine and BUN), and coagulation studies.

I. Neonatal hypertension. One of the reasons to investigate a baby for renal problems may be a persisting high BP. The BP may be indecently detected to be high on monitoring of a sick baby in the NICU; long standing, severe hypertension may present with congestive (feeding difficulty, unexplained tachypnea, lethargy, cool peripheries) encephalopathy (seizures or stroke), hypertensive retinopathy. or renal dysfunction itself.

1. Hypertension. Neonatal hypertension is defined as persistent systolic and/or diastolic BP that exceeds the 95th percentile for postmenstrual age. A value >95th percentile needs monitoring and >99th percentile should be investigated. Normal values for blood pressure in term born neonates depend on postnatal age, gender, and method of measurement (noninvasive/invasive method of measurement) (Table 28.10). Normal values are lower in preterm and depend on gestation. Hypertension is diagnosed if systolic and/or diastolic BP readings on 3 separate occasions are at or above the 95th percentile for postconceptual age.

Table 28.10. Infant Blood Pressures by Postmenstrual Age After 2 Weeks of Life; Systolic Blood Pressure (SBP), Mean Arterial Pressure (MAP), and Diastolic Blood Pressure (DBP) are Presented 95th, and 99th Percentiles

Postmenstrual age	Blood pressure	95th percentile	99th percentile
44 weeks	SBP	105	110
	MAP	*80*	*85*
	DBP	68	73
42weeks	SBP	98	102
	MAP	*76*	*81*
	DBP	65	70
40 weeks	SBP	95	100
	MAP	*75*	*80*
	DBP	65	70
38 weeks	SBP	92	97
	MAP	*74*	*79*
	DBP	65	70
36 weeks	SBP	87	92
	MAP	*72*	*77*
	DBP	65	70
34 weeks	SBP	85	90
	MAP	*65*	*70*
	DBP	55	60

Table 28.10. Infant Blood Pressures by Postmenstrual Age After 2 Weeks of Life; Systolic Blood Pressure (SBP), Mean Arterial Pressure (MAP), and Diastolic Blood Pressure (DBP) are Presented 95th, and 99th Percentiles *(continued)*

Postmenstrual age	Blood pressure	95th percentile	99th percentile
32 weeks	SBP	83	88
	MAP	*64*	*69*
	DBP	55	60
30 weeks	SBP	80	85
	MAP	*63*	*68*
	DBP	55	60
28 weeks	SBP	75	80
	MAP	*58*	*63*
	DBP	50	54
26 weeks	SBP	72	77
	MAP	*57*	*63*
	DBP	50	56

Adapted from Dionne et al. (2012)

Risk factors for hypertension in the NICU include low gestational age and birth weight, specific diseases (BPD, cardiac disease, and renal injury), and use of umbilical artery catheters.

2. **BP measurement in neonates by oscillometric device-practical tips**
   - Measure 1.5 hours after a feed or medical intervention
   - Infant lying supine
   - Appropriately sized BP cuff* (Figure 28.2)
   - Right upper arm
   - After cuff placement, the infant is left undisturbed for 15 minutes.
   - Infant asleep or in quiet awake state
   - Three successive BP readings at 2-minute intervals
3. **Normal blood pressure.** Both systolic and diastolic BP increased with advancing gestational age at birth, advancing PMA, and increased birth weight. The primary determinant of BP is the PMA. BP normative value after 2 weeks for neonates 26 to 44 weeks' postconceptual age.
4. **Evaluation of hypertension** (Table 28.11) includes a review of fluid status, medications, history of umbilical or arterial line placement, and four extremity BP measurements. Both renin-mediated hypertension and fluid overload may

*A proper cuff size is important and has been determined in neonates to be a cuff width to arm circumference ratio in the range of 0.45 to 0.55.

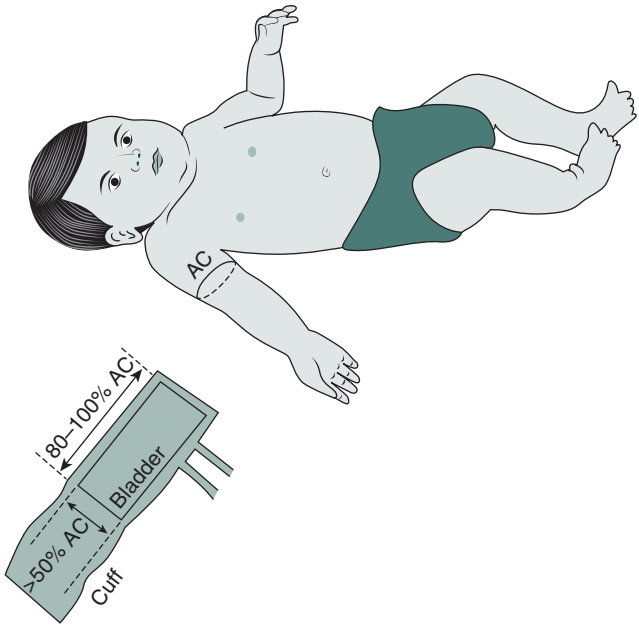

Figure 28.2. Proper cuff size in neonates – cuff width to arm circumference ratio in the range of 0.45 to 0.55 & the length of the bladder is 80-100 % of the arm circumference (AC)

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 thrombosis, although this test is not reliable in neonates and carries the possibility of both false positives and false negatives. A DMSA renal scan which can be done only after the chronological age of 6 weeks may detect segmental renal arterial infarctions. Echocardiogram is indicated if coarctation is suspected and can determine whether left ventricular hypertrophy has occurred from sustained hypertension. Etiology remains undetermined despite evaluation in 50% of cases. It is prudent to evaluate the cause, before beginning pharmacotherapy.

5. **Management** of hypertension in neonates is directed at correcting the underlying cause whenever possible. Antihypertensive therapy is administered for sustained hypertension that is not related to volume overload or concomitant medications. In infants with severe symptomatic hypertension, intravenous infusions of antihypertensives are needed. Nicardipine is the drug of choice. Hydralazine, esmolol, labetalol, and nitroprusside are the alternatives. Oral antihypertensives are avoided in severe/symptomatic hypertension. However, in milder/asymptomatic cases or after initial stabilization with IV infusions, oral therapy with isradipine and amlodipine may be used for the treatment of persistent hypertension. Propranolol is an option in patients not in cardiac failure or not having BPD. ACE inhibitors, angiotensin II receptor blocker (ARB), and sublingual nifedipine are usually avoided. Regardless of the need for antihypertensive medications, most neonatally acquired hypertension

Table 28.11. Causes of Hypertension in the Neonate

1. Vascular (commonest cause, 80%)
   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's disease
   c. Neural crest tumor
   d. Cerebral angioma
   e. Drug withdrawal
5. Pulmonary
   a. Bronchopulmonary dysplasia (common cause in preterm)
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)

resolves within a few weeks or within a few years with the exceptions of hypertension secondary to ARPKD. However, preterm babies born with poor nephron endowment carry the long-term risk of increased salt sensitivity and hypertension in adulthood.

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29 Mechanical Ventilation

Eric C. Eichenwald

KEY POINTS

- Use of noninvasive respiratory support often avoids the need for mechanical ventilation in preterm infants with respiratory distress.
- Volume-targeted, patient-triggered ventilators reduce the risk of bronchopulmonary dysplasia 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 at minimum fractional concentration of inspired oxygen (FiO_2) and ventilator pressures/tidal volume (V_T). The ventilator strategy employed to accomplish this goal depends, in part, on the infant's disease process. In addition, recent advances in technology have brought more options for ventilatory therapy of newborns.

II. TYPES OF VENTILATORY SUPPORT

A. Continuous positive airway pressure

1. **Indications.** See Section III.A.
2. **General characteristics.** A continuous flow of heated, humidified gas is circulated past the infant's airway, typically at a set pressure of 4 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.
3. **Continuous positive airway pressure (CPAP) is usually administered by means of** a ventilator, variable flow 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. 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 sterile water solution to the desired depth to generate pressure ("bubble CPAP"). Variable flow CPAP devices, in which expiratory resistance is decreased via a "fluidic flip" of flow at the nosepiece during expiration, are also available.

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.

4. **CPAP interface.** CPAP is usually delivered by means of nasal prongs, or nasal masks. Nasopharyngeal tube and endotracheal CPAP should not be used because the high resistance increases the work of breathing, especially in small infants.

   The prongs should be short, snugly fitting to the nostrils, of wider lumens, anatomically curved, soft, and gently introduced, ensuring that they do not come in contact with the septum. The mask is preferred if there is nasal injury or for extremely low-birth-weight (ELBW) infants.

5. **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 immediate 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 initial CPAP and mechanical ventilation and early surfactant treatment show similar rates of bronchopulmonary dysplasia (BPD), meta-analyses of the prospective randomized trials of early CPAP show that initial CPAP use is associated with a decreased risk of death or BPD.

   d. CPAP decreases the frequency of obstructive and mixed apneic spells in some infants.

6. **Disadvantages**

   a. CPAP is not effective in patients with frequent apnea or inadequate respiratory drive.

   b. CPAP provides inadequate respiratory support in the face of severely abnormal pulmonary compliance and resistance.

   c. Maintaining nasal or nasopharyngeal CPAP in large, active infants may be technically difficult.

   d. Infants on CPAP frequently swallow air, leading to gastric distension and elevation of the diaphragm, necessitating decompression by a gastric tube.

   e. Preventing nasal injuries. Selection of correctly sized prongs, constant nursing vigilance, and attention to correct positioning are all important. A checklist inspecting the skin integrity, blanching, prong size, symmetry of nostrils, position of septum, color consistency, and frequency of secretions followed by nasal massage and suctioning aids injury prevention.

B. Heated humidified high-flow nasal cannula

1. High-flow nasal cannula (HHFNC) has emerged as an alternative to conventional CPAP devices; parents and nurses find it friendlier to use. Pressure generated by HHFNC is inconsistent, unreliable, and unpredictable and is not recommended for primary support of RDS. It is a good alternative for

weaning from CPAP and for postextubation support. There are limited data of its use in ELBW infants.

2. **General characteristics.** HFNC usually refers to the delivery of blended, heated, and humidified oxygen at flows >1 L/minute via small binasal prongs.

3. **Advantages**

   a. Reported advantages to HFNC include ease of use, a simpler patient interface, and a lower incidence of nasal breakdown compared with conventional CPAP.

   b. Comparing HFNC to CPAP as postextubation support suggests that HFNC may be an acceptable alternative to CPAP in many infants. Data suggest that the failure of HFNC may be higher than of conventional CPAP in infants <26 weeks' gestation.

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 with CPAP.

C. Pressure-limited, time-cycled, continuous flow ventilators

1. **Pressure-limited ventilation.** 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. Peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and respiratory timing (rate and duration of inspiration and expiration) are selected.

2. **Advantages**

   a. Good control is maintained over respiratory pressures.

   b. The system is relatively simple and inexpensive.

3. **Disadvantages**

   a. Tidal volume (V_T) is poorly controlled.

   b. The system does not respond to changes in respiratory system compliance.

   c. In spontaneously breathing infants, asynchrony (fighting) with ventilator results in inadequate ventilation and increased air leak.

D. Synchronized and patient-triggered (assist-control or pressure support)

1. **SIMV.** These ventilators deliver intermittent positive-pressure breaths in synchrony with the baby's inspiratory efforts ("synchronized IMV," or synchronized intermittent mandatory ventilation [SIMV]). During an apnea, SIMV ventilators continue to deliver the set IMV rate.

2. **PTV/synchronized intermittent positive pressure ventilation (SIPPV)/assist-control (A/C).** In patient-triggered ventilation, a positive-pressure breath is delivered only with every inspiratory effort. During apnea, the ventilator in patient-triggered mode delivers an operator-selected IMV ("control") rate. In some ventilators, SIMV breaths can be supplemented by pressure-supported breaths in the spontaneously breathing infant. Ventilators equipped with a flow sensor can also be used to monitor delivered V_T continuously by integration of the flow signal.

a. In A/C ventilation, the ventilator delivers a breath with each inspiratory effort. The clinician sets the inspiratory time and peak inflation pressure or target V_T. The clinician also sets a minimum mandatory ventilator rate to maintain adequate minute ventilation should the spontaneous respiratory rate fall below the minimum selected rate.

b. Pressure support ventilation (PSV) is similar to A/C mode in that each spontaneous patient breath results in a ventilator support breath. However, 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 rate and pattern of breathing (inspiratory time or inspiratory:expiratory ratio).

3. 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.

4. Disadvantages

a. Under certain conditions, the ventilators may inappropriately trigger a breath because of signal artifacts or fail to trigger because of problems with the sensor.

b. Limited data are available comparing patient-triggered ventilation to other modes of ventilation in newborns. PSV may not be appropriate for small premature infants with irregular respiratory patterns and frequent apnea because of the potential for significant variability in ventilation. However, some data suggest that the 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.

5. Indications. SIMV can be used when a conventional pressure-limited ventilator is indicated. Many neonatal intensive care units (NICUs) use PTV modes because of perceived advantages of using lower peak inspired pressure and smaller V_Ts.

E. Volume-limited ventilators. Advances in technology for measuring delivered V_Ts have made these ventilators first-line therapy for newborns with respiratory failure. Only volume-targeted ventilators specifically designed for newborns should be used. Volume-targeted ventilators are always patient-triggered.

1. General characteristics. The operator selects the V_T delivered rather than the PIP. "Volume guarantee" is a mode of pressure-limited SIMV, in which the ventilator targets an operator-chosen V_T (usually 4 to 6 mL/kg) during mechanically delivered breaths. Volume limit allows a rapid decrease of PIP pressures to changing lung compliance and may be particularly useful in infants with RDS who receive surfactant therapy. Pressure-regulated volume control

(PRVC) is a modified pressure-targeted ventilatory mode, in which inspiratory pressure is sequentially adjusted to deliver a target inspiratory volume with the lowest possible pressures.

2. **Advantages.** The pressure 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. Recent data suggest that volume-targeted ventilation reduces the risk of death or BPD in ELBW infants, presumably by reduction of the risk of volutrauma.

3. **Disadvantages**

   a. The system can be complicated and requires more skill to operate.

   b. Because VTs in infants are small, some of the VTs selected are lost in the ventilator circuit or from air leaks around uncuffed endotracheal tubes. Some ventilators compensate for these losses by targeting expired rather than inspired VTs or by accounting for dead space in the circuit.

4. **Indications.** Volume-targeted ventilators are particularly useful if lung compliance is rapidly changing, as in infants receiving surfactant therapy.

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 VTs equal to or smaller than anatomic dead space. These ventilators apply continuous distending pressure to maintain an elevated lung volume; small VTs are superimposed at a rapid rate. The mechanisms of gas exchange are incompletely understood.

2. **Advantages**

   a. **HFV** can achieve adequate ventilation while avoiding the large swings in lung volume required by conventional ventilators (in the hope to decrease lung injury). It 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 a resultant improvement in ventilation–perfusion (V/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 more conventional ventilators. 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, and there is less long-term clinical experience. The initial studies with HFO suggested an increased risk of significant intraventricular hemorrhage, although this complication has not been observed in recent clinical trials.

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.

G. Noninvasive mechanical ventilation. Neonatal nasal intermittent positive-pressure ventilation (NIPPV) provides noninvasive respiratory support to preterm infants who otherwise would require endotracheal intubation and ventilation. It is a supplement to CPAP. NIPPV superimposes inflations set to a peak pressure delivered through nasal prongs or mask. Some devices attempt to synchronize inflations with the infant's spontaneous inspirations. It remains unclear whether NIPPV is superior to conventional CPAP or prevents the need for mechanical ventilation.

NIPPV has been used for the following clinical settings:

a. Apnea of prematurity

b. Following extubation, NIPPV compared with nasal CPAP has been reported to reduce extubation failure in infants who required intubation and ventilation.

c. Primary mode of ventilation in preterm infants with RDS

III. INDICATIONS FOR RESPIRATORY SUPPORT

A. Indications for CPAP include the following:

- Initial stabilization in the delivery room for spontaneously breathing, preterm infants with respiratory distress
- Continued respiratory support to a preterm infant with RDS and good respiratory efforts (to prevent atelectasis)
- Respiratory distress (Silverman Anderson score ≥ 4)
- FiO_2 above 0.30
- In general, infants with RDS who require FiO_2 above 0.35 to 0.40 on CPAP should be intubated, given surfactant replacement therapy, and extubated back to CPAP.
- Postextubation in very low-birth-weight (VLBW) infants
- HFNC is likely equivalent to CPAP in postextubation stabilization; it remains unclear whether it is as effective in stabilization of infants with more severe respiratory distress or in infants <26 weeks' gestation.

B. Indications for mechanical ventilation include the following:

- "Increased work of breathing" in an infant on CPAP with signs of moderate-to-severe respiratory distress

- High CO_2 (>65) and need for high FiO_2 (>50%) while on CPAP
- Frequent apnea unresponsive to methylxanthine therapy

IV. HOW VENTILATOR CHANGES AFFECT BLOOD GASES

A. Oxygenation (see 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 90% to 95% (see Fig. 29.1). Increasing inspired oxygen is the simplest and most direct means of improving oxygenation. In premature infants, the risk of retinopathy and pulmonary oxygen toxicity argue for minimizing PaO_2 and closely monitoring oxygen saturations.
2. **MAP**
   a. MAP is the average area under the curve of the pressure waveform. Ventilators display MAP; 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, and rate; all these changes lead to higher PaO_2,

Table 29.1. Ventilator Manipulations to Increase Oxygenation

Parameter	Advantage	Disadvantage
↑ FiO_2	Minimizes barotrauma	Fails to affect matching
	Easily administered	Direct toxicity, especially >0.6
↑ PIP or V_T	Improves	Lung injury: Air leak, BPD
↑ PEEP	Maintains FRC/prevents collapse	Shifts to stiffer part of compliance curve
	Splints obstructed airways	May impede venous return
		Increases expiratory work and CO_2
		Increases dead space
↑ T_I	Increases MAP	Results in slower rates; may need to increase PIP
	"Critical opening time"	Lower minute ventilation for given PIP–PEEP combination
↑ Flow	Square wave—maximizes MAP	Greater shear force, more lung injury
		Greater resistance at greater flows
↑ Rate	Increases MAP while using lower PIP	Inadvertent PEEP with high rates or long time constant

An increase in any setting (except FiO_2) results in higher MAP. ↑, increase; BPD, bronchopulmonary dysplasia; FiO_2, fractional concentration of inspired oxygen; FRC, functional residual capacity; MAP, mean airway pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; Ti, inspiratory time; Vt, tidal volume.

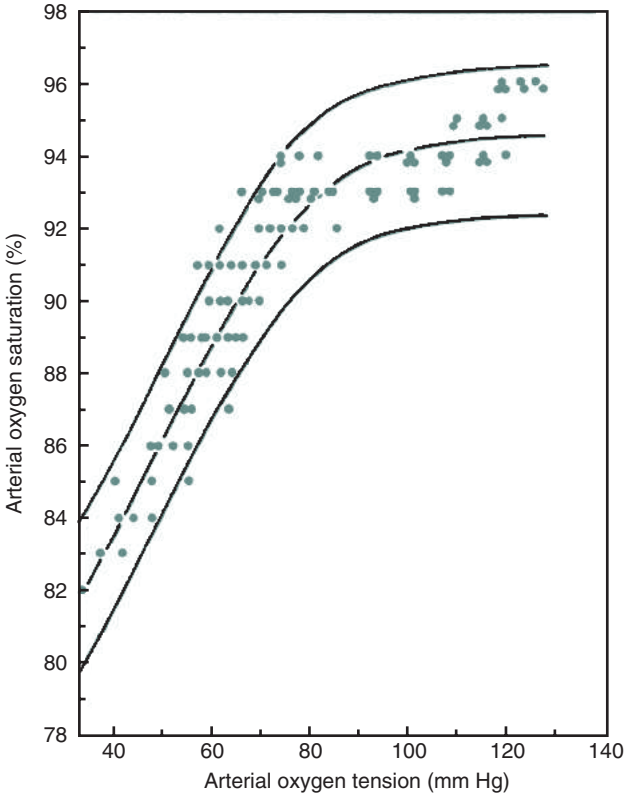

Figure 29.1. Comparison of paired measurements of oxygen saturation by pulse oximetry and of oxygen tension by indwelling umbilical artery oxygen electrode. The lines represent ±2 standard deviations. (Modified from Wasunna A, Whitelaw AG. Pulse oximetry in preterm infants. *Arch Dis Child* 1987;62[9]:957.)

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 cardiovascular 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 and adversely affect the cardiac output.

B. Ventilation (see Table 29.2)

1. CO_2 elimination depends on minute ventilation. Because minute ventilation is the product of respiratory rate and V_T, increases in ventilator rate will lower $PaCO_2$. Increases in V_T can be achieved by increasing the PIP on pressure-cycled ventilators or by increasing targeted volume on volume-limited machines.

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 barotrauma
		Shifts to stiffer compliance curve
↓ PEEP	Increases VT	Decreases MAP
	Decreases 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

↑, increase; ↓, decrease; MAP, mean airway pressure; $PaCO_2$, partial pressure of carbon dioxide, arterial; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; TE, expiratory time TI, inspiratory time; ; VT, tidal volume

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.

2. 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.

V. 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.

- **Compliance** is the distensibility of the lung and chest wall, that is, the change in volume (ΔV) produced by a change in pressure (ΔP), or ΔV/ΔP. It is decreased with surfactant deficiency, excess lung water, and lung fibrosis. It is also decreased when the lungs are hyperexpanded.

- **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 the 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 change rapidly if, for example, secretions partially occlude the endotracheal tube.
- **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. 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 V_T and adequate expiration to avoid inadvertent PEEP.
- **Functional residual capacity (FRC)** is a measure of the volume of the lungs at the end of expiration. FRC is decreased in diseases that permit alveolar collapse, particularly surfactant deficiency.
- **V/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.
- **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. Several of the more common neonatal disease processes are described in the subsequent text and are presented in Table 29.3, along with the optimal ventilatory strategies. 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 a severe decrease in compliance (stiff lung). This causes diffuse alveolar collapse with V/Q mismatching and increased work of breathing.

b. Surfactant replacement. Early initiation of CPAP, usually starting in the delivery room, in symptomatic spontaneously breathing infants, may avoid the need for mechanical ventilation and surfactant therapy in many infants, even at very early gestational ages. Surfactant administration is recommended if the FiO_2 requirement is more than 0.4 on CPAP or the SA score is >4. Surfactant is administered by intubating and delivering the surfactant via the trachea followed by extubating back to CPAP (INSurE technique). Less invasive or minimally invasive surfactant administration (LISA or MIST) via a feeding tube or a catheter introduction under vision is the preferred modality, if expertise exists. This may reduce the incidence

Table 29.3. Neonatal Pulmonary Physiology by Disease State

Disease	Compliance (mL/cm H_2O)	Resistance (cm H_2O/ mL/second)	Time Constant (second)	FRC (mL/kg)	Matching	Work
Normal term	4–6	20–40	0.25	30	—	—
RDS	↓↓	—	↓↓	↓	↓/↓↓	↑
Meconium aspiration	—/↓	↑↑	↑	↑/↑↑	↓↓	↑
BPD	↑/↓	↑↑	↑	↑↑	↓↓/↓	↑↑
Air leak	↓↓	—/↑	—/↑	↑↑	↓/↓↓-	↑↑
VLBW apnea	↓	—	↓↓	—/↓	↓/—	—/↑

—, little or no change; ↓, decrease; /, either/or; ↑, increase; BPD, bronchopulmonary dysplasia; FRC, functional residual capacity; RDS, respiratory distress syndrome; VLBW, very low birth weight.

of chronic lung disease (CLD). Surfactant therapy modifies the distinctive time course of escalation, plateau, and weaning in classic RDS. Ventilatory strategy should anticipate the increased risk of pneumothorax because compliance increases rapidly and higher volumes are delivered at same pressures, after surfactant administration. One must avoid overventilation; a $PaCO_2$ value slightly higher than the physiologic value (target 40 to 50) is acceptable to minimize ventilator-induced lung injury.

c. Ventilator strategy

i. CPAP. In mild to moderate RDS, infants may not require intubation and surfactant administration; CPAP is used very early in the disease course to prevent further atelectasis. CPAP is initiated at 5 cm H_2O and increased to a maximum of 7 to 8 cm H_2O. The risk of pneumothorax may be increased at higher levels of CPAP pressure. CPAP is titrated by clinical assessment of retractions and respiratory rate and by observation of O_2 saturation. NIPPV may be an alternative approach to CPAP in this setting. Additionally, in infants with more severe RDS, consideration may be given to intubation for surfactant administration with prompt extubation followed by CPAP (INSURE technique).

ii. Mechanical ventilation is used when V/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. Data suggest that a ventilator strategy that avoids large changes in V_T may reduce ventilator-induced lung injury; hence, volume-targeted ventilation, as described earlier, is the preferred mode in infants with RDS. The objective of all strategies of assisted ventilation in the infant with RDS should be to provide the lowest level of ventilatory support possible to support adequate oxygenation and ventilation while attempting to reduce acute and chronic lung injury secondary to

barotrauma/volutrauma and oxygen toxicity. Our preferred approach is to maintain the appropriate MAP with a TI initially set at 0.3 second and rate of approximately 30 to 40 breaths per minute. Rarely, a longer TI is required to provide adequate oxygenation.

iii. **VT** is usually initially set at 4 to 6 mL/kg and adjusted for adequate minute ventilation. If pressure-limited ventilation is used, PIP is initially estimated by visible chest excursion and is usually not more than 20 cm H_2O.

iv. **PEEP.** PEEP is usually set at 5 to 6 cm H_2O. Higher PEEP may interfere with cardiac output and must be used only if indicated.

v. **Flow.** Flow rates of 7 to 12 L/minute are needed to provide a relatively square pressure waveform.

vi. **Rates** are generally set initially at 30 to 40 breaths per minute and adjusted according to blood gas results.

vii. **Weaning.** When the patient improves, FiO_2 and PIP or VT are weaned first, alternating with rate, in response to assessment of chest excursion, oxygen saturation, and blood gas results. In volume-targeted ventilation, the PIP will decrease automatically in response to improved compliance; weaning may be accomplished by decreasing the targeted level of VT. In patient-triggered modes, the back-up 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 25 to 30 breaths per minute, or PIP is 14 to 16 cm H_2O to deliver the desired VT. Often, babies improve rapidly after surfactant, and may be extubated to CPAP in 15 to 30 minutes (INSURE). Prior to extubation, caffeine citrate therapy should be started to facilitate spontaneous breathing. Prophylactic caffeine increases the success rate of extubation in VLBW infants.

viii. **Advantages and disadvantages.** This ventilatory strategy maximizes alveolar recruitment but with a potential for greater lung injury secondary to higher PIP and volutrauma secondary to higher VT.

ix. **HFV** may be initiated if conventional ventilation fails to maintain adequate gas exchange at acceptable settings. It should be used only by clinicians familiar with its use. We consider the use of 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 HFO ventilation over other available HFV because of its 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.

- **PIP and PEEP.** Peak pressures on the jet ventilator are initially set approximately 20% lower than those being 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 may be increased to 8 to 10 cm H_2O if needed to improve oxygenation.

- **Rate.** The frequency is usually set at 420 breaths per minute, with an inspiratory jet valve on-time of 0.02 second.
- **Conventional ventilator settings.** Once the HFJ is properly adjusted, the conventional ventilator rate is decreased to 2 to 10 breaths per minute to help maintain alveolar recruitment, with PIP set at 2 to 3 cm H_2O lower than the jet PIP. In air leak syndromes, it may be advantageous to provide no sigh breaths from the conventional ventilator as long as the PEEP is set high enough to maintain lung volume.
- **Weaning** from HFJ ventilation is accomplished by decreasing the jet PIP in response to blood gas determinations and the FiO_2. PEEP is weaned as tolerated if pressures higher than 4 to 5 cm H_2O are used. Frequency and jet valve on-time are generally not adjusted.
- **Similar strategies** outlined for the HFJ apply in use of the HFFI.

b) HFO ventilation. With HFO, operator-selected parameters include MAP, frequency, and piston amplitude.

- **MAP.** In RDS, the initial MAP selected is usually 2 to 5 cm H_2O higher than that being used on the conventional ventilator to enhance alveolar recruitment. MAP used with HFO is titrated to O_2 requirement and to provide adequate lung expansion on chest x-ray. Care must be exercised to avoid lung hyperinflation, which might adversely affect oxygen delivery by reducing cardiac output.
- **Frequency** is usually set at 10 to 15 Hz for the smallest babies; lower frequencies may be selected for bigger babies. Inspiratory time is set at 33% (this option may be preset and may not be available in some ventilators).
- **Amplitude.** Changes in piston amplitude primarily affect ventilation. It is set to provide adequate chest vibration, assessed clinically and by blood gas determinations.
- **Flow rates** of 8 to 15 L/minute are usually adequate. (In some ventilators, the flow rate is set at 30 L/minute, by default, once HFO is selected.)
- **Weaning.** In general, FiO_2 is weaned first, followed by MAP in decrements of 1 to 2 cm H_2O once the FiO_2 falls below 0.6. Piston amplitude is adjusted by frequent 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 will improve ventilation because of effects on delivered V_T. In both HFJ and HFO, we usually wean to extubation after transfer back to conventional ventilation, although infants can be extubated directly from HFV.

2. **Meconium aspiration syndrome (MAS)** (see Chapter 35)
   a. **Pathophysiology.** MAS results from aspiration of meconium-stained amniotic fluid. The severity of the syndrome is related to the associated asphyxial insult and the amount of fluid aspirated. The aspirated meconium causes acute airway obstruction, markedly increased airway resistance, scattered atelectasis with V/Q 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 (as low as 4 cm H_2O) are helpful in splinting open partially obstructed airways and equalizing matching. Higher levels may lead to hyperinflation. If airway resistance is high and compliance is normal, a slow-rate, moderate-pressure/volume strategy is needed. If RDS-like atelectasis is more prominent, more PEEP and rapid rates can be used. Sedation may be used to minimize the risks of air leak in severe MAS because of the high transpulmonary pressures these large infants can generate when "fighting" the ventilator and the ball-valve hyperexpansion caused by their disease. Use of patient-triggered ventilation may be helpful in some infants and avoid the need for sedation. Weaning may be rapid if the illness is primarily related to airway obstruction or prolonged if complicated by lung injury and severe inflammation. Due to secondary surfactant inactivation, the use of surfactant therapy may improve lung compliance and oxygenation and should be considered in more severe cases of MAS.

      HFV has also been successfully used in infants with MAS who are failing conventional ventilation or who have air leak. The strategies are similar to those described in the preceding text. During HFO, slower frequencies (8 to 10 Hz) may be useful to improve oxygenation and ventilation in severe cases.

3. **BPD** (see Chapter 34)
   a. **Pathophysiology.** The old BPD was seen in bigger infants in the pre-CPAP era with poor prenatal steroid and surfactant use. It was characterized by airway injury, inflammation, parenchymal fibrosis, bronchial smooth muscle hypertrophy, and interstitial edema secondary to mechanical ventilation and oxygen toxicity. The new BPD seen in very preterm infants is characterized by disruption of canalicular or saccular phases of lung development. This leads to decreased septation, alveolar hypoplasia, reduction in surface area for gas exchange, and abnormal pulmonary vascular development, leading to an increase in pulmonary vascular resistance. BPD is marked by shifting focal atelectasis, hyperinflation with V/Q mismatch, chronic and acute increases in airway resistance, and a significant increase in the work of breathing.
   b. **Ventilator strategy.** The optimal strategy is to wean infants off the ventilator as soon as possible to prevent further mechanical injury and oxygen toxicity. If this is not feasible, ventilator settings should be minimized to

permit tissue repair and long-term growth. Rates less than about 20 breaths per minute should generally be avoided to prevent increased work of breathing, but longer T_I (0.4 to 0.5 second) may be used to maintain FRC. Higher PIPs are sometimes required because of the stiff lungs, although the high resistance prevents transfer of most of this to the alveoli. Oxygenation should be maintained (saturations of 90% to 92%), but higher $PaCO_2$ values can be permitted (55 to 65 mm Hg), provided the pH is acceptable. Acute decompensations can result from bronchospasm and interstitial fluid accumulation. These must be treated with adjustment of PIP, bronchodilators, and diuretics. Acute BPD "spells" in which oxygenation and airway resistance worsen rapidly are usually due to larger airway collapse and may be treated successfully with 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 be partially ameliorated by using higher PEEP. Weaning is a slow and difficult process, decreasing rate by 1 to 2 breaths per minute or 1 cm H_2O decrements in PIP every day when tolerated. Fortunately, with improved medical and ventilatory care of these infants, it is rare for infants with BPD to require tracheostomy for chronic ventilation.

4. **Air leak** (see Chapter 38)

   a. **Pathophysiology.** Pneumothorax and PIE are the two most common air leak syndromes. Pneumothorax results when air ruptures into the pleural space. In PIE, the interstitial air substantially reduces tissue compliance as well as recoil. In addition, peribronchial and perivascular air may compress the airways and vascular supply, causing "air block."

   b. **Ventilator strategy.** Because air is driven into the interstitium throughout the ventilatory cycle, the primary goal is to reduce MAP through any of its components (PIP or V_T, T_I, or PEEP) and to rely on increased FiO_2 to provide oxygenation. This strategy holds for all air leak syndromes. If dropping the MAP is not tolerated, other techniques may be tried. Because the time constants for interstitial air are much longer than those for the alveoli, we sometimes use very rapid conventional rates (up to 60 breaths per minute), which may preferentially ventilate the alveoli.

      HFV is an important alternative therapy for severe air leak and, if available, may be the ventilatory treatment of choice. HFV strategies for air leak differ from those used in diffuse alveolar disease. As described for conventional ventilation, the ventilatory goal in air leak syndromes is to decrease MAP, relying on FiO_2 to provide oxygenation. With HFJ and HFFI, PEEP is maintained at lower levels (4 to 6 cm H_2O), 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 the attempt to limit the MAP exposure.

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, 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 (12 to 16 cm H_2O) or V_T adjusted to prevent hyperventilation. Prolonged T_I is unnecessary. For infants requiring a ventilator because of intermittent but prolonged apnea, low rates (20 to 30 breaths per minute) may be sufficient.

VI. ADJUNCTS TO MECHANICAL VENTILATION

A. Sedation (see Chapter 70) can be used when agitation or distress is associated with excessive lability of oxygenation and hypoxemia. Although this problem is more common in the neonate receiving long-term ventilation, acutely ill newborns may occasionally benefit from sedation. Morphine (0.05 to 0.1 mg/kg) or fentanyl (1 to 3 µg/kg) can be used but may cause neurologic depression. Prolonged use may lead to dependence. Lorazepam (0.05 to 0.1 mg/kg/dose given every 4 to 6 hours) or midazolam (0.05 to 0.1 mg/kg/dose given every 2 to 4 hours) has been used in more mature infants and in more chronic situations. In preterm infants, nonpharmacologic methods, such as limiting environmental light and noise and providing behavioral supports, may help decrease agitation and limit the need for sedative medications. As discussed, SIMV or patient-triggered ventilation may also help diminish agitation and ventilatory lability.

B. Muscle relaxation with pancuronium bromide (0.1 mg/kg/dose, repeated as needed) or vecuronium (0.1 mg/kg/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. Prolonged muscle relaxation leads to fluid retention and may result in deterioration in compliance. Sedation is 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.

VII. 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

- **BPD** is related to increased airway pressure and changes in lung volume, although oxygen toxicity, anatomic and physiologic immaturity, and individual susceptibility also contribute.
- **Air leak** is directly related to increased airway pressure. Risk is increased at MAPs in excess of 14 cm H_2O.

B. Mechanical

- Obstruction of endotracheal tubes may result in hypoxemia and respiratory acidosis.
- Equipment malfunction, particularly disconnection, is not uncommon and requires functioning alarm systems and vigilance.

C. Complications of invasive monitoring

- Peripheral arterial occlusion with infarction (see Chapter 44)
- Aortic thrombosis from umbilical arterial catheters, occasionally leading to renal impairment and hypertension
- Emboli from flushed catheters, particularly to the lower extremities, the splanchnic bed, or even the brain

D. Anatomic

- Subglottic stenosis from prolonged intubation; risk increases with multiple reintubations.
- Acquired tracheobronchomalacia from prolonged mechanical intubation
- Palatal grooves from prolonged orotracheal intubation
- Vocal cord damage

Suggested Reading

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30 Blood Gas and Pulmonary Function Monitoring

Lawrence M. Rhein

KEY POINTS

- Assessment of oxygenation and ventilation is critical to evaluate respiratory function and optimize supports.
- Pulse oximetry is the primary tool for noninvasive oxygen monitoring in newborns.
- A unit policy is essential for target saturation values and alarm limits.
- Pulmonary graphics enables a better understanding of the interaction between the baby and the ventilator.

I. GENERAL PRINCIPLES. Causes of hypoxemia and hypercarbia in neonates include one or more of hypoventilation, mismatch of ventilation and perfusion, diffusion impairment, and shunt. The correction of the failure in gas exchange should be based on the underlying change in respiratory functions (compliance, resistance). Measurement of oxygen levels, carbon dioxide levels, lung compliance, resistance, and adequacy of respiratory support is facilitated by technology. In this chapter, we will discuss these in detail.

Oxygenation should be monitored in any neonate who receives supplemental oxygen. It is critical to avoid excessive supplemental oxygen in the process of oxygen therapy for hypoxia. Both hypoxia and hyperoxia are associated with mortality and morbidity. In preterm infants, high concentrations of supplemental oxygen are associated with an increased risk of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). Although the level of oxygenation can be assessed in several ways, pulse oximetry, which measures hemoglobin saturation (SpO_2), is the accepted standard for clinical monitoring.

II. OXYGENATION MONITORING. Invasive and noninvasive techniques to monitor respiratory health complement each other. Invasive techniques, including arterial blood gas (ABG) monitoring, and noninvasive techniques such as pulse oximetry and pulmonary graphics allow serial measurements and trends.

A. ABG measurements. Arterial PO_2 (PaO_2) and PCO_2 ($PaCO_2$) 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 arterial catheter is the "gold standard" for oxygen monitoring.

1. Normal values. Target range for newborn PaO_2 is 50 to 80 mm Hg. As underlying lung condition evolves, infants who require respiratory support may

exhibit fluctuations in PaO_2 values. In such circumstances, serial blood gas values better represent the overall trend of oxygenation.

2. **Sampling.** To minimize sampling and dilutional artifacts, ABG samples should ideally 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 of collection or preserved on ice if they must be transported 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. Intermittent arterial punctures may cause discomfort, which may result in agitation and a fall in PaO_2 so that the value obtained underestimates the true steady-state value.

B. Noninvasive oxygen monitoring is particularly useful in infants exhibiting swings in PaO_2 and oxygen saturation. Pulse oximetry measures SpO_2 and reflects the majority (98%) of arterial oxygen content that is carried by hemoglobin. This monitoring technique provides data that are continuous and noninvasive, and minimizes the need for frequent blood sampling and associated blood loss. As a result, in most neonatal intensive care units (NICUs), pulse oximetry is the accepted clinical standard for monitoring sick babies, and SpO_2 has been called the "fifth vital sign." Each NICU should have a policy regarding setting of the acceptable SpO_2 alarm limits to minimize the infant's exposure to hyperoxia and hypoxia.

1. **Pulse oximetry** is the primary tool for noninvasive oxygen monitoring in newborns. Pulse oximeters provide continuous measurement of hemoglobin oxygen saturation (SpO_2) with a high level of accuracy (±3%) when compared to control values measured by co-oximetry, at least down to the limit of a SpO_2 of 70%.

   a. **General characteristics.** The principle of oxygen measurement by pulse oximetry is spectrophotometry; oxygen saturation is measured by differential light absorption of oxygenated (oxyhemoglobin) and deoxygenated (reduced hemoglobin) blood for two light wavelengths: 660 nm (red) and 940 nm (infrared [IR]). The ratio of absorbance at these wavelengths is calculated to establish the pulse oximeter's measure of arterial saturation (SpO_2). 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. The pulse oximeters may get affected by movement artifacts, ambient light, pigmentation, and low perfusion states.

   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.

      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. Signal extraction technology. Recent advances in signal analysis and reflectance technology have improved the performance of pulse oximeters under conditions of motion artifact and low perfusion.

d. Oxygen saturations and preterm. The target saturations in preterm neonates in NICU have been a topic of controversy for decades. Practices have moved from too much to too little! The benefit versus risk of lower saturations in NICU was studied in the NeOProM meta-analysis; no difference was found in the composite outcome (of death or disability at 24 months of age) between lower saturation (85% to 89%) and higher saturation (91% to 95%) targets. However, the low saturation group was associated with marginal increase in deaths (20% vs. 17%) and severe necrotizing enterocolitis (9% vs. 7%), although there was a decrease in ROP (11% vs. 15 %).

The *European Consensus Guidelines on the Management of Respiratory Distress Syndrome* were updated in 2019. "In preterm babies receiving oxygen beyond stabilization, the saturation target should be between 90% and 94%." "Alarm limits should be set to 89% and 95%."

2. Transcutaneous oxygen monitoring ($TcPO_2$) can be useful in the management of acute cardiopulmonary disease during the first 2 postnatal weeks or if arterial catheterization is not possible. Transcutaneous oxygen monitors measure oxygen tension ($TcPO_2$) with a heated blood gas electrode which is applied to the skin surface; however, they need frequent recalibration and can cause erythema. This technique has been largely supplanted in the NICU by pulse oximetry.

III. ASSESSMENT OF PULMONARY VENTILATION.

Alveolar ventilation is assessed by direct or noninvasive measurement of PCO_2. Low PCO_2 values indicate excessive volume distension of the lung and should be avoided because lung injury has been associated with it. A strategy of "permissive hypercapnia" in mechanically ventilated infants allows PCO_2 values in the range of 50 to 65 mm Hg after the first 3 days of life; the strategy has not shown expected benefits of decrease in incidence of BPD. The practice of underventilating and accepting higher CO_2 is being questioned, some trails have shown association with increase in IVH and death. The CO_2 levels in preterm babies should preferably be maintained in normal range (35 to 45 mmHg), very high CO_2 is associated with intraventricular hemorrhage. Extreme hypercapnia, hypocarbia, or fluctuation are detrimental for preterm neonates especially in the first week of life.

A. ABG. 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 pulmonary insufficiency. Blood obtained by percutaneous arterial puncture is an alternative but may not reflect steady-state values because of artifacts introduced by pain and agitation. Sources of errors such as air bubbles in syringe may result in higher PaO_2 and lower $PaCO_2$. Excess heparin may cause falsely lowered $PaCO_2$ and spurious metabolic acidosis.

1. **Venous blood** from a central catheter may be useful in certain circumstances. If alveolar ventilation and circulatory function are normal, venous PCO_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.** Capillary blood sampling is an alternative to arterial blood sampling for the assessment of acid–base balance and adequacy of ventilation ($PaCO_2$). It involves sampling from an area of the skin with the one that is highly vascular. The area of the skin is warmed so as to facilitate free flow of blood and reduce gas difference between arterial and venous blood. A small puncture or incision is made by a lancet on a highly vascularized area such as toe or heel. The sample is collected in a heparinized capillary tube. The pH and $PaCO_2$ correlate well with arterial gas values but PaO_2 does not correlate well. Capillary gases are of little value in assessing oxygenation, and hence have limited utility if the baby is on high FiO_2. They help in minimizing phlebotomy losses, need for arterial lines, and associated serious risks such as thrombosis and gangrenes.
3. **Indications**
   - Blood gas is indicated but arterial access is not possible.
   - Sampling-related blood losses are reduced in preterm neonates.
4. **Contraindications**
   - Shock and poor peripheral perfusion
   - Polycythemia
   - Hypothermia
   - If hyperoxia must be detected and prevented
5. **Limitations**
   - Excessive squeezing may result in lymphatic contamination of the sample.
   - It has a limited utility in neonates with hypothermia, hypovolemia, and hypotension.
6. **Complications**
   - Complications are uncommon, they include infection, hematoma, bleeding, and scarring.

B. Noninvasive carbon dioxide monitoring. Measurement of $PaCO_2$ by ABG is the gold standard for assessing ventilation. $PaCO_2$ can be a dynamic and rapidly changing value; it is not sufficient to guide respiratory support by a single measurement. To overcome these limitations, noninvasive monitors can be used to provide a continuous estimate of $PaCO_2$. The two most available noninvasive monitoring methods are transcutaneous monitoring and capnography.

1. **Transcutaneous CO_2 monitoring** ($TcPCO_2$) 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°C 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. $TcPCO_2$ is

often slightly higher than the corresponding measured $PaCO_2$ value. This is likely due to two main factors. First, the elevated temperature alters the solubility of CO_2. Second, the hyperemia increases the metabolism of the skin cells, which contributes to CO_2 levels. $TcPCO_2$ value may require a correction to represent the true $PaCO_2$ levels. Transcutaneous monitoring of CO_2 is going out of favor due to easier monitoring by end-tidal CO_2 ($EtCO_2$). It is difficult to use in emergencies and less reliable in conditions such as shock, hypothermia, and babies receiving inotropes.

2. **Capnography** refers to the noninvasive measurement of the partial pressure of carbon dioxide 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, or can be used to determine the maximum CO_2 concentration at the end of each tidal breath, or $EtCO_2$.

   Capnography uses IR radiation and absorption to detect CO_2. Molecules of CO_2 absorb IR radiation at a specific wavelength (4.26 μm). CO_2 monitors use lightweight IR sensors to emit IR light through adapter windows to a photodetector that is sensitive to the IR band of CO_2. The IR radiation absorption is highly correlated with the CO_2 concentration present.

   a. Capnography devices are categorized based on their location for sampling.

      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 partial pressure of the CO_2 is calculated and displayed. Mainstream sensors are heated to slightly above the 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 its use is limited to intubated patients.

      ii. Sidestream devices measure CO_2 via nasal or oral/nasal cannula by aspirating a small sample from the exhaled breath through cannula tubing to a sensor located inside the CO_2 monitor. This allows monitoring of nonintubated patients because sampling of the expiratory gases can be obtained from the nasal cavity. Gases can be sampled even 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. Conventional high flow 150 to 200 mL/minute systems underestimate CO_2 in newborn. 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. Several factors limit the utility of $EtCO_2$ measurements in newborns.

a) 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.

b) 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 arterial PCO_2 values. However, in babies with more uniform distribution of ventilation, end-tidal measurements may be useful to monitor trends.

3. Indications for capnography

a. Confirming endotracheal tube placement. The Neonatal Resuscitation Program recommends the use of an exhaled CO_2 detector (colorimetric device or capnograph) to confirm correct tube placement during endotracheal intubation.

b. Monitoring during anesthesia. The Standards for Basic Anesthetic Monitoring of the American Society of Anesthesiology specify 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.

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. A few, such as volume targeting, have shown definite clinical benefits.

A. Tidal volume measurements may be used to assist 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 limit) using minimal peak airway pressure. However, technical issues may limit the 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 respond only to the averaged tidal volumes of 3 to 4 last breaths, thus not correcting each breath. Although newer ventilator modes have improved the consistency of the delivered tidal volume, a substantial proportion of values remain outside the target range. Despite these shortcomings, tidal volume measurements using the same device consistently over time may provide clinically useful information during chronic mechanical ventilation and also with weaning following surfactant treatment when lung compliance changes rapidly.

B. Pulmonary graphic waveforms: Scalars and Loops. The key components of a graphics monitoring system include a sensor to measure flow and pressure. Most devices in use today employ the hot wire anemometer technology. The signals are sent to the computer for analysis, measured, and the calculated values are displayed.

The basic display includes pressure, volume, and flow scalar trace against time (Fig. 30.1).

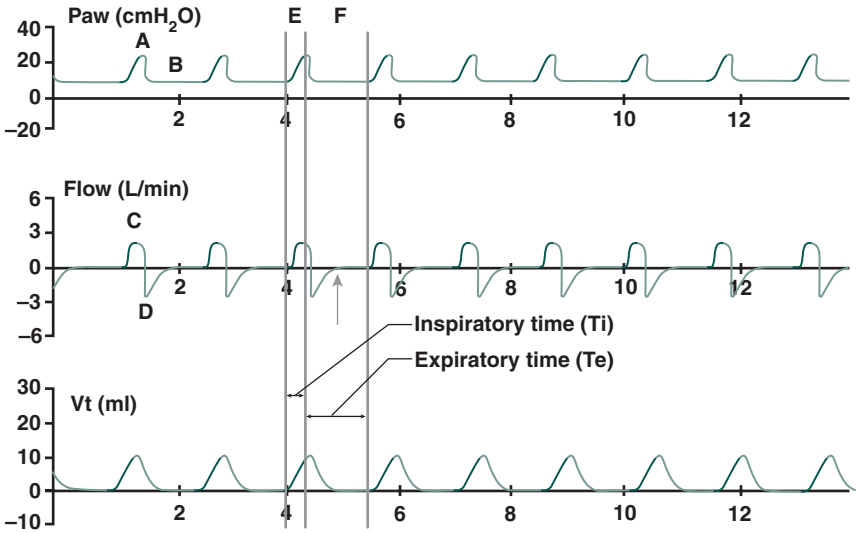

Figure 30.1. Pressure, flow, volume versus time scalar.

1. **Pressure waveform.** The pressure during inspiration and expiration is seen in the waveform. The inspiratory pressure (peak inspiratory pressure [PIP]), baseline pressure (positive end expiratory presure [PEEP]), inspiratory time, and beginning of expiration are seen. The area under the curve depicts the mean airway pressure (MAP) (Fig. 30.2).
2. **Flow waveform (Fig. 30.3).** The flow also has both inspiratory and expiratory phases which are seen as positive and negative deflections. The time from zero flow at the initiation to zero flow at the end inspiration is the inspiratory time.

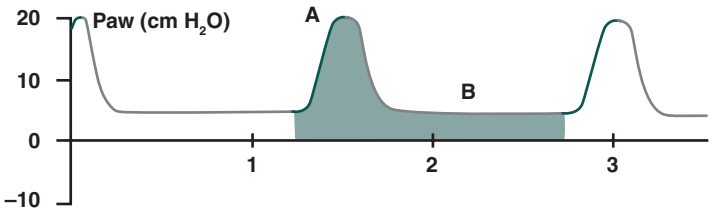

Figure 30.2. Pressure versus time scalar. (A) PIP, (B) PEEP "mean airway pressure represented by shaded area."

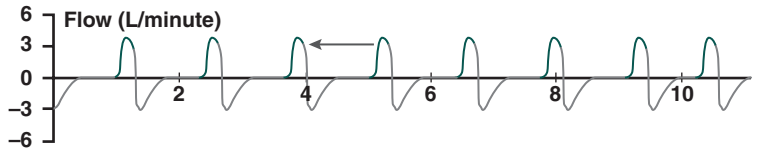

Figure 30.3. Flow versus time scalar. Graph shows flow cycling, the inspiration continues into expiration, without a pause (flat line).

Time from the beginning of expiration to the initiation of the next breath is the expiratory time. The inspiratory flow can be zero (shows as a flat line) for a short while in pressure control ventilation or continuous in volume ventilation. The expiratory flow begins with an accelerated flow and gradually reaches the baseline. In case of increased resistance to the expiratory flow, time required for the flow to reach the baseline will be prolonged. If the expiratory time is short, it results in gas trapping, as reflected by expiratory gas flow never reaching the baseline.

3. **Volume waveform.** Volume is calculated from flow and time. A volume graph can help in assessing air leaks and assessing whether the dialed pressure is adequate for the volume delivery.
4. **Loops**
   a. **Pressure–volume loop.** Pressure is plotted on the *x*-axis and volume on the *y*-axis (Fig. 30.4). This reflects compliance, change in volume for unit pressure changes.

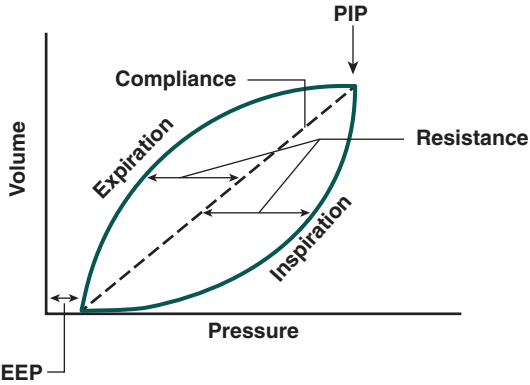

Figure 30.4. Pressure volume loop. In real life, the inspiratory and expiratory components are not symmetrical (see Fig. 30.5).

The loop helps us understand the mechanics of lung physiology in a ventilated newborn. Compliance, hyperinflation, and beaking can be seen (Fig. 30.5). C_{20}/C ratio is defined as the slope (compliance) of the final 20% of the inspiratory limb as compared to the slope (compliance) of the entire breath. When this ratio is <1.0, it suggests hyperinflation.

   b. **Flow–volume loop.** Volume on the *x*-axis and flow on the *y*-axis gives us the flow–volume loop (Fig. 30.6).

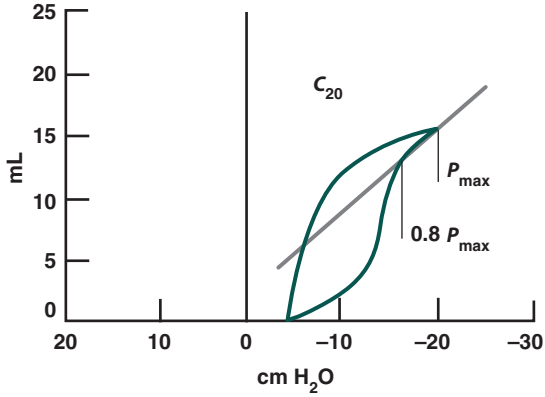

Figure 30.5. Pressure–volume loop showing overdistension and beaking.

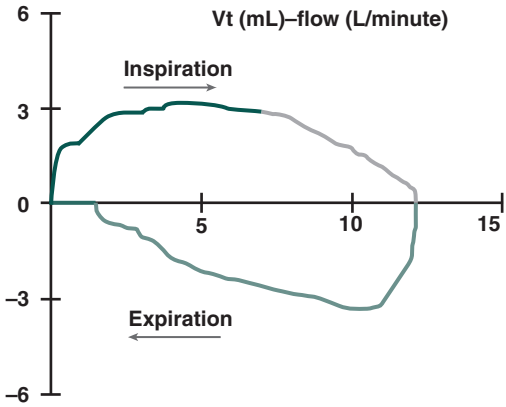

Figure 30.6. Flow versus volume loop.

The loop begins at the zero intercept, positive (+) flow indicates inspiratory flow and negative (–) flow indicated expiratory flow. This helps in assessing the presence of obstruction of airway, in inspiration and expiration, and also the response to bronchodilator (Fig. 30.7A, 30.7B, and 30.7C).

5. **Dynamic measurements.** Real time measurements of tidal volume, minute volume, compliance, pressures, and resistance can help in assessing the adequacy of ventilation.

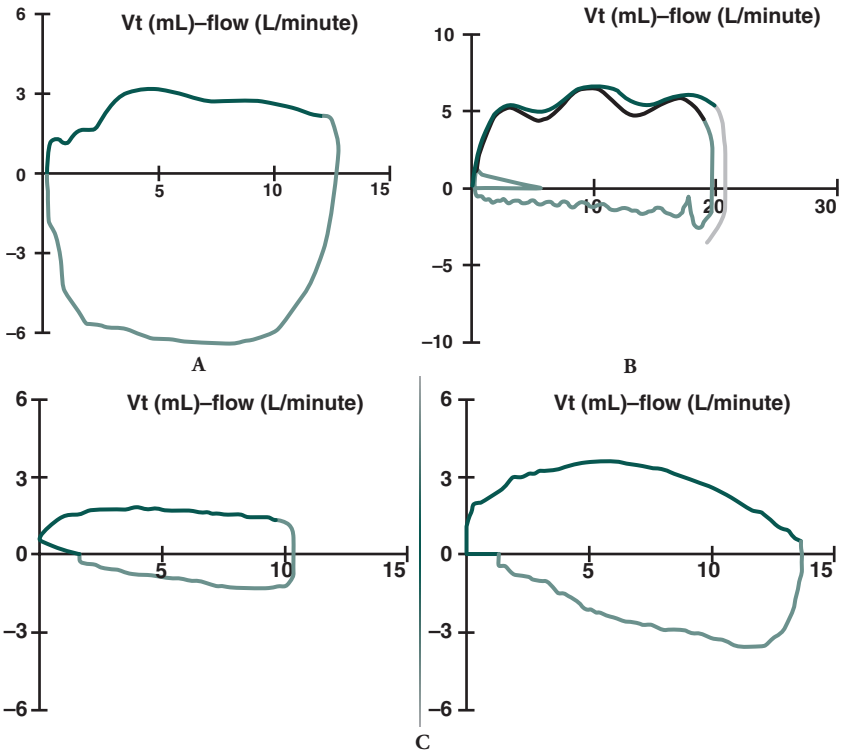

Figure 30.7. (A) Flow volume loop showing inspiratory resistance. (B) Flow volume loop showing expiratory resistance. (C) Flow volume loop showing change in resistance after bronchdilator (image on right) in baby with BPD.

Suggested Readings

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31 Apnea

Ann R. Stark

KEY POINTS

- Apnea spells typically resolve by 34 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 extreme preterm infants.
- Caffeine is a safe and effective treatment for apnea.
- There is variability in the practice of starting and stopping caffeine and the maximum doses used.
- 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.
- Intermittent hypoxia consists of brief, self-resolving episodes of decrease in saturation, without bradycardia or loss of tone; the total hypoxia time over the day is a better determinant of severity than an individual hypoxia event.

I. BACKGROUND

A. Definition. Apnea is defined as the cessation of airflow. It is pathologic (an apneic spell) when absent airflow is accompanied by bradycardia (heart rate <100 beats per minute), hypoxemia (detected clinically by cyanosis or by oxygen saturation monitoring: SpO_2 <80%), hypotonia, or pallor. Bradycardia and desaturation are usually present after 20 seconds of apnea, although they typically occur more rapidly in the small premature infant. As the spell continues, pallor and hypotonia are 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.** Apneic spells may be noted even at birth (due to respiratory distress syndrome); if they do not occur during the first 7 days, they are unlikely to occur later.

2. **Duration.** Apneic spells persist for variable periods postnatally and usually cease by 34 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. Extreme preterm infants may also have multiple brief intermittent hypoxia (IH) 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.

Apnea of prematurity is the reflection of overall physiologic immaturity of respiratory control mechanism. Several mechanisms have been proposed to explain apnea in premature infants. 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 the 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 in a matched group without apnea and is also decreased compared to in 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.

G. IH consists of short and repetitive episodes of hypoxemia and desaturation which are not accompanied by bradycardia or apnea. These self-resolving, clinically undetectable episodes are because of an immature respiratory pattern and are usually associated with periodic breathing. IH episodes can continue till term equivalent age or later in extreme preterm infants. Long-term consequences of IH are not clear; however, recurrent episodes may be a matter of concern and need to be studied. Many extreme preterm infants (<28 weeks) also experience IH and bradycardia episodes even on mechanical ventilation because of cardiorespiratory instability.

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. Pulse oximetry should be monitored to detect episodes of

desaturation and bradycardia. Even with careful monitoring, some spells of apnea and bradycardia may not be recognized.

When a monitor alarm sounds, one should remember to respond to the infant, not the monitor, checking for bradycardia, cyanosis, and airway obstruction.

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.

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.

Table 31.1. Evaluation of an Infant with Apnea

Potential Cause	Associated History or Signs	Evaluation
Infection	Not looking well, feeding intolerance, lethargy, temperature instability, shock, sugar disturbances	Investigate for infection (blood culture, urine culture, complete blood count, CRP)
Necrotizing enterocolitis (NEC)	Feeding intolerance, GI aspirates, abdominal distension	Abdominal x-ray examination
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
Drugs	CNS depression, hypotonia, maternal history	Magnesium; screen for toxic substances in urine
Temperature instability	Lethargy	Monitor temperature of patient and environment
Intracranial pathology (asphyxia, IVH, meningitis, malformations)	Abnormal neurologic examination, seizures	Cranial ultrasonographic examination, CSF examination
Anemia	Blood loss, pallor	Hematocrit

CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; GI, gastrointestinal; IVH, intraventricular hemorrhage.

B. 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 (90% to 95%) (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, 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. The long-term neurodevelopment follow-up also confirmed that caffeine therapy was associated with a reduced risk of motor impairment and improved visuomotor, visuoperceptual, and visuospatial abilities at 11 years of age. More importantly, use of caffeine was found to be safe as no adverse effect on general intelligence, attention, academic performance, and behavior was noted at 11-year follow-up. Caffeine treatment also reduced the rate of bronchopulmonary dysplasia (BPD). Caffeine is clearly indicated in preterm babies with significant/frequent apnea. It is also of proven benefit to give caffeine to VLBW babies before extubation. Early caffeine therapy, within the first 3 days of life, seems to be beneficial in reducing BPD, PDA, and duration of mechanical ventilation in preterms <32 weeks' gestational age and hence may be used in these infants.

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 if no apneic spells have occurred for 5 to 7 days although in some infants it may be continued till 33 to 34 weeks PMA. 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 approximately 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. 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 (HFNC) use for apnea is on the rise; the parents and staff find the HFNC much friendlier and as effective. Synchronized 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; results of studies are conflicting. 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 temporally related. Pharmacologic treatment of GER with agents that increase motility or decrease gastric acidity has not been shown to reduce apnea frequency. Because increased late-onset sepsis and necrotizing enterocolitis have been associated with the use of agents that decrease gastric acidity, we seldom use these medications.

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- gestational-age 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 to 1 week 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), 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

Alhersh E, Abushanab D, Al-Shaibi S, Al-Badriyeh D. Caffeine for the Treatment of Apnea in the Neonatal Intensive Care Unit: A Systematic Overview of Meta-Analyses. *Paediatr Drugs.* 2020;22(4):399–408.

Eichenwald EC, Committee on Fetus and Newborn. Apnea of prematurity. *Pediatrics* 2016;137(1):1–7.

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32 Transient Tachypnea of the Newborn

Mary Lucia P. Gregory

KEY POINTS

- Transient tachypnea of the newborn (TTN) is a self-limited disorder, with symptoms resolving in 12 to 72 hours.
- TTN should be a diagnosis of exclusion; it mimics the early presentation of serious respiratory, cardiac, or infectious disorders in newborns.
- Management is supportive; some babies may need oxygen therapy, noninvasive respiratory support with continuous positive airway pressure (CPAP), or nasal intermittent ventilation (NIV).
- Antenatal steroids in anticipated late preterm birth ameliorate the risk of TTN.

I. DEFINITION. Transient tachypnea of the newborn (TTN), first described by Avery and coworkers in 1966, results from delayed clearance of fetal lung fluid. As the name implies, it is a self-limited process but carries the potential of progression to respiratory failure if other serious conditions such as sepsis, respiratory distress syndrome (RDS), or heart disease in early course are mistaken as TTN, resulting in a delay in therapy. It 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; decreased oxygen saturation is usually alleviated by supplemental oxygen with FiO_2 <0.4.

II. PATHOPHYSIOLOGY. To accommodate the transition to breathing air at birth, the lungs 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 thought to be 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 sodium channels 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 epithelial sodium channels, followed by transport into the interstitium via basolateral Na^+/K^+-ATPase, and passive movement of chloride and water through paracellular and intracellular pathways. Thyroid hormone also contributes to fetal lung fluid clearance by increasing Na^+/K^+-ATPase activity and by β-adrenergic receptor stimulation in lungs and lymphatics. Interstitial lung fluid pools in perivascular cuffs of tissue and in the interlobar fissures and is then cleared into pulmonary capillaries and lung lymphatics.

Transpulmonary hydrostatic pressure gradient created by inspiratory effort is as important as the molecular mechanisms for clearance of airway fluid. Disruption or delay in clearance of fetal lung fluid results in the transient pulmonary edema that characterizes TTN. 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. Because infants usually recover, a precise pathologic definition is lacking.

III. EPIDEMIOLOGY. The incidence of TTN is 0.3% to 0.6% of term deliveries and 1% of preterm deliveries. Risk factors for TTN include cesarean delivery with or without labor, precipitous birth, and preterm birth. These conditions are thought to result in delayed or abnormal fetal lung fluid clearance due to the absence of the hormonal changes that accompany spontaneous labor. The presence of labor and the gestational age at delivery impact the risk of respiratory complications for infants delivered by an elective cesarean section; onset of labor, oxytocin exposure, and term gestation provide some degree of protection. Delivery at lower gestational ages, including late preterm birth, and maternal hypotension during spinal anesthesia increase the risk of TTN. Diagnosis at earlier gestations is complicated by the presence of comorbidities such as RDS. Other risk factors include male gender and family history of asthma (especially mother). The mechanism underlying the gender- and asthma-associated risks is unclear but 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 epithelial sodium channel expression as well as explain the correlation between TTN and wheezing in the first years of life. Macrosomia, maternal diabetes, pregnancy-induced hypertension, and multiple gestations also increase the risk of 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. Antenatal corticosteroids given to mothers at risk for late preterm births (34 to 36 weeks, 6 days) and prior to an elective cesarean section at ≥37 weeks' gestation reduce the risk of TTN.

IV. CLINICAL PRESENTATION. Affected term or late preterm infants usually present within the first 6 hours after birth with tachypnea; respiratory rates are typically more than 60 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 FiO_2. Respiratory failure and need for mechanical ventilation should trigger investigations to rule out infection, RDS, or heart disease. 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 pneumonia/sepsis, RDS, pulmonary hypertension, 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.

VI. EVALUATION

A. History and physical examination. A careful history identifies elements such as prematurity, infectious risk factors, meconium-stained liquor, 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 (LUS) can differentiate TTN from RDS with good specificity but is not in common clinical use. Absence of consolidation, replacement of A-lines by B-lines, numerous compact B-lines producing "white lung," and double-lung point (DLP) sign are findings suggestive of TTN on LUS. 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, a cardiac evaluation should be considered. Respiratory alkalosis may reflect central hyperventilation due to CNS pathology or metabolic disorder.

VII. TREATMENT.

Treatment is mainly supportive with provision of supplemental oxygen as needed. One must be prepared to start continuous positive airway pressure (CPAP) or high flow nasal canula (HFNC). Invasive ventilation (intubation) is rarely required; if respiratory distress is severe, one must investigate for and exclude serious illnesses like infection, lung malformations, inherited lung diseases (like primary ciliary dyskinesia, cystic fibrosis etc) before labeling as TTN. Early CPAP in the delivery room using T-piece resuscitator may reduce the severity and duration of respiratory

distress in TTN. 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 historical risk factors for infection. If tachypnea persists and is associated with increased work of breathing, gavage feedings or intravenous fluids may be needed. 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. Inhaled therapy with short-acting β-agonist salbutamol and nebulized budesonide has not been found to be useful.

VIII. COMPLICATIONS. Although TTN is a self-limited process, one must be prepared for advance respiratory support and complications associated with conditions that mimic TTN. Delayed initiation of oral feeds may interfere with parental bonding and establishment of breastfeeding and may prolong hospitalization.

IX. PROGNOSIS. By definition, 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 Reading

Stroustrup A, Trasande L, Holzman IR. Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. *J Pediatr* 2012;160(1):38–43.e1.

33 Respiratory Distress Syndrome

Susan Guttentag

KEY POINTS

- Respiratory distress syndrome (RDS), a disease of preterm infants, is characterized by atelectasis of alveoli due to insufficient pulmonary surfactant.
- Antenatal corticosteroids (ANS) given to a pregnant woman in anticipation of preterm birth significantly decrease the incidence and severity of RDS.
- Treatment entails establishment and maintenance of functional residual capacity, preferably by the 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 generalized atelectasis of alveoli due to insufficient pulmonary surfactant.

Pulmonary surfactant is a complex mixture of phospholipids, neutral lipids, and surfactant-specific proteins that is synthesized, packaged, and secreted from alveolar type II cells of the lung. In the alveoli, the surfactant disrupts the surface tension generated at the air–liquid interface. The alveoli and respiratory bronchioles are lined by a liquid layer over the surface of the lung epithelium. The surface tension exerted by this lung liquid is sufficient to promote atelectasis in the distal lung and oppose re-expansion of atelectatic airspaces. The polar head groups of surfactant phospholipids interposed between water molecules break the hydrogen bonding that mediates the surface tension. Therefore, an inadequate or dysfunctional surfactant in infants with RDS leads to an inappropriately high alveolar surface tension, resulting in difficulties in recruiting atelectatic alveoli and in progressive atelectasis of recruited airspaces. An absent or insufficient surfactant due to developmental immaturity of alveolar type II cells (rarely due to mutations of surfactant-related genes), or inactivation of the surfactant due to inflammation (pneumonia), chemical modification (meconium), or lung injury, results in high surface tension and atelectasis. Preterm infants are particularly prone to RDS because alveolar type II cells do not develop until early in the third trimester, and their number and capacity to produce a surfactant increase throughout the third trimester.

Advances in preventive and rescue treatment strategies, including antenatal corticosteroids (ANS), exogenous surfactant, and continuous positive airway pressure (CPAP), have greatly reduced the impact of RDS on neonatal morbidity and mortality. Respiratory mortality and morbidity remain a particularly vexing problem for

extremely low-birth-weight (ELBW) infants; they have a combined insufficiency of the surfactant and extreme immaturity of the lung (pulmonary insufficiency).

II. PATHOPHYSIOLOGY

A. Lung maturity. The preterm lung has insufficient numbers of alveolar type II cells to generate enough surfactant to avoid RDS. By 34 weeks of gestation, RDS is uncommon because the newborn generally has enough alveolar type II cells and surfactant stores. Toward lower gestations (<28 weeks), the problem of surfactant insufficiency is compounded by underdeveloped alveoli (saccules) and respiratory bronchioles. By 24 weeks of gestation, structural lung development is just sufficient to provide gas exchange across lung epithelial and endothelial cells and provide a surface area sufficient to meet the oxygen needs of the infant.

1. **Factors that affect lung maturation**

   a. **Maternal diabetes.** Poorly controlled maternal diabetes is associated with RDS due to enhanced production of fetal insulin which inhibits the production of surfactant phospholipids important for surfactant function. Strict glycemic control allows the lungs to mature in a near-normal fashion.

   b. **Labor.** Due to the production of endogenous maternal glucocorticoids, may enhance lung fluid clearance by enhancing sodium reabsorptive properties of epithelial sodium channels (E-NaC). Preterm babies delivered by a cesarean section before the onset of labor have a higher incidence of RDS. Preterm labor (PTL) may in some cases be due to infection; this can downregulate the production of many surfactant components.

   c. **Mutations** in surfactant-related proteins, specifically surfactant protein B and ABCA3, result in severe RDS typically in term infants from either dysfunctional surfactant or severely limited production, respectively. Infants with these mutations die without lung transplantation. Some mutations in ABCA3 and mutations of surfactant protein C are associated with progressive interstitial lung disease, often diagnosed beyond the neonatal period.

   d. **Fetal sex.** Male infants are at a higher risk for RDS due to the presence of circulating weak fetal androgens that inhibit the production of surfactant phospholipids.

   e. **Race.** Infants of African ancestry are at a lower risk for developing RDS, due in part to the increased presence of protective genetic polymorphisms.

III. DIAGNOSIS

A. Antenatal testing

1. Because gestational age itself is a strong predictor of RDS risk, invasive testing (amniocentesis) to confirm lung maturity in amniotic fluid samples is a procedure of the past; it is almost never done in clinical practice these days. The widespread use of ANS reduced the RDS incidence significantly, and made the invasive testing of amniotic fluid for lung maturity unnecessary for fetuses facing preterm delivery.

2. Lecithin/sphingomyelin (L/S) ratio and the presence of lamellar bodies in amniotic fluid were used in the past.

B. Clinical features. RDS should be suspected in a preterm infant, typically <34 weeks of gestation, with signs of respiratory distress that develop soon after birth. These include retractions, grunting, cyanosis, tachypnea, and flaring of the nasal alae. Blood gas measurement will demonstrate hypoxemia and hypercarbia.

1. Infants with RDS who are spontaneously breathing try to overcome atelectasis due to surfactant deficiency by using a set of physiologic maneuvers to establish functional residual capacity (FRC) and optimize gas exchange. These result in characteristic signs/symptoms of RDS.

   a. **Retractions.** To maximize the negative inspiratory pressure and thus lung inflation, affected infants use accessory muscles of breathing in addition to strong diaphragmatic contractions. This strong negative inspiratory pressure draws in the highly compliant chest wall resulting in subcostal, intercostal, and suprasternal retractions.

   b. **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 patent but surfactant-poor alveoli.

   c. **Hypoxia.** Need to give more oxygen (higher FiO_2) is the simplest marker of severity of RDS in preterm neonates with respiratory distress. Most neonatologists recommend surfactant administration for preterm babies requiring 0.3 FiO_2 on optimal CPAP.

   d. **Tachypnea.** Inadequate FRC leads to inadequate tidal volumes. To maintain minute ventilation (the product of tidal volume and respiratory rate), infants with RDS increase the respiratory rate.

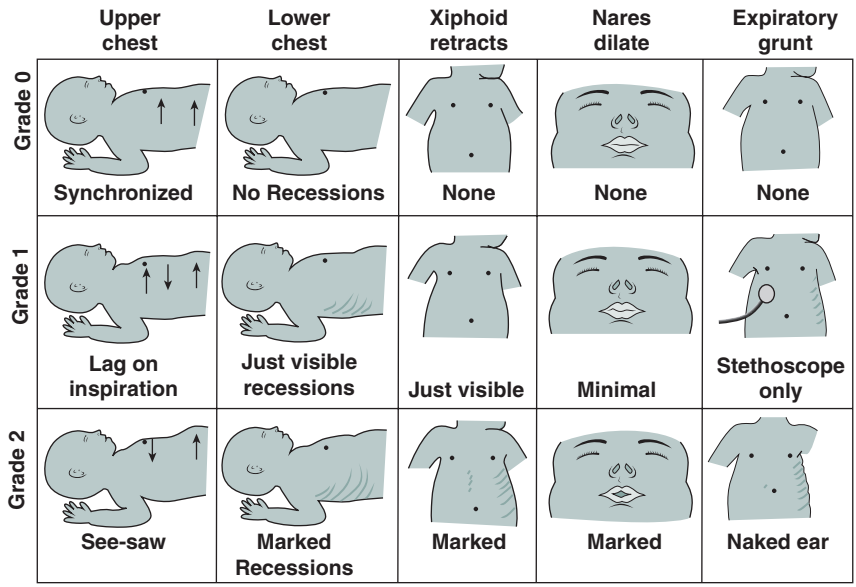
   e. **Flaring of the alae nasi.** Flaring of the alae nasi reduces the resistance to air flow through the upper airways.

   f. **Silverman–Andersen Score** (Table 33.1) is a useful clinical severity grading score. Higher the score (≥5), more is the work of breathing and higher the need for respiratory support to improve FRC.

C. Radiographic evidence. Typical radiographic findings result from homogeneous atelectasis of alveoli (homogenous white lung) with contrast "black" bronchi that do not collapse (air bronchograms: black bronchi stand out on the white background). Low lung volumes (rib spaces) are most evident before initiating CPAP/ventilation. In severe RDS, the cardiac border and diaphragm border are not visible; the airless "white lung" merges with the "white" heart and liver shadows.

1. Lung ultrasound is an evolving bedside tool to differentiate RDS from transient tachypnea of the newborn (TTN) and other neonatal respiratory disorders presenting at birth. Consolidation with air bronchogram, irregular and thickened pleural line, compact B-lines from the base to the apex, A-line disappearance on the transthoracic view, and diffuse retrodiaphragmatic hyperechogenicity replacing the normal diaphragm echo complex on the transabdominal view are the main findings on the lung ultrasound.

Table 33.1. Silverman–Andersen Scoring to Assess the Severity of Respiratory Distress



Source: Silverman WA, Andersen DH. A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. *Pediatrics* 1956;17:1–10.

IV. DIFFERENTIAL DIAGNOSIS

A. Transient Tachypnea of Newborn (TTN) (see Chapter 32). Excess fetal lung fluid can mimic RDS and can complicate it. TTN is common in late preterms, and RDS is the dominant pathology in early preterms (34 weeks, especially if antenatal steroids not given). Babies who need more oxygen (FiO_2) to achieve target saturations or have moderate to severe retractions/grunting are treated as RDS and initiated on CPAP. TTN often resolves rapidly over the first several hours after birth. Radiographic findings are 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 and often fluid retained in the lateral fissure of the right lung.

B. Pneumonia. Proinflammatory cytokines elaborated in the course of an infection can inactivate surfactant constituents and downregulate surfactant production. Signs and radiographic findings of group B *Streptococcus* (GBS) sepsis/pneumonia in the west and gram-negative infections in Asia are indistinguishable from RDS; therefore, obtaining blood cultures and initiating antibiotics should be considered. The bacterial pneumonia can be a fulminant, rapidly progressive fatal illness unlike RDS.

C. Obstructed total anomalous pulmonary venous connection (TAPVC). The venous congestion of the lungs gives a reticulogranular pattern to the lungs similar to RDS. No response to surfactant, normal-volume lungs, and 2D echo are useful in making a diagnosis.

D. Genetic disorders of the surfactant system. A high index of suspicion of genetic disorders of the surfactant system needs to be kept, especially in term and near-term infants with clinical presentation and radiographic findings identical to RDS with a severe clinical course. The diagnosis is highly likely if RDS is recurring in term babies in the family/sibling. Respiratory signs may be evident at birth or may develop over hours in a vigorous term infant able to initially spontaneously recruit FRC. However, the infant shows short-lived or no response to the administration of artificial surfactant. Genetic mutations in surfactant protein B and ABCA3 can result in an RDS picture in the immediate newborn period.

E. Disordered lung development. Like genetic disorders of the surfactant system, these rare disorders typically present in term and near-term infants with severe respiratory failure at birth and do not show sustained improvement with surfactant therapy. This category includes alveolar capillary dysplasia with malalignment of the pulmonary veins, congenital alveolar dysplasia, and brain–heart–lung disease due to mutations in NKX2.1/TTF1.

V. 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 ANS in anticipation of preterm birth is effective in preventing RDS. ANS modifies surfactant readiness 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 (PTL) or planned preterm delivery, although emerging evidence suggests some benefit in gestations as low as 23 weeks. A complete course of ANS is considered to be either betamethasone at 12 mg intramuscular (IM) q24h × 2 doses OR dexamethasone 6 mg IM q12h × 4 doses, course completed at least 24 hours before the delivery. Meta-analyses have not demonstrated superiority of one drug over the other. No contraindications exist to treatment. ANS must be given even if delivery is imminent. Animal studies have demonstrated beneficial effects on lung structure even after incomplete dosing. However, benefits of prior treatment on lung maturity may diminish if PTL stops and pregnancy continues more than a week after ANS 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.

VI. MANAGEMENT.

The key principles of treatment of RDS are to establish and maintain FRC, at the earliest. The most important role of pulmonary surfactant in the alveoli and distal respiratory bronchioles is to maintain a low surface tension that permits the alveoli to remain patent at low pressures.

A. CPAP has its physiologic basis in the grunting that infants with RDS do to maintain FRC. Application of CPAP via binasal 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-analysis of CPAP trials have demonstrated the effectiveness of

CPAP in babies with RDS, and more recent trials showed that this strategy could be applied to even the least mature preterm infants. Early CPAP reduces the need to intubate and give surfactant and has potential in decreasing the incidence of bronchopulmonary dysplasia (BPD).

1. **Components of CPAP delivery systems**
   a. **Pressure generator.** Options for application include bubble CPAP, constant-flow devices (mechanical ventilators), and variable-flow devices. Bubble CPAP devices provide a gentle oscillation of positive pressure in addition to CPAP that may assist in recruitment and CO_2 elimination in addition to supporting alveoli. Ventilator CPAP allows easy change to assisted ventilation, if RDS is severe. Variable-flow CPAP is associated with a decrease in the work of breathing, as the flow to the patient is modified as per need in inspiration and expiration. In any of the devices used, a pressure of at least 5 cm H_2O is needed to prevent atelectasis (continuous bubbling in both inspiration and expiration must be noted in bubble CPAP; the other devices measure the actual delivered pressure).
   b. Compressed Air, compressed Oxygen and Blender. The blender should be able to deliver oxygen from FiO2 of 0.21 to 0.60 or more)
   c. **Humidification.** Warm, humidified air–oxygen mixture is critical for the health of the respiratory epithelium. If cold, dry air is used by head box or CPAP, it results in drying and breaking of the airway epithelium and increases the risk of infections.
   d. **Patient interface.** A variety of nasal prongs and nasal masks can be used for CPAP delivery. The need for occlusion may lead to pressure necrosis of the nasal septum that can be rarely severe enough to require surgical intervention. This can often be alleviated by appropriate fixation of interface, avoiding blanching of the nose, care of the pressure points, frequent cleaning of the nares, moistening the nares with instillation of saline drops, and nasal barrier dressings. Daily rounds should include a discussion of the interface and status of the nasal septum.

      The nasal masks seem to have advantage over nasal prongs; some units alternate the applied interface (prong/mask) to decrease pressure-related injuries.

2. **Managing a baby on CPAP**
   a. **Initiation of CPAP.** Start CPAP in the delivery room or soon after the onset of respiratory distress. The earlier the CPAP is started, the better is the neonatal outcome. Initiate nasal CPAP at 5 to 6 cm H_2O pressure and adjust based on the chest retractions, work of breathing, and oxygen requirement. Optimal FRC should be associated with a gradual reduction in FiO_2 to 0.21 as well as normalization of respiratory rate in a lung with pure surfactant deficiency. Monitoring of blood gases in the acute phase of recruitment may be necessary, but once adequate recruitment has been established, noninvasive monitoring (pulse oximetry) is usually sufficient to guide therapy.
   b. **Monitoring of an infant on CPAP.** While on CPAP, the baby is monitored for adequacy of pressure and FiO_2. Saturation targets are 90% to 95%. The

baby must not have significant retractions or tachypnea. High FiO_2 need or severe respiratory distress prompts an assessment of the interface, delivery systems, and gas flow. Persistent respiratory distress and FiO_2 need may indicate the need for surfactant and/or mechanical ventilation.

Monitoring includes adverse event prevention like nasal injury, abdominal distension, or signs of cardiovascular compromise.

Caffeine therapy. Successful use of nasal CPAP to treat RDS depends on adequate spontaneous breathing which is facilitated by early use of caffeine.

c. Weaning from CPAP. Because successful application of CPAP is defined by achieving and maintaining a normal FRC, weaning of support should be initiated only after reduction of oxygen requirements (FiO_2)to at least <30%, preferably <25%. For the preterm infant >30 weeks of gestation, discontinuation of CPAP can generally be considered at CPAP 4 to 5 and <25% FiO_2. For infants born at <30 weeks of gestation, poor chest wall compliance alone can lead to progressive atelectasis, and longer use of CPAP may be advantageous, even when oxygen supplementation is no longer needed (room air CPAP, 21% FiO_2). Atelectasis can occur with weaning and discontinuation of CPAP due to insufficient endogenous surfactant stores and/or poor chest wall compliance and may be clinically evident only hours after stopping CPAP. Signs of unsuccessful CPAP weaning include increases in oxygen requirement and respiratory rate, as well as retractions.

d. Contraindications. Few contraindications exist to using CPAP. The most important is poor respiratory effort, with frequent and severe apnea. A trial of CPAP is contraindicated in infants with frank apnea in the delivery room.

i. However, preterm babies with respiratory distress or those at high risk for developing RDS and apnea (<30 weeks of gestation) may have less frequent apnea when CPAP is combined with early initiation of caffeine therapy.

ii. Air leak is a relative contraindication to CPAP because air leak may worsen in the face of continuous positive pressure.

e. Complications associated with CPAP therapy

i. Overdistension of lungs. Rapid changes in lung compliance as atelectatic regions are recruited and supported, especially after administration of surfactant, can lead to overdistension of airspaces. In turn, this can result in the following: (i) inadequate tidal volumes leading to hypercarbia; (ii) tamponade of the alveolar capillary bed, with ventilation–perfusion (V/Q) mismatch leading to hypercarbia and hypoxemia; and (iii) poor venous return sufficient to reduce cardiac output. Bedside monitoring and optimization of positive end-expiratory pressure (PEEP) is easy, and this complication is uncommon in practice.

ii. Air leak. Although overdistension 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. **Nasal septum trauma** (described earlier)

iv. **Failure of CPAP.** The ease of application of CPAP has resulted in its widespread use. If the medical/nursing team is not experienced, they may fail to recognize early signs of ineffective CPAP. Failure to establish FRC will result in persistent need for oxygen supplementation and persistent retractions, due to poorly supported airspaces. This is more often due to inappropriate application of CPAP interface and rarely due to an open mouth that presents a path for the release of distending pressure. Some centers try closing the mouth, most do not. In some babies, the RDS may be severe and the decision to give a surfactant must be made early, if CPAP need is as high as 8 cm H_2O to decrease retractions OR FiO_2 is more than 0.30 to achieve a right upper limb saturation of 90%.

B. Heated humidified high-flow nasal cannula (HHHFNC). The development of humidification devices enabling the administration of high-flow heated humidified oxygen via nasal cannulas (HHHFNC) has led to their use in RDS with a patient interface that may be less traumatic than nasal prongs. The pharyngeal pressures delivered with high-flow nasal cannula (HHHFNC) are variable and the current evidence does not support the routine use of HFNC as an alternate to CPAP for primary respiratory therapy of RDS in most preterm babies (<28 weeks of gestation). HFNC is a proven respiratory support in the postextubation management of newborns with RDS.

C. Restore alveolar surfactant. The widespread use of ANS has reduced the need for surfactant administration, but in precipitous delivery or circumstances that preclude ANS administration, RDS may be severe. For infants with RDS, exogenous surfactant therapy can acutely supplement insufficient endogenous stores. The combination of ANS and postnatal surfactant administration is more effective in reducing the morbidity and mortality of RDS than either intervention alone.

1. **Prophylaxis versus treatment.** Evidence demonstrates an advantage to early surfactant treatment of infants at the onset of RDS signs as compared to waiting to establish a diagnosis of RDS. However, prophylaxis (before the onset of RDS signs) would lead to many infants being intubated to receive surfactant who either might not develop RDS or who could be successfully managed with CPAP. For infants on optimal CPAP, if the FiO_2 is >0.30, the surfactant may be administered by the InSurE method. The baby is extubated to CPAP within 15 minutes of surfactant delivery. Newer methods of least/minimally invasive surfactant therapy (MIST) allow surfactant delivery using a catheter, completely avoiding the need to intubate. For all infants needing intubation in the delivery room for stabilization, a surfactant is recommended to be administered.

2. **Surfactant preparations.** Natural surfactants are better than synthetic surfactants. Available surfactants include a variety of animal-derived products and protein-free synthetic surfactants. Synthetic surfactants modified by the surfactant proteins B and C are also available, and overcome the major difference from animal-derived surfactants.

3. **Dosing and dosing interval.** Surfactant is administered to achieve a phospholipid dose that is at least 100 mg/kg. A second and occasionally a third dose of

surfactant may be given if there is ongoing evidence of RDS such as persistent high oxygen requirement and other problems have been excluded.

4. **Administration.** A surfactant is typically given to infants with RDS through an endotracheal tube (ETT) that either remains in place for mechanical ventilation or is inserted for surfactant dosing in an infant on CPAP and removed following the procedure (InSurE). 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 equal breath sounds can be confirmed by auscultation. To minimize reflux up the ETT, administer via a sterile feeding tube inserted into the ETT with the tip at or above the end of the ETT. 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. Positional maneuvers that were initially recommended to assist in surfactant distribution are not necessary and should be avoided because they could result in ETT malposition or extubation. MIST or less invasive surfactant administration (LISA), administered by insertion of a small-bore catheter or a gastric tube into the trachea, is preferred over InSurE if technical expertise is available. It reduces the need to intubate. Aerosolization devices for surfactant administration are currently in clinical trials.

5. **Complications associated with surfactant therapy**

   a. **Airway obstruction.** Hypoxemia, bradycardia, and apnea may occur acutely during surfactant administration due to obstruction of large airways until the surfactant distributes fully. Divided dose administration and recovery on mechanical ventilation minimize these transient events and are rarely a cause of concern.

   b. **Air leak.** More serious complications may result from a rapid increase in lung compliance that occurs as the surfactant lowers the surface tension, fostering alveolar recruitment. Infants receiving pressure-limited mechanical ventilation may develop pneumothorax as delivered tidal volumes increase (see Chapter 38). This may be avoided by converting to volume-targeted mechanical ventilation or rapid changes in positive inspiratory pressure (PIP) in response to clinical assessment of respiratory distress supplemented by arterial blood gas, if necessary.

   c. **Hemorrhagic pulmonary edema.** It is a rare complication. As compliance improves, pulmonary vascular resistance drops and can result in hemorrhagic pulmonary edema, commonly referred to as pulmonary hemorrhage, especially in the presence of a patent ductus arteriosus that can exacerbate the process with pulmonary overcirculation.

D. Ensure appropriate ventilation. Although poor oxygenation is the most evident feature of RDS, atelectasis also reduces CO_2 gas exchange resulting in hypercarbia.

1. **Mechanical ventilation** (see Chapter 29). Babies with poor respiratory effort, recurrent apnea, or severe RDS (high FiO_2 need, high CO_2 despite optimal CPAP and surfactant) should be identified early and supported with mechanical ventilation. Optimal ventilator strategy for infants with RDS includes the application of sufficient PEEP to allow the maintenance of FRC. As discussed

earlier, optimization of FRC should result in the need for a decreased concentration of supplemental oxygen to maintain appropriate oxygen saturation. As with CPAP, complications include overdistention, volutrauma, and air leak.

Volume-limited ventilation in infants with RDS has many benefits—decrease in hypocarbia, BPD, and peri-ventricular leucomalacia (PVL). On this ventilation mode, targeted tidal volume is set at 4 to 6 mL/kg; this results in automatic weaning of peak inspiratory pressures, as lung compliance improves in response to surfactant treatment, thus avoiding volutrauma and air leak.

In infants with a large leak around the ETT due to a tube relatively small compared to the airway size, pressure-limited, time-cycled ventilation may be safer. In this case, we closely monitor for sometimes dramatic changes in lung compliance and reduce peak inspiratory pressures to avoid delivering supraphysiologic tidal volumes, volutrauma, and air leak. PIP must be at the lowest support necessary to get a gentle chest rise.

VII. OUTCOMES OF RDS. In the presurfactant era, RDS in preterm infants typically resolved at 2 to 4 days of age, often preceded by spontaneous diuresis. With the widespread use of ANS, early use of CPAP, and exogenous surfactant, the time course of RDS has become much shorter, often just few minutes to hours. In some babies, association of preterm birth with chorioamnionitis may affect the time to resolution. RDS in infants born at ≥32 weeks of gestational age and without other complications typically resolves fully with no long-term pulmonary sequelae. Infants <32 weeks of gestational age are at risk for BPD; the risk increases with decreasing gestational age (see Chapter 34).

Suggested Readings

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34 Bronchopulmonary Dysplasia/Chronic Lung Disease

Richard B. Parad and John Benjamin

KEY POINTS

- Bronchopulmonary dysplasia (BPD) affects 30% to 50% of extremely low-birth-weight infants.
- Arrested lung development and reduced gas exchange surface area are hallmarks of "new" BPD.
- Contributing factors include inflammation and lung injury from volutrauma, barotrauma, oxytrauma, atelectotrauma, and infection.
- Minimizing invasive ventilation (CPAP, noninvasive ventilation), minimizing ventilator-associated pneumonia, volume limit ventilation, early caffeine therapy, breast milk, optimizing (protein) nutrition, fluid management and prevention of patent ductus arteriosus and vitamin A are some of the therapies that have been tried in decreasing BPD rates.
- Glucocorticoids, diuretics, and bronchodilators are often used for the treatment of characteristic respiratory symptoms in BPD, although evidence-based strategies are lacking.

I. DEFINITION. Even after 50 years of the first description by Northway, defining bronchopulmonary dysplasia (BPD) is still imprecise. A 2001 National Institutes of Health (NIH) consensus conference proposed definitions for BPD (also known by the more general term *chronic lung disease* [CLD] of prematurity).

A. For infants born at <32 weeks' gestation who received supplemental oxygen for their first 28 days, the NIH defined BPD at 36 weeks' postmenstrual age (PMA) as follows:

1. **Mild.** No supplemental O_2 requirement
2. **Moderate.** Supplemental O_2 requirement <30%
3. **Severe.** Supplemental O_2 requirement ≥30% and/or continuous positive airway pressure (CPAP) or ventilator support

B. For infants born at ≥32 weeks, the NIH defined BPD as supplemental O_2 requirement for the first 28 days with severity level based on O_2 requirement at 56 days.

C. In 2016, the National Institute of Child Health and Human Development (NICHD) convened a workshop and suggested refinements to this definition (Table 34.1).

D. Physiologic definition of BPD. The need for supplemental oxygen is based on oxygen saturation (SpO_2) during a room air challenge performed at 36 weeks' PMA

Table 34.1. Suggested Refinements to the Definition of BPD by the 2016 NICHD Workshop

A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease and radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires one of the following FiO_2 ranges/oxygen levels/O_2 concentrations for ≥3 consecutive days to maintain arterial oxygen saturation in the 90% to 95% range.

Grades	Invasive IPPV	N-CPAP, NIPPV, or Nasal Cannula ≥3 L/minute	Nasal Cannula Flow of 1 to <3 L/minute	Hood O_2	Nasal Cannula Flow of <1 L/minute
I	—	21	22–29	22–29	22–70
II	21	22–29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (e.g., necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis)				

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; NICHD, National Institute of Child Health and Human Development; NIPPV, nasal intermittent positive pressure ventilation; PMA, postmenstrual age.

(or 56 days for infants >32 weeks' PMA) or before hospital discharge. Persistent SpO_2 <90% is the cutoff below which supplemental O_2 should be considered.

E. Operationally, many clinicians simply define BPD as requirement for oxygen supplementation at 36 weeks' PMA. Lung parenchyma usually appears abnormal on chest radiographs. This definition can also apply to term infants who require chronic ventilatory support following meconium aspiration syndrome, pneumonia, and certain cardiac and gastrointestinal (GI) anomalies. BPD is associated with the development of chronic respiratory morbidity (CRM).

II. EPIDEMIOLOGY.

Approximately 10,000 to 15,000 new cases of BPD occur in the United States each year. The incidence of BPD increases with decreasing gestational age at birth. Infants <28 weeks' gestation or <1,000 g birth weight are most susceptible, with incidence rates of 35% to 50%. Data from a major cohort study globally demonstrate a BPD prevalence of 11% to 50%. Differences in populations (gestational age/race/ethnicity/socioeconomic status), clinical practices, and definitions account for the wide variation in the rate reported. The relative risk is decreased in African Americans and females. Of infants with BPD, 44% develop CRM (defined as a requirement for pulmonary medications at 18 months corrected age). Of similar preterm infants who do not require O_2 at 36 weeks' PMA, 29% also develop CRM.

III. ETIOLOGY AND PATHOGENESIS (Fig. 34.1)

A. Etiology. A number of factors have been associated with BPD, some of which may be causal.

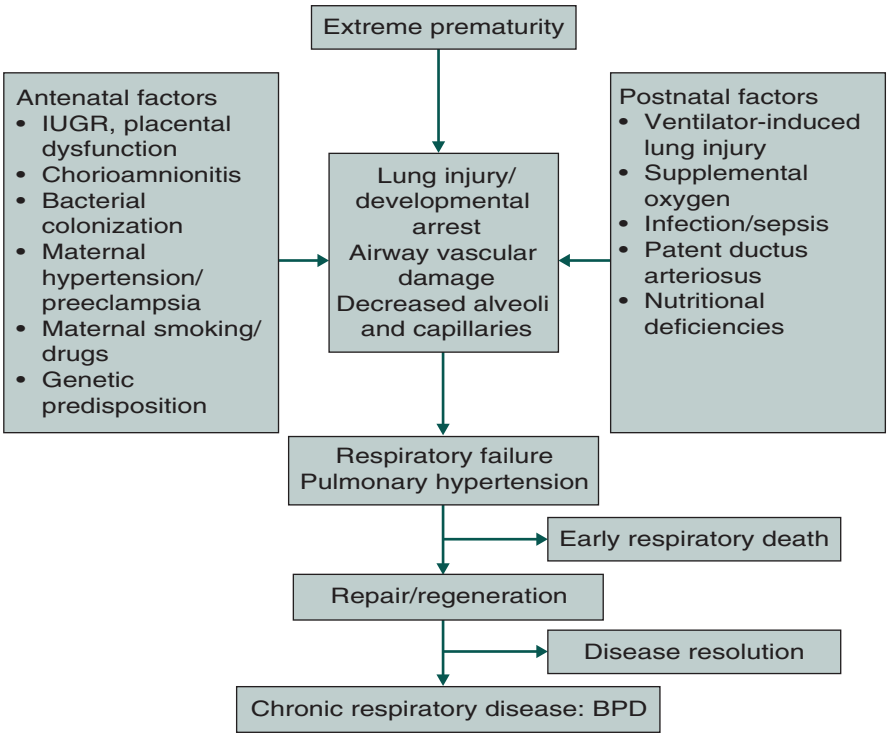

Figure 34.1. Pathogenesis of BPD.

1. **Antenatal factors**
   - **a.** Prematurity and low birth weight are the strongest risk factors. Almost 80% of infants who are born at 22 to 24 weeks' gestation develop BPD, whereas in infants born at 28 weeks' gestation only 20% develop BPD. The lung is most susceptible before alveolar septation begins. Injury at this stage may lead to an arrest of alveolarization and simplified lung structures that are the hallmark of new BPD.
   - **b.** Genetic factors may contribute to BPD risk. Several genetic markers have been identified.
   - **c.** Maternal smoking is an important modifiable risk factor.
   - **d.** Intrauterine or perinatal infection such as chorioamnionitis, with cytokine release, may contribute to the etiology of BPD or modify its course. *Ureaplasma urealyticum* has been associated with BPD in premature infants, although whether this relationship is causal is uncertain. Intrauterine *Chlamydia trachomatis* and other viral infections have also been implicated.
   - **e.** Intrauterine growth restriction has been linked to later development of BPD, although whether this is a causal mechanism for disease or just an association is uncertain.
2. **Postnatal factors**

a. Volutrauma and lung injury from mechanical ventilation or bag-and-mask ventilation

b. Oxygen toxicity. Insufficient production of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase and/or deficiency of free radical sinks such as vitamin E, glutathione, and ceruloplasmin may predispose the lung to O_2 toxicity. Similarly, inadequate antiprotease protection may predispose the lung to injury from the unchecked proteases released by recruited inflammatory cells.

c. Excessive early intravenous fluid administration, perhaps by contributing to pulmonary edema

d. Persistent left-to-right shunt through the patent ductus arteriosus (PDA). Although prophylactic PDA ligation or administration of indomethacin or ibuprofen does not prevent BPD, persistent left-to-right shunt and late PDA closure appear to be associated with increased BPD risk. However, surgical PDA closure is also associated with increased BPD risk.

e. Alterations of the lung microbiome and lung dysbiosis have been increasingly linked to the development of BPD.

f. Lack of breastfeeding and poor early nutrition predispose to BPD. The nutrients such as vitamin A, antioxidants, growth factors in breast milk, and the lower infections associated with breastfeeding contribute to the protective effect of breast milk.

B. Pathogenesis

1. **Acute lung injury** is caused by the combination of O_2 toxicity, barotrauma, and volutrauma from mechanical ventilation. Cellular and interstitial injury results in the release of proinflammatory cytokines (interleukin-1β [IL-1β], IL-6, IL-8, tumor necrosis factor-alpha [TNF-α]) that cause secondary changes in alveolar permeability and recruit inflammatory cells into interstitial and alveolar spaces; further injury from proteases, oxidants, additional chemokines, and chemoattractants causes ongoing inflammatory cell recruitment and leakage of water and protein. Airway and vascular tone may be altered. Sloughed cells and accumulated secretions not cleared adequately by the damaged mucociliary transport system cause inhomogeneous peripheral airway obstruction that leads to alternating areas of collapse and hyperinflation and proximal airway dilation. Inflammation may also alter critical molecular pathways required for lung development leading to impaired alveolarization and emphysematous changes in the lung. In the original report by Northway in 1967 of the "old" BPD affecting infants with mean gestational age of 33 weeks and birth weight of 2,000 g, the pathology of nonsurvivors showed predominantly small airway injury, fibrosis, and emphysema. In contrast, in the postsurfactant therapy era, "new" BPD affects mostly extremely preterm infants and the most significant pathologic finding in nonsurvivors is decreased alveolarization with fewer and larger alveoli and decreased pulmonary vascular development.
2. In the **chronic** phase of lung injury, the interstitium may be altered by fibrosis and cellular hyperplasia that results from excessive release of growth factors and cytokines, leading to dysregulated repair. Interstitial fluid clearance is disrupted, resulting in pulmonary fluid retention. Airways develop increased

muscularization and hyperreactivity. The physiologic effects are decreased lung compliance, increased airway resistance, and impaired gas exchange with resulting ventilation–perfusion mismatching and air trapping.

Arrest of alveolarization and dilated simplified terminal airspaces are characteristic histologic features of "new" BPD seen at lower gestational ages. The resultant emphysematous changes and impairment in alveolar development lead to diminished surface area for gas exchange. In severe cases, pathology may reflect that seen in "old" BPD with detectable changes observed within the first few days after birth. In these cases, necrotizing bronchiolitis, obstruction of small airway lumens by debris and edema, and areas of peribronchial and interstitial fibrosis are present. Changes in both large airways (glandular hyperplasia) and small airways (smooth muscle hyperplasia) likely form the histologic basis for reactive airway disease.

Pulmonary hypertension (PH) and related pulmonary vascular changes are strong contributors to poor survival in BPD. Early disruption of lung vascular growth and function can impair the growth of distal airspace (the vascular hypothesis of BPD). There may be associated cord blood biomarkers of impaired angiogenesis and early ECHO findings of PH.

IV. CLINICAL PRESENTATION

A. The infants present with chronic respiratory insufficiency and oxygen dependency, and intermittent cyanotic or life-threatening episodes—"**BPD spells**."

B. Physical examination typically reveals tachypnea, retractions, and rales on auscultation.

C. Arterial blood gas (ABG) analysis shows hypoxemia and hypercarbia with eventual metabolic compensation for the respiratory acidosis.

D. The **chest radiograph** appearance changes as the disease progresses. With "new" BPD, the initial appearance is often diffuse haziness, increased density, and normal-to-low lung volumes. In more severe disease, chronic changes may include inhomogeneous regions of opacification and hyperlucency with superimposed hyperinflation.

E. Cardiac evaluation. Nonpulmonary causes of respiratory failure should be excluded. Electrocardiogram (ECG) can show persistent or progressive right ventricular hypertrophy if *cor pulmonale* develops. Left ventricular hypertrophy may develop with systemic hypertension. Two-dimensional echocardiography may be useful in excluding left-to-right shunts (see Chapter 41) and PH. Biventricular failure is unusual when good oxygenation is maintained, and the development of PH is avoided. Cardiac catheterization, the gold standard for the evaluation of PH in BPD, is often not feasible in the sick infants.

F. Infant pulmonary function testing (iPFT). Increased respiratory system resistance (Rrs) and decreased dynamic compliance (Crs) are hallmarks of BPD. In the first year after birth, iPFTs reveal decreased forced expiratory flow rate, increased functional residual capacity (FRC), increased residual volume (RV), and increased RV/total lung capacity ratio and bronchodilator responsiveness, with an overall pattern of mild-to-moderate airflow obstruction, air trapping,

and increased airway reactivity. Although such testing is feasible, it is not typically used in clinical practice.

V. SCREENING AND PREDICTION. Infants with a persistent need of respiratory support at 10 to 14 days of age are at the highest risk of BPD at 36 weeks. Postnatal nutritional deficit is an independent predictor of BPD. NTproBNP at 14 days of life could be used as an early marker of later BPD. Ongoing research has identified several biomarkers in the blood, tracheal aspirates, and even urine which could predict BPD and thereby identify infants who would benefit from preventive therapy. However, most have a low predictive accuracy.

In recent years, newer systems-biology-based "omic" approaches, including but not limited to genomics, microbiomics, proteomics, and metabolomics, have helped several novel biomarkers in BPD that may improve the prediction of BPD.

VI. INPATIENT TREATMENT. The goals of treatment during the neonatal intensive care unit (NICU) course are to prevent or minimize further lung injury (barotrauma and volutrauma, O_2 toxicity, inflammation), maximize nutrition, and diminish O_2 consumption.

A. Pharmacologic prevention

1. **Vitamin A** (5,000 IU intramuscular [IM], three times weekly for the first 28 days of age) reduced the incidence of CLD in extremely low-birth-weight (ELBW) infants by 10%. One trial has found benefit with oral vitamin A given as a syrup 10,000 units/dose on alternate days for 28 days. Nonavailability, need of IM injections, and uncertain long-term impact have limited its routine use.
2. **Caffeine citrate** (20 mg/kg loading dose and 5 mg/kg daily maintenance) started during the first 10 days after birth in infants 500 to 1,250 g birth weight reduced the rate of BPD from 47% to 36% and improved the rate of survival without neurodevelopmental disability at 18 to 21 months corrected age. Recent evidence suggests that beginning caffeine therapy within the first 72 hours of age and a higher loading and maintenance dose results in the greatest reduction in the BPD risk.
3. **Postnatal steroids** are the proven strategies to prevent BPD.
   a. **Dexamethasone.** In early trials, in infants who remained ventilator-dependent for 2 to 3 weeks, dexamethasone resulted in increased Crs, decreased Rrs, and diminished O_2 requirement, and facilitated earlier extubation. Although the most recent meta-analysis on early dexamethasone (<8 days) found reduced BPD risk, it is not recommended due to unacceptable side effects such as GI perforation, hypertrophic cardiomyopathy, cerebral palsy, and major neurosensory disability. The benefits of "late" dexamethasone (>7 days) are much less. A meta-analysis has shown that it reduces the BPD risk, but there are short-term side effects of hyperglycemia, glycosuria, and hypertension. In contrast to early use, it did not find clear evidence of increased cerebral palsy (CP) risk, although none of the trials were powered for this outcome.
   b. **Hydrocortisone.** Randomized trials of systemic hydrocortisone started in the first week have found a reduced risk of BPD. The largest of these trials is the PREMILOC trial that compared a 10-day course of low-dose

hydrocortisone to placebo in infants <28 weeks. The hydrocortisone group received 1 mg/kg of hydrocortisone hemisuccinate per day divided into two doses per day for 7 days, followed by one dose of 0·5 mg/kg/day for 3 days. BPD-free survival was improved and there were no short-term or neurodevelopmental adverse effects. However, a subgroup analysis found higher sepsis rates among the most preterm infants (24 to 25 weeks) treated with hydrocortisone.

c. Inhaled steroids. The meta-analysis of inhaled steroids demonstrates improved BPD-free survival. However, in the largest trial in the meta-analysis—the NEuroSIS trial—the decreased BPD rates among survivors were at the expense of greater mortality. However, intratracheal budesonide combined with surfactant holds promise in preventing BPD.

The clinician must balance the beneficial respiratory effects of steroids against the potential adverse effects on long-term neurodevelopment. If treatment with dexamethasone is undertaken, we discuss the potential neurodevelopmental harm with parents before use. One approach to **BPD prevention** is to estimate the risk of developing BPD using the NICHD Neonatal Research Network Neonatal BPD Outcome Estimator. As BPD itself is a risk factor for poor neurodevelopmental outcomes, steroids may actually reduce the risk of death or CP, if the risk of BPD exceeds 60% at 2 weeks of age (https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start). In such cases, a short tapering course of dexamethasone in the dosing regimen used in the DART study (0.89 mg/kg administered over 10 days) could be considered.

Common acute complications of glucocorticoids include glucose intolerance, systemic hypertension, and transient catabolic state. Total neutrophil counts, band counts, and platelet counts increase during steroid treatment. Hypertrophic cardiomyopathy has been reported but is transient and does not appear to affect cardiac function. Intestinal perforation and gastric ulcerations can occur with early postnatal use, especially in combination with indomethacin, and resulted in termination of trials of dexamethasone and hydrocortisone. Adrenal suppression is transient.

4. Investigational therapies without proven efficacy

a. Inhaled nitric oxide (iNO). iNO is an accepted treatment for persistent pulmonary hypertension (PPHN) in term infants. It is not as effective in the ill preterm infant. A meta-analysis showed no benefit of early routine use in preterm infants in improving survival without BPD. However, an meta-analysis showed that certain ethnic populations such as African Americans could benefit from iNO. Later use of iNO could be effective but requires further study. Considering lack of robust evidence and also logistics of continuous treatment with an inhalational medication, iNO is not recommended as a preventive strategy for BPD.

b. In <27-week-gestation infants, intratracheal **recombinant human Cu/Zn superoxide dismutase** administered intratracheally every 48 hours while intubated resulted in an approximately 50% reduction in the use of asthma medications, emergency room visits, and hospitalizations in the first year of life.

c. **Insulin-like growth factor-1** (IGF-1) is an important regulator of fetal growth, lung angiogenesis, and development. In animal studies and in a small phase II trial, treatment with recombinant human IGF in combination with its binding protein reduced the risk of severe BPD.

d. **Recombinant human club cell protein 10**, a natural innate anti-inflammatory protein abundant in the lung, is undergoing evaluation for intratracheal administration for prophylaxis against CRM.

e. **Mesenchymal stem cells** (MSCs) protect and repair lung injury by preventing lung inflammation. Bone marrow– and cord blood–derived MSCs are being evaluated in human trials for the prevention of BPD.

f. Whether **azithromycin** may decrease the risk of developing BPD in infants with documented *Ureaplasma* colonization or infection is under investigation.

B. Mechanical ventilation

1. **Acute phase.** One important strategy to reduce BPD is to minimize invasive ventilation. A meta-analysis of available data has shown that CPAP is associated with a small but significant reduction in the risk of death or BPD. As a result, the American Academy of Pediatrics Committee on Fetus and Newborn recommends early use of CPAP with subsequent selective surfactant administration in extremely preterm infants as an evidence-based strategy to reduce the risk for death or BPD.

   Nasal intermittent positive pressure ventilation (NIPPV) after extubation may further improve this benefit. We sometimes use heated, humidified high-flow nasal cannula (HHHFNC) for postextubation care in preterm infants >28 weeks' gestation. HHHFNC therapy may decrease the risk of extubation failure with the additional benefit of inducing less nasal trauma as compared to CPAP. The impact of HHHFNC use on BPD risk has not been evaluated.

   Volume-targeted compared to pressure-limited ventilation appears to reduce the incidence of the combined outcome of BPD or death and of BPD, as well as air leak. We initially target 3 to 5 mL/kg/breath while ensuring adequate gas exchange (see Chapter 29). It is possible that the use of patient-controlled ventilator modalities such as patient-triggered breaths and pressure-supported spontaneous breaths may lower the BPD risk.

   In most circumstances, we avoid hyperventilation and target arterial carbon dioxide tension ($PaCO_2$) at ≥55 mm Hg, with pH ≥7.25, and target SpO_2 at 90% to 95% and arterial oxygen tension (PaO_2) 55 to 80 mm Hg. Although routine use of high-frequency oscillatory ventilation (HFOV) does not prevent BPD, follow-up at 11 to 14 years of age of infants enrolled in a large trial found better lung function in those treated with HFOV compared to with conventional ventilation.

2. **Chronic phase.** Baseline ventilator settings are maintained with an aim to keep $PaCO_2$ <70 mm Hg with a compensated respiratory acidosis. Although an effort to transition to CPAP or HHHFNC as soon as possible is encouraged, subsequent support is not aggressively weaned until a pattern of steady weight gain is established.

C. Supplemental oxygen

is supplied to maintain the PaO_2 >55 mm Hg. The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

of low (85% to 89%) versus high (91% to 95%) SpO_2 targets in infants <28 weeks' gestation revealed a higher mortality rate and no reduction in BPD rate in the low SpO_2 group, although severe retinopathy of prematurity (ROP) was less frequent in survivors. One approach for infants who receive supplemental oxygen is to target SpO_2 at 92% to 95% with alarm limits at 84% to 96%. Another is to adjust the target saturations according to gestational age or PMA (Table 34.2). Oximeter alarm limits may be set 0% to 2% outside the appropriate target range.

When end-expiratory pressure is no longer needed and FiO_2 is <0.3, we supply O_2 by nasal cannula (NC). We use a flow meter that is accurate at low rates and gradually decrease the flow of 100% O_2 while maintaining the appropriate SpO_2. Alternatively, flow can be decreased to the lowest marking on the flow meter as tolerated, and then O_2 concentration can be decreased. Estimates of the actual concentration of O_2 delivered to the lungs by NC at different flows of 100% O_2 have been generated by hypopharyngeal measurements (see Fig. 34.2). Once the infant remains stable on a low flow rate, we attempt a trial of withdrawal of NC support with close monitoring of O_2 saturation to determine whether continued

Table 34.2. Postmenstrual Age Target Oxygen Saturations

Gestational Age (weeks)	Target SpO_2 on O_2 (%)	Target SpO_2 off O_2 (%)
<32	90–95	90–100
32–36	92–97	92–100
>36	94–98	94–100

O2, supplemental oxygen; SpO_2, oxygen saturation.

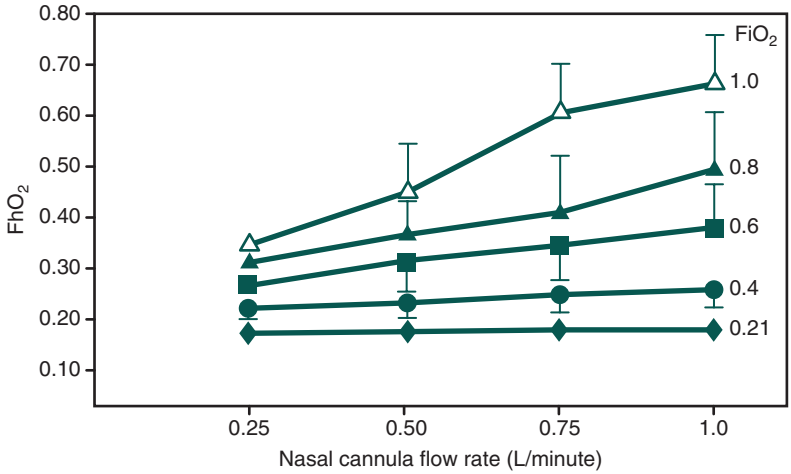

Figure 34.2. Approximate conversion from nasal cannula flow at different FiO_2 to hypopharyngeal FiO_2 (FhO_2). FiO_2, fraction of inspired O_2. (From Vain NE, Prudent LM, Stevens DP, et al. Regulation of oxygen concentration delivered to infants via nasal cannulas. *Am J Dis Child* 1989;143[12]:1458–1460. With permission.)

O_2 supplementation is required. In general, SpO_2 should remain >90% during sleep, feedings, and active periods before supplemental O_2 is discontinued. An "oxygen challenge test" can be performed at 36 weeks' PMA to confirm whether an infant requires supplemental oxygen to maintain SpO_2 >90% and thus meets the physiologic definition of BPD.

D. Surfactant replacement therapy decreases the combined outcome of O_2 requirement or death at 28 days of age, although it has made little or no impact on the overall incidence of BPD. Meta-analyses suggest that the incidence is decreased in larger premature infants but is higher in smaller premature infants who would have died without surfactant therapy (see Chapter 33). If mechanical ventilation is needed, early surfactant <2 hours improves survival without BPD compared to surfactant therapy >2 hours. Protein-containing surfactants, either animal derived or newer synthetic surfactants with peptide analogues, are more beneficial in improving BPD-free survival compared to the older protein-free surfactants. Late surfactant exhaustion may contribute to the development of BPD, although the TOLSURF trial of late surfactant dosing in ventilated preterm infants receiving iNO did not improve survival without BPD.

Administration of a surfactant avoiding standard endotracheal intubation such as intratracheal instillation of a surfactant with a thin catheter (e.g., nasogastric tube), typically referred to as less invasive surfactant administration (LISA) or minimally invasive surfactant therapy, has been shown to reduce BPD among survivors by 30%.

E. Human milk is perhaps the most underrated strategy to prevent BPD. Breast milk is the preferred nutrition for all preterm infants. In addition to the known reduction in necrotizing enterocolitis (NEC) and late-onset sepsis, recent observational studies have shown that it reduces the risk of BPD. The odds of BPD reduced by 9.5% for every 10% increase in the use of mother's own milk (MOM).

F. PDA. We consider treatment of a hemodynamically significant PDA in infants who have respiratory decompensation or cannot be weaned from mechanical ventilation (see Chapter 41).

G. Fluid management. Initial fluid intake is limited to the minimum required. Initially, we provide intake adequate to maintain urine output of at least 1 mL/kg/hour and serum sodium concentration of 140 to 145 mEq/L. In the chronic phase, we may limit fluids to as low as 130 mL/kg/day with monitoring for adequate urine output and attention to higher-caloric-density nutrients to provide sufficient calories for growth. We regularly recalculate fluid intake for weight gain, once it is above the birth weight. Later, when respiratory status is stable, fluid restriction is gradually relaxed.

H. Medications. When an infant remains ventilator-dependent on restricted fluid intake in the absence of PDA or intercurrent infection, we consider trying additional pharmacologic strategies.

1. **Diuretics** are used to treat pulmonary fluid retention. They indirectly attenuate signs of respiratory distress and result in decreased Rrs and increased Crs; gas exchange is variably affected. An acute clinical response may be seen within 1 hour, although maximal effect may not be achieved until 1 week of therapy. The clinical improvement is likely due to decreased lung water content, with decreased interstitial and peribronchial fluid resulting in less resistance and

better compliance. The mechanisms of action may be due to either diuretic or nondiuretic effects. Diuretics have not been shown to improve long-term clinical measures such as duration of ventilator dependence, hospital length of stay, or the incidence of BPD.

a. **Furosemide is used initially** at a dose of 1.0 mg/kg intravenously (or 2 mg/kg PO/pg) daily. We give furosemide at the time of blood transfusions if these have been associated with increased pulmonary fluid and respiratory distress. Immature infants are at an increased risk for toxicity from larger or more frequent doses because of the prolonged drug half-life. Side effects include hypercalciuria, nephrocalcinosis, ototoxicity, electrolyte imbalance, and nephrolithiasis.

b. **Chlorothiazide.** If a trial of furosemide given on 3 consecutive days suggests clinical improvement, we prefer treatment with chlorothiazide (20 to 40 mg/kg/day orally, divided BID) or hydrochlorothiazide (2 to 4 mg/kg/day orally, divided BID) to avoid furosemide toxicities. Thiazide diuretics decrease calcium excretion and, if used in combination with furosemide, may minimize calcium loss and reverse nephrocalcinosis due to furosemide. The combination may allow for the use of a lower furosemide dose, although we prefer to use a thiazide diuretic alone.

2. **Bronchodilators.** Acute obstructive episodes or chronically increased resistance may be related to increased airway tone or bronchospasm and may respond to bronchodilator therapy. In general, bronchodilators are most commonly used in older infants who remain ventilator-dependent; however, airway reactivity has been reported as early as 2 to 3 weeks of age in some infants.

   a. Administration of nebulized β-adrenergic agonists (BAAs) such as albuterol results in decreased Rrs and increased Crs and can be administered by metered-dose inhaler (MDI) with a spacer devise placed in line with the ventilator near the endotracheal tube.

   b. MDI (one puff) or nebulized (25 mg/kg/dose) ipratropium bromide, a muscarinic agent, increases Crs and decreases Rrs. Combination MDI containing both BAAs and muscarinic agents may provide a synergistic effect, but this has not been studied in preterm infants.

3. **Caffeine citrate.** The methylxanthine caffeine has airway dilation effects in asthmatics similar to aminophylline. This response has not been studied in the setting of BPD; however, infants with known airway reactivity who are weaning off caffeine should be observed for possible respiratory deterioration.

4. **Steroids.** There is no clear indication for the use of systemic/enteral steroids in established BPD. In clinical practice, a short course of oral steroids is often used during BPD "exacerbation" or intercurrent viral illness to reduce work of breathing or to wean off supplemental oxygen.

5. **Medications for pain control.** Pain management and sedation are used for physical or autonomic signs of pain or discomfort. These responses may interfere with the ability to ventilate and oxygenate. Oral sucrose, morphine sulfate or fentanyl, and short-acting benzodiazepines (in term infants) may be used (see Chapter 70).

6. **Electrolyte supplements.** Hyponatremia, hypokalemia, and hypochloremia with secondary hypercarbia are the common side effects of chronic diuretic therapy that are corrected by lowering the diuretic dose or adding NaCl and KCl supplements. Adequate sodium intake should be provided. We provide NaCl supplement when serum sodium level falls to or below 130 mEq/L. Although hypochloremia may occur with compensated respiratory acidosis, low serum chloride concentration from diuretic-induced loss and inadequate intake can cause metabolic alkalosis and $PaCO_2$ elevation. Hypochloremia may also contribute to poor growth. Chloride deficit should be corrected with KCl. Electrolytes should be monitored at regular intervals until equilibrium is reached (see Chapter 23).

I. Monitoring (see Chapter 30)

1. **ABG** analysis is used to monitor gas exchange and confirm correlation of noninvasive monitoring values.
2. We use **continuous pulse oximetry** for long-term monitoring of infants with BPD. The long-term goal is to keep the saturation >90 (PaO_2 ≥55 mm Hg) and avoid hyperoxemia (saturation 95).
3. **Capillary blood gas** (CBG) values are useful to monitor pH and PCO_2. Because pH and PCO_2 on CBGs sometimes vary from central values, we may compare them with ABG values if we have clinical concerns. If CBG and ABG values are similar, we monitor stable ventilator-dependent infants with pulse oximetry and one or two CBG analyses per day initially, and then less often if clinical condition remains unchanged. Less frequent CBG measurements are obtained for patients receiving supplemental oxygen with CPAP or HHHFNC, or by low-flow NC.
4. **Transcutaneous PCO_2 monitors** have undergone recent technical improvements so that they require less frequent calibration and operate at lower temperatures (minimizing skin injury). They may be useful to monitor PCO_2 trends, which allow more real-time ventilator adjustment to both minimize barotrauma and respond earlier to decompensations.
5. **Pulmonary function testing** is used in some centers to document functional responses to trials of bronchodilators and diuretics.

J. Nutrition (see Chapter 21)

1. **Metabolic rate** and energy expenditure are elevated in BPD, although caloric intake may be poor. Providing more calories by the administration of lipids instead of carbohydrates lowers the respiratory quotient, thereby diminishing CO_2 production. To optimize growth, we try to minimize wasteful energy expenditure and maximize caloric and protein intake. Prolonged parenteral nutrition may be required. Early administration of fish oil–containing lipid emulsions reduces inflammatory mediators IL-1β and IL-6 and is associated with a shorter duration of ventilatory support and less BPD. As enteral feeding is started, we feed by orogastric or nasogastric tube and advance oral feeding gradually to avoid tiring the infant. We increase the caloric density from 24 to 30 cal/oz human milk or formula, as required, to maintain daily growth of at least 10 to 15 mg/kg. All efforts are made to provide MOM to the infant, which is shown to reduce the risk of BPD. The next option is donor human milk.

2. **Vitamin, trace element, and other dietary supplementation.** Vitamin E and antioxidant enzymes diminish oxidant toxicity, although vitamin E supplementation does not prevent BPD. Vitamin A may promote epithelial repair and minimize fibrosis. Selenium, zinc, and copper are trace elements vital to antioxidant enzyme function, and inadequate intake may interfere with protection.

K. Blood transfusions. We generally maintain hematocrit approximately 30% to 35% (hemoglobin 8 to 10 g/dL) as long as supplemental O_2 or ventilator support is needed. Fluid-sensitive patients may benefit from furosemide given immediately following the transfusion. Improved O_2 delivery may allow better reserves for growth in the infant with increased metabolic demands.

L. Behavioral factors. Attention to behavioral and environmental factors through individualized developmental care plans may minimize BPD risk and severity (see Chapter 14).

VII. ASSOCIATED COMPLICATIONS

A. Upper airway obstruction. Trauma to the nasal septum, larynx, trachea, or bronchi is common after prolonged or repeated intubation and suctioning. Abnormalities include laryngotracheobronchomalacia, granulomas, vocal cord paresis, edema, ulceration with pseudomembranes, subglottic stenosis, and congenital structural anomalies. Stridor may develop when postextubation edema is superimposed on underlying stenosis. Abnormalities are not excluded by the absence of stridor and may be asymptomatic, becoming symptomatic at the time of a viral upper respiratory tract infection. We consult otolaryngology specialists to perform flexible fiberoptic bronchoscopy to evaluate stridor, hoarseness, persistent wheezing, recurrent obstruction, or repeated extubation failures.

B. Pulmonary hypertension (PH) is a major complication of BPD that is associated with a 2-year mortality rate of 38% to 43% after diagnosis. The development of PH in infants with BPD may involve both reversible and fixed components. Chronic hypoxemia leads to hypoxic vasoconstriction, PH, and eventual right ventricular hypertrophy and failure. Decrease in cross-sectional perfusion area and abnormal muscularization of more peripheral vessels have been documented. Left ventricular function also can be affected.

1. Supplemental O_2 is used to maintain SaO_2 between 92% and 95% or higher in infants with mature retinas. We obtain an echocardiogram by 36 to 37 weeks' PMA in infants with BPD who still require assisted ventilation or an inspired O_2 concentration of >30% to maintain adequate O_2 saturation, or have a PCO_2 of ≥60 mm Hg. In the more severely affected infants, we may begin monitoring as early as 32 weeks' PMA. These studies can exclude structural heart disease, assess left ventricular function, and estimate pulmonary vascular resistance and right ventricular function. Further studies are needed to determine whether earlier screening echocardiograms in the first month of life can identify the development of PH in infants with BPD.
2. iNO is a useful therapy in the setting of acute PH and may improve oxygenation in infants with established BPD, although efficacy of iNO in long-term treatment of PH associated with BPD has not been determined. Sildenafil, a phosphodiesterase-5 inhibitor, may also improve oxygenation in patients

with PH associated with BPD. It offers the benefits of oral dosing and a long half-life, making administration at scheduled intervals of time possible. Other pulmonary vasodilators, including calcium channel blockers such as nifedipine and endothelin receptor antagonists such as bosentan, remain investigational in infants with BPD. We monitor the response to therapy with serial echocardiograms to follow pulmonary vascular pressures and right ventricular function. Patients with persistent PH in spite of treatment may need further evaluation by cardiac catheterization to delineate their pulmonary vascular anatomy and disease severity.

C. Systemic hypertension, sometimes with left ventricular hypertrophy, may develop in infants with BPD receiving prolonged O_2 therapy and should be treated (see Chapter 28).

D. Systemic-to-pulmonary shunting. Left-to-right shunt through collateral vessels (e.g., bronchial arteries) can occur in BPD. Risk factors include chest tube placement, thoracic surgery, and pleural inflammation. When left-to-right shunt is suspected and echocardiography fails to show intracardiac or PDA shunting, angiography may demonstrate collaterals. In this setting, occlusion of large vessels has been associated with clinical improvement.

E. Metabolic imbalance secondary to diuretics (see section V.H.1 and V.H.6)

F. Infection. Because these chronically ill infants are at an increased risk, episodes of pulmonary and systemic decompensation should be evaluated for infection. Viral and fungal infections should also be considered when fever or pneumonia develops. In infants with unresponsive clinical courses, we may assess tracheal aspirates for the presence of *Ureaplasma* sp. and *Mycoplasma hominis* and treat if these organisms are identified. Postnatal cytomegalovirus (CMV) infection has been associated with an increased risk of BPD. One must consider excluding all infections before postnatal steroids are initiated for BPD.

G. Central nervous system (CNS) dysfunction. A neurologic syndrome presenting with extrapyramidal signs has been described in infants with CLD.

H. Hearing loss. Ototoxic drugs (furosemide, gentamicin) and ischemic or hypoxemic CNS injury increase the risk of sensorineural hearing loss. Screening with auditory brainstem responses should be performed at discharge (see Chapter 68).

I. ROP (see Chapter 67). ELBW infants with BPD are at a high risk for developing ROP. Use of phenylephrine-containing eye drops before eye examinations can cause an increase in airway resistance in some infants with BPD.

J. Nephrocalcinosis is frequently documented on ultrasonographic examination and has been linked to the use of furosemide and possibly steroids. Hematuria and passage of stones may occur. Most infants are asymptomatic, with eventual spontaneous resolution, but renal function should be followed (see Chapter 28).

K. Osteopenia may result from prematurity, inadequate calcium and phosphorus retention, and prolonged immobilization. Calcium loss due to furosemide and corticosteroids may also contribute. Supplementation with vitamin D, calcium, and phosphorus should be optimized (see Chapters 21 and 59).

L. Gastroesophageal reflux (GER). We try to document and treat GER in older infants when reflux or aspiration may contribute to pulmonary decompensation, apnea, or feeding intolerance with poor growth. Because trials have not shown

acid neutralization and propulsive agents to be effective, we attempt management with optimized positioning, avoid excessive feeding volumes, and thicken feeds if needed. If decompensations associated with feeding may be related to swallow discoordination and microaspiration, we obtain fluoroscopic evaluations of swallowing while feeding contrast-laced human milk or formula to document aspiration. If aspiration is present, we sometimes test modification of feed viscosity. If nectar-thick feedings do not eliminate aspiration, we temporarily halt oral feeding and revert to nasogastric feeding until we confirm that aspiration with feeding has resolved. In severe cases, a gastrostomy tube and possible fundoplication may help avoid aspiration until swallow coordination has adequately matured.

M. Inguinal hernia. The incidence of inguinal hernia is increased by the presence of the patent processus vaginalis in very low-birth-weight (VLBW) infants, particularly boys, with BPD. If the hernia is reducible, surgical correction should be delayed until respiratory status is improved. Spinal, rather than general, anesthesia avoids reintubation and postoperative apnea.

N. Early growth failure may result from inadequate intake and excessive energy expenditure and may persist after clinical resolution of pulmonary disease. Premature withdrawal of supplemental O_2 may contribute to slowing of growth.

VIII. DISCHARGE PLANNING.

The timing of discharge depends on the availability of home care support systems and parental readiness (see Chapter 18).

A. Weight gain and oxygen therapy. Supplemental O_2 should be weaned when the SpO_2 is consistently maintained >92%, no significant periods of desaturations occur during feedings and/or sleep, good weight gain has been established, and respiratory status is stable. We prefer to delay discharge until O_2 has been discontinued. However, if long-term O_2 supplementation seems likely in an infant who is stable, is growing, and has capable caretakers, we offer the option of home O_2 therapy.

B. Teaching. The involvement of parents in caregiving is vital to the smooth transition from hospital to home care. Parents should be taught cardiopulmonary resuscitation and early signs of decompensation. Teaching about equipment use, medication administration, and nutritional guidelines should begin when discharge planning is initiated.

C. Documentation. Baseline values of vital signs, daily weight gain, discharge weight and head circumference, blood gases, SpO_2, hematocrit, electrolytes, and the baseline appearance of the chest radiograph and ECG are documented at discharge. Echocardiograms are obtained in more severely affected infants. This information is useful to evaluate subsequent changes in clinical status. Follow-up eye examination and hearing screening should be scheduled as needed.

D. Subspecialist and multidisciplinary management. Prior to discharge, we arrange for a baseline evaluation and interaction with the parents by the pulmonologist, cardiologist, and other subspecialists who will follow the infant as an outpatient.

IX. OUTPATIENT THERAPY

A. Supplemental oxygen can be delivered by tanks or an O_2 concentrator. Portable tanks allow mobility. Weaning is based on periodic assessment of SpO_2.

B. Medications. We monitor electrolytes periodically in infants receiving diuretics. When the infant is stable, we allow him or her to outgrow the diuretic dose by 50% before discontinuing the drug. If bronchodilators have been used, they are tapered when respiratory status is stable in room air. Nebulized medications are tapered last. Discontinued medications should remain available for early use when symptoms recur.

C. Immunizations. In addition to standard immunizations, infants with BPD should receive pneumococcal and influenza vaccines and palivizumab (Synagis) (see Chapter 16). Family members are also advised to take vaccines against influenza and pertussis while the baby is in the NICU itself.

D. Nutrition. Weight gain is a sensitive indicator of well-being and should be closely monitored. Infants often require caloric supplementation to maintain good growth after discharge. At discharge, we supplement calories in a transitional formula or, optimally, breast milk.

E. Passive 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. OUTCOME

A. Mortality in severe BPD is estimated at 10% to 20% during the first year of life. The risk increases with the duration of O_2 exposure and level of ventilatory support. Death is frequently caused by infection. The risk of sudden, unexpected death may be increased, but the cause is unclear.

B. Long-term morbidity

1. **Pulmonary.** Tachypnea, retractions, dyspnea, cough, and wheezing can be seen for months to years in seriously affected children. Reactive airway disease occurs more frequently, and infants with BPD are at an increased risk for bronchiolitis and pneumonia. The rehospitalization rate for respiratory illness during the first 2 years of life in infants with BPD is approximately twice that in matched-control infants. Although complete clinical recovery can occur, the underlying pulmonary function, gas exchange, and radiographic abnormalities may persist beyond adolescence. Persistent parenchymal and airway abnormalities are detectable on high-resolution computed tomography (CT) scans of children and adults with a previous history of BPD. In addition, respiratory symptoms such as wheezing and lung functional abnormalities are also seen with higher frequency in these individuals. CRM measures at 6 and 12 months corrected age are being evaluated as potential outcomes in studies of early therapeutic interventions aimed at preventing or attenuating BPD.
2. **Neurodevelopmental delay/neurologic deficits.** BPD is an independent predictor of adverse neurologic outcome. Respiratory and neural injury may be due to a common antecedent such as oxidative stress. Children with BPD have higher rates of motor, cognitive, educational, and behavioral impairments.
3. **Growth failure.** The degree of long-term growth delay is inversely proportional to birth weight and probably is influenced by the severity and duration

of CLD. Weight is most affected, and head circumference is least affected. Delayed growth (<2 standard deviation for the mean) in weight persists in approximately 20% of the infants and in length and head circumference in approximately 10% of infants at 20 months corrected age.

Suggested Readings

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35 Meconium Aspiration

Erin J. Plosa

KEY POINTS

- Meconium aspiration occurs due to the combination of meconium-stained amniotic fluid (MSAF) and gasping by the fetus or newly born. Most cases appear to be caused by intrauterine pathology.
- Routine intrapartum oral suctioning and/or endotracheal suctioning of nonvigorous infants born through MSAF is no longer 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 10% to 15% of deliveries. Incidence of MSAF has decreased significantly in developed countries due to better perinatal care but remains high in developing countries. The incidence of MSAF in preterm infants is very low. Most babies with MSAF are 37 weeks or older, and many meconium-stained infants are postmature and small for gestational age. Approximately 3% to 4% of neonates born through MSAF develop meconium aspiration syndrome (MAS) in Western countries, but a higher incidence of around 11% to 28% is reported in the developing world. Approximately 30% to 50% of these infants require continuous positive airway pressure (CPAP) or mechanical ventilation.

II. PATHOPHYSIOLOGY.

Meconium is a sterile, thick, black-green, odorless material that results from the accumulation of debris in the fetal intestine starting in the third month of gestation. 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.

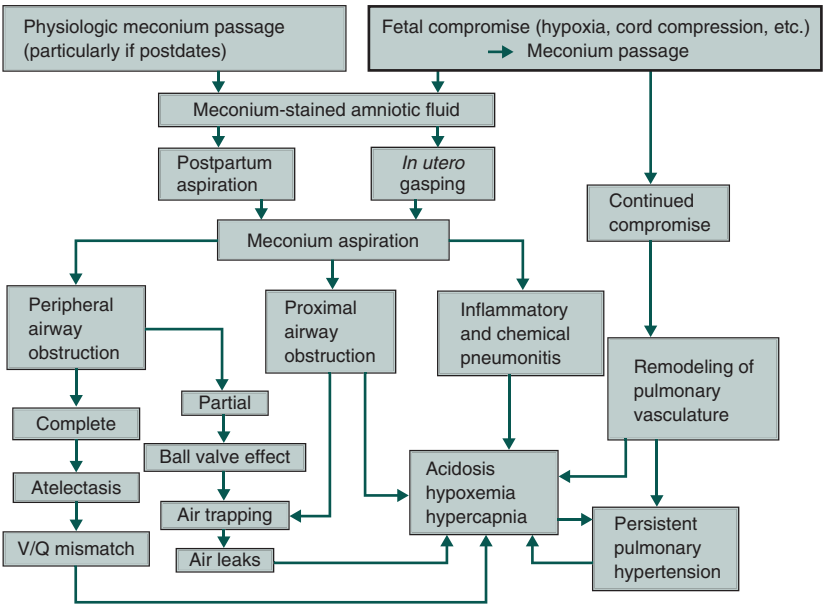

Figure 35.1. Pathophysiology of meconium aspiration. V/Q, ventilation–perfusion ratio. (From Wiswell T, Bent RC. Meconium staining and the meconium aspiration syndrome: unresolved issues. *Pediatr Clin North Am* 1993;40:955–981. Used with permission.)

A. Passage of meconium *in utero*. MSAF occurs more commonly in term or post-term pregnancies and rarely prior to 34 weeks' gestation. It may result from a post-term fetus with rising motilin levels and normal gastrointestinal function, vagal stimulation produced by cord or head compression, or *in utero* fetal stress. The amniotic fluid that is thinly stained is described as *watery*. The moderately stained fluid is opaque without particles, and fluid with thick meconium with particles is sometimes called *pea soup*. The severity of MAS appears not to be related to thickness of MSAF.

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 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 that leads to extrapulmonary right-to-left shunting through the ductus arteriosus or the foramen ovale, resulting in worsened ventilation–perfusion (V/Q) 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 of the 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. It is considered severe in infants who require assisted ventilation and/or CPAP 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 the 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, post-term pregnancy, and heavy smokers. These women should be carefully monitored during pregnancy.

B. Amnioinfusion. Amnioinfusion is associated with substantive improvements in the perinatal outcome only in settings where facilities for perinatal surveillance are limited. It is not clear whether the benefits are due to dilution of meconium or relief of oligohydramnios. In settings with standard peripartum surveillance, either amnioinfusion is ineffective or its effects are masked by other strategies to optimize neonatal outcome.

C. Timing and mode of delivery. In pregnancies that continue past the due date, induction as early as 41 weeks may help prevent MAS by avoiding the passage of meconium. The delivery mode does not appear to impact the risk of aspiration.

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. Although intubation and endotracheal suctioning for meconium in nonvigorous infants were previously recommended, evidence to support this intervention in improving respiratory and neurodevelopmental outcomes is insufficient, and this procedure is no longer recommended. According to the 2015 Neonatal Resuscitation 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 (see Chapter 4).

If an infant does not improve with intubation and positive-pressure ventilation, the trachea may be obstructed by thick secretions, including meconium. 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 recommended suction pressure should be less than 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. A chest radiograph may help determine those infants who are most likely to develop respiratory distress, although a significant number of asymptomatic infants will have an abnormal-appearing chest film. The classic roentgenographic findings are diffuse, asymmetric patchy infiltrates, areas of consolidation, often worse on the right, and hyperinflation.
2. Monitoring of oxygen saturation during this period aids assessment of the severity of the infant's condition and avoids hypoxemia.

B. Care for neonate with meconium aspiration syndrome

1. The infant should be maintained in a neutral thermal environment, and tactile stimulation should be minimized.
2. Blood glucose and calcium levels should be assessed and corrected if necessary. Severely depressed infants may have severe metabolic acidosis that may need to be corrected.
3. Infants may also require specific therapy for hypotension and poor cardiac output, including cardiotonic medications such as dopamine.
4. Circulatory support with normal saline or packed red blood cells should be provided in patients with marginal oxygenation. In infants with substantial oxygen and ventilator requirements, we usually maintain a hemoglobin concentration above 15 g (hematocrit above 40%).
5. Renal function should be continuously monitored (see Chapter 28).
6. We avoid chest physiotherapy because of the potential adverse effect of exacerbating PPHN.
7. Airway and oral suctioning may be required 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 and by monitoring blood gases and pH. 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 FiO_2 requirements exceed 0.40, a trial of CPAP may be considered. CPAP is often helpful, and the appropriate pressures must be individualized for each infant. However, CPAP may sometimes aggravate air trapping and should be instituted with caution if hyperinflation is apparent clinically or radiographically.
2. **Mechanical ventilation.** Infants with severe disease may have substantial gas exchange abnormalities. Mechanical ventilation is indicated for excessive

carbon dioxide retention ($PaCO_2$ >60 mm Hg) or for persistent hypoxemia (PaO_2 <50 mm Hg).

a. Peak inspiratory pressure (PIP) must be limited to pressures resulting in gentle chest movement and tidal volumes 5 to 6 mL/kg; 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 seconds at a rate of 30 to 40 breaths per minute. Some infants may respond better to conventional ventilation at more rapid rates.

c. 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. There are no prospective, randomized controlled trials comparing the efficacy of the various ventilator modes in MAS.

3. **Inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO)** 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 the bacterial disease, if present, and to determine the duration of the antibiotic course.

2. **Surfactant.** Endogenous surfactant activity may be inhibited by meconium and 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. Bronchoalveolar lavage with dilute surfactant might be beneficial in MAS. But there are only a few studies, and the results are inconsistent to make a clear recommendation.

3. **Corticosteroids.** We do not routinely 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 neonatal intensive care unit stay. However, these studies did not show a difference in mortality and did not address differences in neurodevelopmental outcomes.

4. **Sedatives.** The use of sedation and muscle relaxation (rarely) may be warranted in infants who require mechanical ventilation (see Chapter 36).

5. **Antioxidants.** The use of antioxidants such as *N*-acetylcysteine and recombinant human superoxide dismutase to mitigate reactive oxygen species (ROS)–induced lung injury in MAS has been recently investigated in animal models. Human studies are needed to define the efficacy and potential adverse effects in infants with MAS.

F. Complications

1. **Air leak.** Pneumothorax or pneumomediastinum occurs in approximately 15% to 33% of patients with MAS. Air leaks occur more frequently with mechanical ventilation, especially in the setting of air trapping. A high index of suspicion for air leak is necessary. Equipment should be available to evacuate a pneumothorax promptly (see Chapter 38).
2. **PPHN** is associated with MAS in approximately one-third of cases and contributes to the mortality associated with this syndrome (see Chapter 36). Depending on the extent of hypoxemia, echocardiography should be performed to ascertain the degree to which the right-to-left shunting is contributing to the infant's overall hypoxemia and to exclude congenital heart disease as the etiology. In severely ill infants with MAS and PPHN, iNO reduces the need for ECMO.
3. **Pulmonary sequelae.** Approximately 5% of survivors require supplemental oxygen at 1 month and a substantial proportion may have an abnormal pulmonary function, including increased functional residual capacity, airway reactivity, and a higher incidence of pneumonia.

Suggested Readings

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36 Persistent Pulmonary Hypertension of the Newborn

Linda J. Van Marter and Christopher C. McPherson

KEY POINTS

- Severe refractory hypoxia in a newly born baby is likely to be due to failed transition from fetal to neonatal circulation (persistent pulmonary hypertension of the newborn [PPHN]), immediate care is necessary to prevent mortality and neuromorbidity.
- PPHN is a common comorbidity in babies with asphyxia and meconium aspiration syndrome (MAS).
- An echocardiogram (ECHO) is an essential component of evaluation. Higher pulmonary than systemic vascular resistance leads to right-to-left shunting (across patent foramen ovale and patent ductus arteriosus); intrapulmonary shunts cannot be demonstrated on ECHO.
- ECHO is important to exclude cyanotic congenital heart disease. Ventricular function is an important determinant of outcomes and guides therapy such as milrinone.
- In babies with PPHN associated with lung disease (white lung on x-ray) such as MAS, respiratory distress syndrome in late preterm, and congenital pneumonia early surfactant therapy and optimal pressures (high-frequency ventilation) to recruit alveoli are most important.
- Inhaled nitric oxide is a targeted evidence-based therapy and is associated with significant survival benefits and decreased need for ECMO.
- Supportive care includes optimizing hemoglobin, blood glucose, and calcium, and minimizing agitation.
- Therapies used in the past—hyperventilation and alkali therapy—are associated with risks and not recommended.

I. DEFINITION. Persistent pulmonary hypertension of the newborn (PPHN) presents as severe unresponsive hypoxic respiratory failure. It reflects failure of the transition of fetal to neonatal circulation. Fetal circulation is characterized by high pulmonary vascular resistance (PVR) that normally falls rapidly at birth, allowing blood flow through the lungs. If PVR remains high and does not fall below systemic vascular resistance (SVR), blood flows from right to left across the patent foramen ovale (PFO) and patent ductus arteriosus (PDA) resulting in severe hypoxia. PPHN is associated with a high mortality risk and risk of neurodevelopmental disabilities. Contemporary neonatal intensive care, including ventilator management, surfactant therapy, high- frequency ventilation, inhaled nitric oxide (iNO), and extracorporeal

membrane oxygenation (ECMO), collectively has improved survival among infants with PPHN.

Perinatal circulatory transition. The normal perinatal circulatory transition is characterized by a rapid fall in PVR accompanying the first breath and a marked increase in SVR associated with clamping of the umbilical cord. Increased arterial oxygen content, increase in pH, and lowered $PaCO_2$ cause rapid fall in PVR. These physiologic events raise SVR relative to PVR, cause functional closure of the foramen ovale, and signal the normal perinatal transition in pulmonary and systemic circulations.

PPHN physiology mimics the fetal circulation in which PVR exceeds SVR and right-to-left hemodynamic shunting occurs through the foramen ovale and/or ductus arteriosus. Because of the similarity to the cardiovascular physiology of fetal life, PPHN also has been called "persistent fetal circulation." Before birth, this circulatory configuration results in systemic delivery of oxygenated blood from the placental circulation; if this circulation continues in postnatal life, it causes blood to bypass the lungs and results in severe hypoxia.

II. EPIDEMIOLOGIC ASSOCIATIONS.

PPHN occurs at a rate of 1 to 2 per 1,000 live births and is most common among full-term and post-term infants. Perinatal risk factors reported in association with PPHN include meconium-stained amniotic fluid and maternal conditions such as fever, anemia, and pulmonary disease. Case–control studies of risk factors for PPHN suggest associations between PPHN and several antenatal and perinatal factors, including maternal diabetes mellitus, urinary tract infection during pregnancy, selective serotonin reuptake inhibitor (SSRI) consumption during pregnancy, and cesarean section delivery. Male infants and those of black or Hispanic race are also at an increased risk for PPHN. Although mechanisms of antenatal pathogenesis remain uncertain, there are a number of additional perinatal and neonatal conditions that have well-established links with PPHN.

A. Perinatal asphyxia is the most common associated comorbidity. Long-standing fetal stress and hypoxemia lead to remodeling and *abnormal muscularization* of pulmonary arterioles. Acute birth asphyxia also causes release of vasoconstricting humoral factors and suppression of pulmonary vasodilators, thus contributing to pulmonary vasospasm.

B. *Pulmonary parenchymal diseases*, including surfactant deficiency, pneumonia, and aspiration syndromes, such as meconium aspiration, also are associated with an increased risk of PPHN. In most such cases, the pulmonary hypertension is easily reversible, suggesting a transient vasospasm. The risk of pulmonary hypertension appears to be greater when the fetus is of more advanced gestational age, suggesting that the stage of pulmonary vascular development might play a role in susceptibility to PPHN.

C. Abnormalities of *pulmonary development* contribute structurally to PPHN, either by pruning of the vascular tree, as occurs in congenital diaphragmatic hernia, Potter's syndrome, and other forms of pulmonary parenchymal hypoplasia, or by malalignment of pulmonary veins and arteries, as is seen in alveolar capillary dysplasia.

D. Pneumonia and/or sepsis of bacterial or viral origin can initiate PPHN. Underlying pathophysiologic mechanisms that contribute to pulmonary hypertension in this clinical setting include suppression of endogenous nitric oxide

(NO) production, endotoxin-mediated myocardial depression, and pulmonary vasoconstriction associated with release of thromboxanes.

E. Myocardial dysfunction, myocarditis, intrauterine constriction of the ductus arteriosus, and several forms of congenital heart disease, including left- and right-sided obstructive lesions, can lead to pulmonary arterial/venous hypertension.

F. Although familial recurrence of PPHN is uncommon, genetic predisposition might play a role in PPHN risk. Infants with PPHN have low plasma levels of arginine and NO metabolites and also exhibit diminished endothelial nitric oxide synthase (eNOS) expression. Polymorphisms associated in case reports of PPHN involve several genes, including ABCA3, TMEM70 (mitochondrial), CRHR1, ACE, and SPINK5 (Netherton's syndrome). Furthermore, PPHN associated with alveolar capillary dysplasia has been linked with mutation of FOXF1.

III. PATHOLOGY AND PATHOPHYSIOLOGY

A. Pulmonary vascular remodeling is pathognomonic of idiopathic PPHN and has been reported among a series of infants with fatal PPHN. Abnormal muscularization of the normally nonmuscular intra-acinar arteries, with increased medial thickness of the larger muscular arteries, results in a decreased cross-sectional area of the pulmonary vascular bed and elevated PVR. Mechanisms leading to the vascular remodeling in PPHN are under investigation. One possible stimulus to pulmonary vascular remodeling is fetal hypoxemia. Humoral growth factors released by hypoxia-damaged endothelial cells promote vasoconstriction and overgrowth of the pulmonary vascular muscular media. Laboratory and limited clinical data suggest that vascular changes might also occur following fetal exposure to nonsteroidal anti-inflammatory agents that cause constriction of the fetal ductus arteriosus and associated fetal pulmonary overcirculation.

B. Pulmonary hypoplasia affects both alveolar and pulmonary arteriolar development. It may be an isolated anomaly or be a part of congenital diaphragmatic hernia, oligohydramnios syndrome, or renal agenesis (i.e., Potter's syndrome)

C. Reversible pulmonary vasospasm is the likely pathophysiologic mechanism among infants with nonfatal PPHN, often due to lung disease, infections, or acute asphyxia. Hypoxia induces profound pulmonary vasoconstriction, and this response is exaggerated by acidemia. Neural and humoral vasoactive substances each might contribute to the pathogenesis of PPHN. These include factors associated with platelet activation and production of arachidonic acid metabolites. Suppression of endogenous NO, prostacyclin, or bradykinin production and release of thromboxanes (A_2 and its metabolite, B_2), and leukotrienes (C_4 and D_4), appear to mediate the increased PVR seen with sepsis and hypoxemia.

D. Myocardial dysfunction with elevated PVR. Congenital diaphragmatic hernia is often associated with intractable PPHN. A combination of right ventricular (RV) hypertrophy and/or failure and left ventricular (LV) hypoplasia (because of reduced pulmonary venous return during fetal life) with pulmonary venous hypertension results in severe PPHN. This kind of PPHN will not respond to conventional pulmonary vasodilator therapy, until ventricular function improves.

1. **RV dysfunction** can be caused by intrauterine constriction of the ductus arteriosus, which results in higher PVR, RV failure, and an atrial right-to-left shunt.

Furthermore, RV failure resulting in altered diastolic compliance causes right-to-left atrial shunting, even in the absence of elevated PVR.

2. **LV dysfunction** causes pulmonary venous hypertension and secondary pulmonary arterial hypertension (PAH), often to suprasystemic levels, contributing to right-to-left hemodynamic shunting through the ductus arteriosus. Treating this form of pulmonary hypertension requires an approach that improves LV function rather than simply lowering PVR.

E. Mechanical factors that influence PVR include cardiac output and blood viscosity. Low cardiac output recruits fewer pulmonary arteriolar channels, and raises PVR by this mechanism as well as by its primary effect of lowering mixed venous oxygen content. Hyperviscosity, associated with polycythemia, reduces pulmonary microvasculature perfusion.

IV. DIAGNOSIS. PPHN should always be considered in evaluating a cyanotic newborn with disproportionate oxygen requirement and lability in saturation.

A. Among cases of suspected PPHN, the most common **alternative diagnoses** are congenital cyanotic heart disease (CCHD), sepsis, and severe pulmonary parenchymal disease.

B. The infant with PPHN appears very sick and has unresponsive cyanosis. In some infants, the cyanosis might be appreciably different between regions perfused by preductal and postductal vasculature (differential cyanosis). The cardiac examination may be normal, or there may be a prominent precordial impulse, a single or narrowly split and accentuated second heart sound, and sometimes, a systolic murmur consistent with tricuspid regurgitation (TR). A significant murmur misleads the neonatologist and CCHD looks the likely diagnosis.

C. A **gradient of 10% or more in oxygenation saturation** between simultaneous preductal (right upper extremity) and postductal (lower extremity) arterial blood gas (ABG) values or transcutaneous oxygen saturation (SaO_2) measurements documents the presence of a ductus arteriosus right-to-left hemodynamic shunt and suggests PPHN. Because a subset of infants with PPHN has closure of the ductus arteriosus and their hemodynamic shunting occurs only at the foramen ovale, the absence of differential cyanosis or SaO_2 does not exclude PPHN.

D. The **chest radiograph** usually appears normal or shows associated pulmonary parenchymal disease. The cardiothymic silhouette is normal, and pulmonary blood flow is normal or diminished.

E. The **electrocardiogram (ECG)** most commonly shows RV predominance that is within the range considered normal for age. Less commonly, an axis that is left (or "normal") suggests poor RV function and poor prognosis. An abnormal axis may also point to CCHD.

F. An **echocardiographic study** should be performed in all infants with suspected PPHN to confirm diagnosis by measuring pulmonary artery (PA) pressures and shunting patterns across PDA and PFO, evaluate ventricular function, and exclude conditions mimicking PPHN. Echocardiography is the clinical gold standard diagnostic tool in PPHN.

- Assessment of PA pressures. Systolic PA pressure is measured by TR jet peak velocity + mean right atrial (RA) pressure (mean pressure in central venous line

can be used as a surrogate) and mean PA pressure is assessed by peak pulmonary regurgitation (PR) jet velocity + mean RA pressure.

- The severity of PAH is best described in relation to aortic pressures (systemic pressures).
- At times when good TR or PR signals are not available, approximate PA systolic pressures can be obtained by assessing the end-systolic position of the intact interventricular septum (IVS). The PA systolic pressure is suprasystemic if the IVS bows into the left ventricle (banana-shaped LV) and PA systolic pressure is more than 50% of systemic pressure if the IVS is flat.
- Shunting pattern across PFO and PDA may be determined by the color Doppler; the shunting pattern which is normally left to right tends to reverse in PPHN. It is usually bidirectional or purely right to left depending on severity resulting in hypoxia and differential cyanosis.
- Assessment of ventricular function. The RV and LV functions should be assessed for any evidence of dysfunction. Milrinone is preferred if there is evidence of LV or RV dysfunction. iNO is to be used only if LV function is good.
- Excluding PPHN mimics. A number of conditions, associated with secondary pulmonary hypertension, may be misdiagnosed as PPHN. The common conditions to be excluded are the following:

1. **Obstructed total anomalous pulmonary venous connection (TAPVC).** Refractory hypoxemia, absence of differential cyanosis, and white out of the lungs on chest x-ray due to pulmonary venous hypertension are useful clues favoring TAPVC. Initial echocardiographic clues include dilated right heart structures with small left-sided chambers, atrial septal defect (ASD)/patent foramen ovale (PFO) completely shunting right to left, and inability to image the pulmonary veins draining to left atrium (LA). On detailed study, the confluence of pulmonary veins (PVs) and the venous channel (vertical vein) draining to the anomalous site of the right heart can be visualized.
2. **LV outflow obstruction.** These lesions include aortic stenosis, coarctation of aorta, aortic arch interruption, and variants of hypoplastic left heart syndrome. The PAH is secondary to severe pulmonary venous hypertension due to elevated LV end-diastolic pressures resulting from LV dysfunction. Weak or absent lower limb pulses and features of shock with end-organ insult are suggestive features.
3. **Isolated origin of one of the branch PAs from aorta (hemitruncus).** PAH results from direct transmission of systemic pressures to respective pulmonary vascular bed. The systemic oxygenation is usually preserved unless there is reversal of shunt across PFO/PDA from severe PAH.
4. **Vein of Galen malformation.** It refers to a rare lesion presenting with high-output cardiac failure and refractory PAH. Bounding pulses, cardiomegaly, and hepatomegaly along with continuous murmur over anterior fontanelle should alert toward this lesion. The diagnosis is confirmed by cranial ultrasound.
5. **Primary LV myocardial diseases.** These include conditions primarily affecting myocardial function such as myocarditis, cardiomyopathies, endocardial fibroelastosis, and storage disorders (Pompe disease). PAH results from pulmonary venous hypertension secondary to LV dysfunction.

V. MANAGEMENT. PPHN is a medical emergency in which immediate, appropriate intervention is critical to reverse hypoxemia, improve pulmonary and systemic perfusion, and preserve end-organ function. Adequate respiratory support to optimize oxygenation, ventilation (carbon dioxide), and acid–base status (pH) facilitates the fall in PVR. Once stability is achieved, cardiorespiratory support should be tapered conservatively with careful attention to the infant's response to each drop in support.

A. Supplemental oxygen. Hypoxia is a powerful pulmonary vasoconstrictor. Normoxia is the most important pulmonary vasodilator that will dramatically reduce PVR. Ventilation and oxygen (FiO_2) should be administered to maintain adequate PaO_2 (50 to 80 mm Hg) and preductal saturation of 90 to 95. In refractory hypoxia not responding to high ventilator supports, one may accept a lower PaO_2 (40 mm Hg) and postductal saturation of 80%, if perfusion and lactate are normal (one must avoid overventilation to try and reach the magic numbers of saturation; overventilation will critically compromise venous return to the heart and increase PVR and thus seriously worsen the PPHN). Optimal ventilator support would be determined by clinical evaluation, pulmonary graphics, x-rays, and blood gas. Therefore, in the infant with suspected or documented PPHN, preductal and postductal SaO_2 should be continuously monitored. Arterial access is indicated for frequent blood gas and continuous invasive blood pressure monitoring.

Laboratory data suggest that excessive oxygen exposure releases free radicals that worsen pulmonary hypertension. Hyperoxia inactivates surfactant, increases PVR, and contributes to the pathophysiology of PPHN. In addition to direct inactivation of NO, reactive oxygen species can decrease eNOS activity and soluble guanylate cyclase (sGC) activity, and increase phosphodiesterase 5 (PDE5) activity, resulting in decreased cyclic guanosine monophosphate (cGMP) levels that potentiates vasoconstriction. Currently, we aim to maintain preductal SaO_2 low to mid-90s and PaO_2 levels between 50 and 80 mm Hg to ensure adequate tissue oxygenation and avoid hypoxia-induced pulmonary vasoconstriction.

B. Assisted ventilation. Babies with PPHN are severely hypoxic and often have respiratory distress, issues with perfusion, and even poor sensorium; they mostly are on assisted ventilation. Specific approaches to respiratory support and mechanical ventilation vary among centers. Recruitment of the lung is important for any lung strategy that is used.

1. Babies with respiratory distress (retractions) and "white lung" on x-ray, i.e., with atelectasis due to respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), or pneumonia, will benefit with higher positive end-expiratory pressure (PEEP) (6 to 8 mm Hg), modest peak inspiratory pressure (PIP) (not more than 25), modest inspiratory time, and 40 to 60 supported breaths. (These values are just illustrative; actual values will be individualized.) Synchronization with advanced modes of ventilation and analgesia sedation as necessary should minimize agitation, this is very important in management of PPHN. Early use of surfactant in these babies with white lung PPHN and optimal PEEP/MAP will open up the lung; hypoxia, hypercarbia and acidosis correct rapidly. One may need high-frequency ventilation if higher pressures are necessary to optimize oxygen and carbon dioxide exchange. Our approach is to maintain physiologic PaO_2 (50 to 80) and $PaCO_2$ (40 to 50) values, and avoids less and more of both the gases. Because infants with PPHN demonstrate

marked lability, a conservative approach to tapering support is indicated until stability is achieved for 12 to 24 hours.

2. In the absence of pulmonary alveolar disease, as evidenced by not much respiratory distress and black lung on x-ray, the optimal strategy for assisted ventilation employs lower pressures and short inspiratory time to minimize intrathoracic pressure; overventilation decreases pulmonary venous return and cardiac output in addition to increasing PVR.

C. Surfactant has been shown to be a useful adjunctive therapy in cases of primary or secondary (e.g., meconium-induced) surfactant deficiency. Surfactant improves oxygenation (and reduces the need for ECMO) when PPHN is secondary to parenchymal lung disease. Use of surfactant is recommended when there is clinical and radiological evidence of surfactant deficiency. Surfactant therapy helps in pulmonary recruitment. It is better to use it early; maximum benefit is seen in babies with mild disease— oxygenation index (OI) between 15 and 25.

D. iNO. iNO is a produced by endothelial cells. Whether produced by pulmonary endothelium or delivered through the ventilator circuit, NO diffuses into smooth muscle cells, increases intracellular cGMP, relaxes the vascular smooth muscle, and causes pulmonary vasodilation. In the circulation, NO is bound by hemoglobin and biologically inactivated and, therefore, when delivered by inhalation, it causes little or no systemic vasodilation or hypotension. iNO administered by conventional or high-frequency ventilation in doses of 1 to 20 ppm causes pulmonary but not systemic vasodilation and, thus, selectively decreases PVR. In a systematic review conducted by the Cochrane Collaboration, iNO was deemed useful in reducing the need for ECMO among term infants with severe respiratory failure. iNO is most effective when administered after adequate alveolar recruitment. This can be accomplished among infants with PPHN with diffuse pulmonary disease by the concomitant use of high frequency ventilation (HFV) and/or surfactant treatment

1. Starting dose of iNO is 20 ppm. The patient is considered iNO responsive if there is an increase in PaO_2 by 20 mm Hg or more in 20 minutes. As the neonate improves, the first parameter to be weaned is FiO_2; FiO_2 is weaned to 60% in steps, provided PaO_2 stays more than 60 mm Hg. After that, weaning of iNO can be considered. iNO is tapered gradually at intervals no more frequent than every 4 hours: 20 to 15, 15 to 10, 10 to 5, 5 to 2, 2 to 1, and then off. The infant's oxygen saturation in response to each step-down is observed before further weaning and/or discontinuing the medication. Decrease in mean airway pressure (MAP) is guided by clinical and radiological assessment of lung.

2. iNO should not be stopped abruptly; hypoxemia may resurface in babies with unresolved PVR. iNO blunts endogenous production of NO. For this reason, iNO should be tapered very gradually and not discontinued until adequate oxygenation can be maintained at an iNO dose of 1 ppm with an FiO_2 of <50% to 60%. Another pulmonary dilator acting through the same pathway, sildenafil can be started as an adjunct if severe PPHN is likely. Methemoglobinemia is a potential toxicity of iNO treatment, but is rare at doses of 20 ppm and below. At our center, we check the methemoglobin (metHb) level at 24 hours

of therapy and then subsequently as clinically indicated. Some pulseoximeters can continuously measure methemoglobin noninvasively.

3. Other several potential side effects of iNO are platelet dysfunction, pulmonary edema, and production of toxic by-products such as nitrates. In combination with superoxide (oxygen free radicals), it further potentiates oxidative injury by forming peroxynitrites.

4. Because not all infants with PPHN respond to iNO and some may deteriorate rapidly, it would be ideal to manage such critically ill infants with PPHN at a center in which both iNO and ECMO are readily accessible. In most Asian neonatal intensive care unit (ICU), both iNO and ECMO are mostly not available and transfer of such a sick neonate in the absence of advanced transfer ambulance and teams is not safely possible.

E. ECMO. In the absence of pulmonary hypoplasia, ECMO is a lifesaving therapy with approximately 75% to 85% survival among infants with PPHN who fail conventional management and/or iNO treatment (see ECMO; Chapter 39). Among term or near-term infants meeting ECMO criteria (alveolar–arterial oxygen difference [$AaDO_2$] >600 or OI >30 on two ABGs ≥30 minutes apart), both iNO and HFOV appear to reduce the need for ECMO treatment. Therefore, when the infant's clinical status permits, a brief trial of HFOV and/or iNO is generally instituted before commencing ECMO.

F. Sedation and analgesia. Because catecholamine release activates pulmonary α-adrenergic receptors, thereby potentially raising PVR, an opioid analgesic that minimizes pain, such as fentanyl (1 to 4 μg/kg/hour infusion), is a useful adjunct therapy. Morphine sulfate (0.05 to 0.1 mg/kg/hour infusion) is an alternative analgesic that is best used when the infant is not hypotensive. Fentanyl is preferred over morphine. Midazolam (0.06 mg/kg/hour infusion) may also be useful to provide sedation, in babies who have no hypotension. Infants with PPHN rarely require neuromuscular blockade to synchronize the infant's breathing with mechanical ventilation.

G. Hemodynamic support (see Chapter 40). Optimal cardiac output is necessary to maximize tissue perfusion and oxygenation. Functional echocardiography is a valuable adjunct to clinical evaluation of hemodynamic status (capillary refill time, heart rate, blood pressure, urine output, lactate, sensorium, etc.). Echocardiogram (ECHO) can measure PVR and response to therapy, and LV and RV function, cardiac filling in diastole, etc. End-organ perfusion is assessed indirectly via acid–base balance (i.e., presence or absence of lactic acidosis). Because many infants with PPHN experience PVR that is at or near-normal systemic blood pressure, we usually set initial treatment goals of gradually raising systemic blood pressure with inotrope therapy to levels of 50 to 70 mm Hg (systolic) and 45 to 55 mm Hg (mean) and assessing the hemodynamic shunt at each interval increase. As the infant improves and PVR falls, he or she will remain well with "normal" blood pressures. In case of cardiac dysfunction, therapy to improve cardiac output is as critical as pulmonary vasodilatation.

1. **Volume expansion.** Intravascular volume support is important in conditions associated with intravascular volume depletion (e.g., hemorrhage, hydrops, capillary leak) or decreased SVR (e.g., septic shock). Normal saline (0.9% NS 10 mL/kg over 20 to 30 minutes) is used most often; in the case of

hemorrhage, packed red blood cells may be necessary when anemia is present. In treating infants with evidence of marked capillary leak, we avoid the use of 5% albumin because it also leaks from capillaries and worsens interstitial edema. It is important to remember that myocardial activity of these neonates is compromised and without evidence of intravascular depletion, use of colloids or crystalloid can be counterproductive. Also, it is important to maintain optimum hemoglobin (above 12 g/dL).

2. **Inotropes.** Choice of inotropes (Table 36.1), if needed, depends on etiology and evaluation of circulation, assisted by functional echocardiography.
   - **a.** Dobutamine, a synthetic catecholamine, is the preferred inotrope in babies with PPHN and associated LV dysfunction. It increases myocardial contractility (inotrope) and heart rate (chronotropic), and decreases PVR via β_1- and β_2- adrenergic receptor activity and increases SVR via α_1 adrenergic receptor activity. Moderate dose (5 to 10 µg /kg/minute) increases cardiac output and higher doses (10 to 20 µg/kg/minute) increase cardiac output and blood pressure. However, high doses are associated with tachycardia and increased myocardial oxygen consumption. For infants with myocardial dysfunction and increased SVR (perinatal asphyxia), dobutamine is a drug of choice.
   - **b.** Milrinone, a selective phosphodiesterase-3 inhibitor, has both inotropic and lusitropic actions (myocardial relaxation). By inhibiting phosphodiesterase 3 (PDE 3), milrinone also functions as pulmonary vasodilator. It increases cyclic adenosine monophosphate (cAMP) levels in cardiac muscle cells and improves ventricular function both directly and indirectly by reducing afterload. Its main indication in neonates with PPHN is in the setting of ventricular dysfunction. In babies with PPHN, if intra atrial shunt is left to right (this may indicate high left atrial pressures resulting from LV dysfunction), milrinone may be useful. This is commonly seen in asphyxia, congenital diaphragmatic hernia, and sepsis associated with PPHN. Milrinone is thought to be useful as an adjuvant to iNO, targeting cAMP and cGMP pathways and benefiting from synergistic effect of both. Because of longer half-life in neonates, it takes longer to achieve steady-state levels and hence loading dose is recommended. The loading dose is 50 µg/kg followed by infusion of 0.33 to 1 µg/kg/minute. Systemic vasodilation is the most common dose-limiting adverse effect. Studies involving milrinone in neonates with PPHN have shown to decrease OI and improve ventricular function. Although evidence from systemic randomized control trials is lacking, it should be considered in iNO nonresponders before considering ECMO.
   - **c.** Vasopressor therapy in infants with PPHN has traditionally been composed of dopamine and epinephrine. Although these nonselective vasopressors may increase SVR, they have not been shown to improve pulmonary blood flow.
   - **d.** Norepinephrine (0.05 to 1 µg/kg/minute) is a potent adrenergic agent that stimulates both α_1- and α_2-adrenergic receptors, and, as a result, is expected to raise SVR disproportionately to PVR. Stimulation of α_2 also increases endogenous nitric release. There are limited data on the use of norepinephrine in neonates. In a single case series, norepinephrine treatment of infants with PPHN was associated with improved oxygenation and ratio

Table 36.1. Cardiovascular Effects of Vasopressors and Inotropes

Physiologic Goal				
	Dose	**Receptors Stimulated**	**Primary Indication**	**Potential Adverse Cardiovascular Effects**
Increase cardiac output				
Dobutamine	5–20 μg/kg/minute	β_1, β_2, α_1	Cardiac dysfunction requiring rapid resolution	Tachycardia (++) Systemic vasodilation
Increase cardiac output and decrease pulmonary vascular resistance				
Milrinone	0.33–1 μg/kg/minute	PDE3 inhibition	Cardiac dysfunction Pulmonary hypertension	Systemic hypotension
Increase both cardiac output and systemic vascular resistance				
Dopamine*	0.5–2 μg/kg/minute	Dopaminergic	Poor urine output	Tachycardia (++) Pulmonary vasoconstriction
	2–6 μg/kg/minute	β_1, dopaminergic	Cardiac dysfunction	
	>6 μg/kg/minute	α_1, β_1, dopaminergic	Hypotension	
Epinephrine*	0.05–0.1 μg/kg/minute	β_1, β_2	Cardiac dysfunction	Tachycardia (+++) Lactic acidosis Hyperglycemia
	0.1–0.5 μg/kg/minute	α_1, α_2, β_1, β_2	Hypotension refractory to dopamine	
Increase systemic vascular resistance				
Vasopressin	0.1–1.2 milliunits/kg/minute	V1, V2	Hypotension	Hyponatremia

*Dose ranges based on limited evidence and vary between patients.

of pulmonary arterial pressure to systemic arterial pressure. Responses to adrenergic stimulation can be highly variable and appear to be influenced by a multiplicity of factors, including disease state and developmental stage. Norepinephrine is considered over epinephrine and dopamine as the vasopressor of the first choice due to its superior vasopressor effect and its potential beneficial effects on PVR.

e. Arginine vasopressin (AVP), a V1 receptor agonist, selectively vasodilates coronary, cerebral, pulmonary, and renal vascular beds while causing vasoconstriction in other systemic vascular beds. One case series suggests that low-dose AVP (0.1 to 1.2 milliunits/kg/minute) might be a potential adjunctive therapy in infants with PPHN refracting to iNO treatment, improving blood pressure, urine output, and OI.

H. Correction of metabolic abnormalities. Biochemical abnormalities might contribute to right-to-left shunting by impairing cardiac function. Correction of hypoglycemia and hypocalcemia is important in treating infants with PPHN in order to provide adequate substrates for myocardial function and appropriate responses to inotropic agents (see Chapters 40 and 41).

I. Correction of polycythemia. Hyperviscosity, associated with polycythemia, increases PVR and is associated with release of vasoactive substances through platelet activation. Transfusion should not be used indiscriminately, for packed cell volume (PCV) more than 65% may be harmful (see Chapter 46).

J. Pulmonary vasodilators other than iNO. iNO is considered the first- line therapeutic for the treatment of PPHN because of its effect on pulmonary vasculature without any systemic effects. But half the babies with PPHN do not respond to iNO; also, most of Asian neonatal units have no access to iNO. Pharmacologic agents acting at different pathways and resulting in pulmonary dilatation provide options for the treatment of PPHN unresponsive to iNO or where iNO is contraindicated. Pulmonary vascular endothelium-derived vasodilators act through cAMP and cGMP pathways. Blocking of endothelin (acting on receptors on the smooth muscle results in vasoconstriction) is another pathway.

J.a. Agents acting via cGMP pathway

Sildenafil, a phosphodiesterase-5 inhibitor that increases endogenous NO by inhibiting its metabolism, offers promise for the treatment of PPHN. It is available in oral as well as intravenous form. It can be used in the following ways: (i) as an adjuvant to iNO in resistant PPHN or to facilitate weaning of iNO, (ii) as a primary treatment, and (iii) in PPHN associated with bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia. In neonates, the volume of distribution is four times higher and the clearance is slower, resulting in a longer half-life of 48 to 56 hours. There are not many serious adverse events associated with the use of sildenafil. Systemic hypotension was observed in some infants treated with IV sildenafil.

J.b. Agents acting via cAMP pathway. Neonates with PPHN who have inadequate response to NO may have impaired cGMP-mediated pulmonary vasodilatation and may benefit from the cAMP pathway. Prostacyclins activate adenylate cyclase to increase cAMP concentration in vascular smooth muscle cells. Two types of prostaglandins have therapeutic application for the

treatment of PPHN: prostacyclin (prostaglandin I_2 [PGI_2]) and prostaglandin E_2 (PGE_2). Epoprostenol, treprostinil, iloprost, and beraprost are prostacyclins available in various forms for the treatment of PPHN. All PGI_2 analogues have an extremely short half-life. Epoprostenol is available in intravenous and inhalation forms. In a small study, oxygenation improved after inhaled epoprostenol. Iloprost resulted in improvement in OI, when used in IV or inhalation form. It is administered as an inhalation form, which requires a jet nebulizer. If severe PPHN causes RV dysfunction, prostaglandin (PGE_1) may be considered for opening the ductus. Opening of the ductus acts like a pop-off valve to severe resistance from PA on the failing right ventricle. It is available in intravenous and inhalation forms. Studies demonstrated that the inhaled form is safe. It is beneficial as it causes selective pulmonary vasodilatation in hypoxic respiratory failure.

J.c. Agents acting via endothelin pathway. Endothelin pathway also helps in the regulation of pulmonary vascular tone. Endothelin causes vasoconstriction and proliferation.

Bosentan is Endothelin-1 (ET-1) agonist, which acts on both ET-A and ET-B. It is safe and effective, and is available in oral form. It can be used for BPD-associated PPHN. Liver function needs to be monitored at regular intervals as it is shown to raise liver enzymes. Other side effects include angioedema, anemia, leukopenia, and thrombocytopenia.

K. Glucocorticoids. There is a growing evidence to suggest the role of steroid. It is shown to be beneficial in restoring normal pulmonary vasculature. In animal model, it is shown to improve arterial to alveolar ratios and attenuate oxidative stress, in part by increasing superoxide dismutase (SOD) activity. Hydrocortisone increases cGMP by normalizing sGC and PDE5 activity and by attenuating abnormalities induced by oxidative stress. It has potent anti-inflammatory effect and can be used as a rescue strategy before considering ECMO.

L. Combination therapies. Combining two molecules which can act through different pathways has shown to be beneficial. It is very common to add sildenafil, bosentan, or milrinone to niticoxide, if response is poor.

M. Newer therapies directed to newer targets. L-Citrulline, soluble guanylate stimulator and activator, Rho-kinase inhibitor, and peroxisome proliferator–activated receptor (PPAR)-Y agonists are various molecules currently been tried on various targets responsible for pulmonary vasoconstriction.

1. **L-Citrulline** improves NO signaling via recoupling of eNOS and by reducing superoxide generation. In animal studies, it was shown to be effective in ameliorating hypoxia-induced pulmonary hypertension and increased NO production in animals with chronic hypoxia.
2. **Soluble guanylyl cyclase activators/stimulators** directly relax vascular smooth muscles independent of NO. Riociguat is used for pulmonary hypertension as monotherapy or in combination with other drugs. So far its use is limited to adult population. Cinaciguat, an sGC activator, is shown to be effective in animal population.
3. **Rho-kinase inhibitor** modulates contraction of vascular smooth muscle cells in systemic and pulmonary circulation. Rho-kinase activity is potential future

target for the treatment of PPHN in neonates. Inhibition of Rho-kinase combining with activation of PPAR-Y results in restored growth of pulmonary arterial smooth muscles. It is not used in the newborns yet.

VI. POSTNEONATAL OUTCOMES AMONG INFANTS WITH PPHN. The combined availability of iNO and ECMO led to reductions in PPHN-associated mortality from 25%–50% to 10%–15%. Survivors of PPHN remain at risk for medical and neurodevelopmental sequelae. Infants who develop PPHN are at an approximately 20% risk of rehospitalization within 1 year of discharge and have a 20% to 46% risk of audiologic, neurodevelopmental, or cognitive impairments. We recommend close neurodevelopmental infant follow-up. Some of the infants have persisting pulmonary hypertension, ECHO must be repeated at 3 to 6 months or till complete resolution.

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37 Pulmonary Hemorrhage

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KEY POINTS

- Pulmonary hemorrhage is common in preterm, growth-restricted infants, and in those with severe respiratory distress syndrome (RDS).
- Symptomatic patent ductus arteriosus 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 defined as the presence of hemorrhagic fluid in the trachea accompanied by respiratory decompensation that requires increased respiratory support or intubation within 60 minutes of the appearance of fluid.

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. Acute left ventricular failure, caused by hypoxia and other conditions, may lead to increased pulmonary capillary pressure and injury to the capillary endothelium. This may result in increased transudation and leak into the interstitium and, ultimately, pulmonary airspace.

C. An alternative hypothesis suggests that a fall in pulmonary vascular resistance after birth causes increased left-to-right shunt through patent ductus arteriosus (PDA); this in turn leads to increased pulmonary blood flow and capillary leak.

D. Other factors that alter the integrity of the epithelial–endothelial barrier in the alveolus or that change the filtration pressure across these membranes may also predispose infants to pulmonary hemorrhage.

E. Disorders of coagulation may worsen pulmonary hemorrhage but are not thought to initiate the condition.

F. Intrauterine neutrophil activation may also predispose to the development of pulmonary hemmorage (PH) in preterm infants with respiratory distress (RD).

III. EPIDEMIOLOGY.

Pulmonary hemorrhage complicates the course of 3% to 5% of preterm infants ventilated for respiratory distress syndrome (RDS). Reported incidence of PH is 1 to 12/1,000 live births. However, this may be much higher at 50/1,000 live births in the risk group of preterm or fetal growth restriction (FGR) infants. Approximately 80% of pulmonary hemorrhages in preterm infants occur within 72 hours of birth. In autopsy studies, pulmonary hemorrhage is much more prevalent.

IV. PREDISPOSING FACTORS.

Pulmonary hemorrhage has been linked to many predisposing factors and conditions, including RDS, FGR, intrauterine and intrapartum asphyxia, male gender, multiple gestation, infection, congenital heart disease, oxygen toxicity, maternal blood aspiration, severe hypothermia, diffuse pulmonary emboli, polycythemia, maternal cocaine exposure, and urea cycle defects accompanied by hyperammonemia. Risk factors include conditions predisposing the infant to increased left ventricular filling pressures, increased pulmonary blood flow, compromised pulmonary venous drainage, or poor cardiac contractility. Antenatal steroids may be protective, while thrombocytopenia and requirement of positive-pressure ventilation in the delivery room may be predisposing to PH. The following factors have been linked to pulmonary hemorrhage:

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 screening echocardiograms for PDA were associated with increased pharmacologic treatment for PDA and decreased rates of pulmonary hemorrhage and in-hospital mortality.

B. Exogenous surfactant. Pulmonary hemorrhage may complicate surfactant therapy, likely related to changes in lung compliance, increased left-to-right shunting across a PDA, 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 the associated thrombocytopenia and coagulopathy.

V. CLINICAL PRESENTATION.

The clinical diagnosis of pulmonary hemorrhage is made when sudden cardiorespiratory decompensation occurs in the setting of hemorrhagic fluid in the upper respiratory tract. Only a small percentage of pulmonary hemorrhages observed at autopsy are evident clinically. This is most likely due to the difficulty in diagnosing hemorrhage confined to the interstitial space without spread to the airways. 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 the presence of a 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, isolated bleeding may result from 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 fluffy infiltrates or opacification of one or both lungs with air bronchograms.

C. Laboratory studies. The laboratory evaluation reflects the cardiopulmonary compromise with associated metabolic or mixed acidosis, a drop in hematocrit, and sometimes evidence of coagulopathy.

VII. TREATMENT.

Because the underlying pathogenesis remains unclear, treatment remains supportive. The general approach involves clearing the airways of hemorrhagic fluid and restoring adequate ventilation.

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.

B. Restore hemodynamic stability. Correct hemodynamic instability with volume resuscitation, including packed red blood cell replacement, and consider the addition of vasoactive medications as needed.

C. Correct acidosis. Restore both adequate ventilation and blood pressure to improve acidosis.

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 and coagulopathy 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 or 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 the surfactant. Exogenous surfactant replacement may reverse the inhibition, as demonstrated in the setting of meconium aspiration. Case reports and case series suggest that a surfactant may reduce mortality and morbidity from pulmonary hemorrhage. However, a 2020 Cochrane Review failed to identify any randomized controlled trials that address the use of a surfactant to treat pulmonary hemorrhage. Given

the positive results from nonrandomized studies, it suggests further research. Treatment should be decided on a case-by-case basis.

I. Epinephrine. Endotracheal or nebulized epinephrine at a dose of 0.1 mL/kg of 1:10,000 dilution may be useful due to its vasoconstrictive action. However, the benefits are not proven by controlled trials.

J. Activated recombinant factor VII (rFVIIa). It works by activating the extrinsic pathway and promoting hemostasis. Used in hemophilia patients, there are anecdotal reports of use in newborns with refractory pulmonary hemorrhage. Risk of thromboembolism is high and use in newborns has a higher risk, but that is likely to benefit.

K. Hemocoagulase. It is derived from the venom of *Bothrops atrox*. It promotes conversion of prothrombin to thrombin and fibrinogen to fibrin. In a prospective study of 48 preterm newborns with pulmonary hemorrhage on ventilator, babies who received endotracheal hemocoagulase (28 babies) had significant reduction in PH and lower mortality. The study has many limitations, and routine use cannot be recommended.

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. In a secondary analysis of the trial of indomethacin prophylaxis in preterm infants, prophylactic indomethacin reduced the rate of early serious pulmonary hemorrhage. The risks of death or survival with neurosensory impairment at 18 months of age were increased in infants with serious pulmonary hemorrhage. Overall mortality rate has been reported up to 50%. PH survivors have a higher incidence of bronchopulmonary dysplasia, seizures, cerebral palsy, and periventricular leukomalacia on follow-up.

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38 Pulmonary Air Leak

Melinda Markham

KEY POINTS

- Pneumothorax in neonates is most commonly associated with an underlying lung disease requiring mechanical ventilation.
- Pneumothorax should be considered as a diagnosis in any ventilated infant with sudden and significant deterioration in the respiratory or cardiovascular status.
- Chest tube or pigtail placement is often required for infants with pneumothorax on positive-pressure ventilation.
- Spontaneous pneumothorax in term infants may be managed conservatively if the infant remains clinically stable.

I. BACKGROUND

A. Risk factors. The primary risk factors for air leak are mechanical ventilation and lung disorders. Babies resuscitated in the delivery room with a self-inflating/flow inflating device (without manometer) are at risk of exposure to high pressures to the lung. Risk factors in premature infants include respiratory distress syndrome (RDS) and pneumonia. Risk factors common in term infants are aspiration of meconium and blood, pneumonia, and congenital malformations leading to hypoplasia of lungs.

Surfactant therapy for RDS has markedly decreased the incidence of pneumothorax. Ventilating the babies with volume limit mode also has reduced pneumothorax.

B. Pathogenesis. Transpulmonary pressures that exceed the tensile strength of the noncartilaginous terminal airways and alveolar saccules can damage the respiratory epithelium. Loss of epithelial integrity permits air to enter the interstitium, causing **pulmonary interstitial emphysema (PIE)**. Preterm babies have more perivascular connective tissue, which is less dissectible than in term babies; this results in air trapping in the perivascular space, leading to 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.

Many factors contribute to air leaks:

- **Elevations in transpulmonary pressure.** The infant'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 overdistension and rupture. Similarly, aspiration of blood or meconium can cause alveolar overdistension by a ball-valve mechanism.
- **In the presence of pulmonary disease, PPV 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. Use of volume-limited ventilation can decrease the risk by automatically decreasing the pressures, as compliance improves. Mechanically ventilated preterm infants who make expiratory efforts against ventilator breaths (asynchrony) are also at an increased risk for pneumothorax.
- **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 of these infants is symptomatic. Clinical signs of pneumothorax range from insidious changes in vital signs to the complete cardiovascular collapse that often accompanies a tension pneumothorax. As intrathoracic pressure rises, there is decreased lung volume, mediastinal shift, compression of the large intrathoracic veins, and increased pulmonary vascular resistance. The net effect is an increase in central venous pressure, a decrease in preload, and, ultimately, diminished cardiac output. A pneumothorax must be considered in mechanically ventilated infants who develop unexplained alterations in hemodynamics, pulmonary compliance, or oxygenation and ventilation. Pneumothorax in preterms has been associated with intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and death.

1. Diagnosis

a. Physical examination

i. Respiratory distress—tachypnea, grunting, flaring, worsening saturations

ii. Chest asymmetry with overexpansion of the affected side

iii. Shift in the point of maximum cardiac impulse

iv. Diminished or distant breath sounds on the affected side

v. 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 PO_2 and increased 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, and mediastinal shift. Smaller collections of intrapleural air can be detected beneath the anterior chest wall by obtaining a cross-table lateral view; however, an AP view is needed to identify the affected side. The lateral decubitus view, with the side of suspected pneumothorax up, may be helpful in detecting a small pneumothorax and may help differentiate skin folds, 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 or dark skin.

e. **Ultrasound lung.** It has high sensitivity in the diagnosis of pneumothorax. Absence of lung sliding, absence of comet-tail artifact, and presence of lung point suggest the presence of pneumothorax.

f. **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" or "hold point" should be done with the nurse to confirm the correct patient, diagnosis, and laterality (side affected).

a. **Conservative therapy.** Close observation may be adequate for infants who are asymptomatic, coupled with serial monitoring with ultrasound or chest x-ray to document resolution. The extrapulmonary air will usually resolve in 24 to 48 hours. Oxygen should be administered only if the baby develops hypoxemia. 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 an intravenous (IV) catheter with an inner needle can be used to treat a symptomatic pneumothorax. Needle aspiration may be curative in infants not receiving mechanical ventilation and is frequently a temporizing measure in mechanically ventilated infants. In infants with severe hemodynamic compromise, thoracentesis may be a lifesaving procedure.

i. Attach a 22G IV catheter (blue cannula) to a 10- to 20-mL syringe (with some saline) 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 (identify the sternal angle of Louis and palpate down the sternal ridge; the second ICS is opposite to it).

iii. Insert the needle firmly into the ICS in a perpendicular fashion and pass it just above the top of the third rib. This will minimize the chance of lacerating an intercostal artery because these vessels are located on the inferior surface of the ribs. As the needle is inserted, have an assistant apply continuous suction with the syringe. A rapid flow of air into the syringe occurs when the needle enters the pleural space (gush of bubbles). 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. One will note a rapid improvement in the baby's saturations and heart rate if the tension pneumothorax is relieved.

A continuous air leak can be aspirated while a chest tube is being inserted. The needle can be removed and the plastic catheter used for emergency thoracentesis left in place for further aspiration. A short piece of IV extension tubing, for example, a "T" connector, attached to the IV catheter hub will allow flexibility during repeated aspirations. 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 tubing should be clamped or the stopcock left in the "off" position. This is less of a concern for babies who are on PPV.

c. Chest tube drainage. Chest tube drainage is generally needed to evacuate a pneumothorax that develops in infants receiving PPV. Frequently, these air leaks are continuous and will result in severe hemodynamic compromise if left untreated.

i. Insertion of a chest tube

a) Ensure monitoring with pulse oximetry and electrocardiogram (ECG) throughout the invasive procedure.

b) Trocar within the straight chest tubes has been reported to be associated with lung perforation, hemothorax, scars, and laceration of vessels and thoracic structures. Pigtail catheters are safe alternatives.

c) Select a chest tube of the appropriate size; French size 10 (smaller) and 12 (larger) catheters are adequate for most infants.

d) Prepare the chest area with an antiseptic solution. For neonates younger than 28 weeks, use chlorhexidine 0.05% (not 2%). The subcutaneous tissues overlying the fourth to sixth ribs at the midaxillary line can be infiltrated with a 1% lidocaine solution for analgesia (0.3 mL/kg or 3 mg/kg of 1% strength, maximum 1 mL). Alternatively, we often give narcotics for pain management because local analgesia may obscure landmarks needed to guide the procedure.

e) In the midaxillary line in the sixth ICS, parallel to the rib, make a small incision (0.5 to 1.0 cm) through the skin. Avoid incision of breast tissue by locating the position of the nipple and surrounding tissue. An alternative site is in the anterior-superior portion of the chest wall; however, there is a risk of injury to the internal mammary artery and other regional vessels with this approach.

f) After the pleural space has been entered, direct the chest tube anteriorly and cephalad. Be certain that the side ports of the chest tube are in the pleural space. The anterior pleural space drainage is generally most effective for infants in the supine position.

g) Palpate the chest wall around the entry site to confirm that the chest tube is not in the subcutaneous tissues.

h) Attach the chest tube to a Heimlich valve (for transport) or an underwater drainage system. Negative pressure (10 to 20 cm H_2O) may be applied to the underwater drainage system.

i) 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.

j) 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.

k) AP and lateral chest radiographs are obtained to confirm tube position and ascertain drainage of the pleural air.

l) 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 a 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

a) 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.

b) Pigtail catheters are inserted using a modified Seldinger technique (5F for babies <1500 g and 6F for bigger babies). After locating and sterilizing the insertion site, an 18G needle or an 18G IV catheter is inserted into the pleural space. The guidewire is advanced through the catheter. The needle or the IV catheter is removed, keeping the guidewire in place, and a dilator is advanced over the wire. The pigtail catheter is then inserted in the pleural space over the guidewire.

The catheter is advanced until the curve of the catheter is inside the chest.

d. Removal of a chest tube. 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 tube under water seal. If radiographic examination shows no reaccumulation of extrapulmonary air in the next 12 to 24 hours, the chest tube should be removed. A narcotic is given for pain control prior to the chest tube removal. To reduce the chance of introducing air into the pleural space, cover the chest wound with a small occlusive dressing while removing the tube.

e. Persistent pneumothorax refractory to routine measures. 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. 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 of pneumothorax

- Profound ventilatory and circulatory compromise can occur and, if untreated, result in death.
- IVH may result, possibly secondary to a combination of fluctuating cerebrovascular pressures, impaired venous return, hypercapnia, hypoxia, and acidosis.
- Inappropriate antidiuretic hormone secretion may occur.

B. PIE. PIE occurs most often in mechanically ventilated, extremely preterm infants with RDS or pneumonia. Interstitial air can be localized or can spread to involve significant portions of one or both lungs. It 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: cystlike and linear. Linear lucencies radiate from the lung hilum. Occasionally, large cystlike 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 utilized in infants with PIE to avoid large tidal volumes.

b. Unilateral PIE may improve if the infant is positioned with the affected lung dependent.

c. Endotracheal suctioning and manual PPV should be minimized.

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.

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 seen on a 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 ultrasound-guided percutaneous mediastinotomy drainage. If the infant is mechanically ventilated, reduce mean airway pressure, if possible.

3. Complications. Pneumomediastinum may be associated with other air leaks.

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 unrecognized 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 or distant heart sounds. A pericardial knock (Hamman's 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.

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. ECG. Decreased voltages, manifest by 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 PPV 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° 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, peritoneal drainage may be necessary.

2. Subcutaneous emphysema. Tracheal injury as a result of traumatic deliveries or traumatic intubation, more so in agenesis or tracheal stenosis, can lead to

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, though usually of no clinical significance, can partially occlude or obstruct the compressible, cartilaginous trachea of the premature infant. The treatment might include lifesaving neck incision and securing airway.

3. **Systemic air embolism.** 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. Air embolism may lead to hemodynamic collapse, multiorgan failure, and death; early suspicion, urgent echo, and immediate treatment are lifesaving.

Suggested Readings

Cates LA. Pigtail catheters used in the treatment of pneumothoraces in the neonate. *Adv Neonatal Care* 2009;9:7–16.

Clark SD, Saker F, Schneeberger MT, et al. Administration of 100% oxygen does not hasten resolution of symptomatic spontaneous pneumothorax in neonates. *J Perinatol* 2014;34:528–531.

39 Extracorporeal Membrane Oxygenation

Gerhard K. Wolf and John H. Arnold

KEY POINTS

- Indications for neonatal extracorporeal membrane oxygenation (ECMO) are severe respiratory failure and circulatory or cardiac failure that are considered reversible.
- Venovenous ECMO only supports oxygenation and ventilation however, venoarterial ECMO supports gas exchange and circulation.
- Common ECMO complications include mechanical problems with the circuit, intracranial hemorrhage, other bleeding, infection, and renal failure.

I. BACKGROUND. Extracorporeal membrane oxygenation (ECMO) is the application of a modified cardiopulmonary bypass for neonates in cardiac or respiratory failure not responding to conventional measures or treatments as a lifesaving therapy. ECMO is an effective supportive therapy and serves as a bridge to recovery, bridge to transplant, or bridge to decision. As the support extends beyond oxygenation, the term extracorporeal life support (ECLS) is used in a broader perspective to include ECMO and other forms of life support such as ventricular assist device with an oxygenator.

ECMO has been offered to over 43,000 neonates worldwide to date (Tables 39.1 and 39.2). The use of ECMO for neonatal respiratory failure began to decline in the late 1990s due to improved strategies of lung-protective ventilation and has been

Table 39.1. Overall Outcomes for Neonatal Extracorporeal Membrane Oxygenation (ECMO) Worldwide by Indication, Extracorporeal Life Support Organization (ELSO), January 2020

Neonatal	Total Patients	Survived ECLS	Survival to Discharge or Transfer
Respiratory	32,385	28,417 (87%)	23,675 (73%)
Cardiac	8,830	6,097 (69%)	3,818 (43%)
ECMO-CPR	2,035	1,427 (70%)	861 (41%)

"Total Patients" refers to all neonatal ECMO therapies reported in the ELSO registry. "ECMO-CPR" refers to neonatal patients placed emergently on ECMO during cardiopulmonary resuscitation. CPR, 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; January 2020.

Table 39.2. Neonatal Respiratory Runs by Diagnosis, Extracorporeal Life Support Organization (ELSO), January 2020

Neonatal Categories	Total Runs	Percentage Survived
MAS	9,444	94
CDH	8,621	51
PPHN/PFC	5,444	77
Sepsis	2,980	72
RDS	1,580	84
Pneumonia	402	57
Air leak syndrome	137	74
Other	3,843	64

CDH, congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; PFC, persistent fetal circulation; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome.

more constant since 2000. Approximately 40 centers in the USA offer neonatal ECMO; only a few centers offer neonatal ECMO in India.

II. INDICATIONS AND CONTRAINDICATIONS. Considerations before initiating ECMO include the following:

- Is the condition a potentially reversible respiratory or cardiac or cardiorespiratory illness?
- Is the neonate unwell enough to warrant ECMO?
- Are the neurologic status and functions of other systems consistent with reasonable outcome?
- Are there any contraindications to heparin?

A. Respiratory failure. The indications for neonatal ECMO are the following: (i) reversible respiratory failure and (ii) predicted mortality with conventional therapy great enough to warrant the risks of ECMO. ECMO is also considered in patients with life-threatening air leaks not manageable with optimal ventilatory support and chest drainage.

1. **Oxygenation index (OI)** is a measure of the severity of respiratory failure and is calculated as follows: OI = mean airway pressure (MAP) × FiO_2/PaO_2 × 100. It is essential to document OIs from serial blood gases over time because the OI may vary. ECMO indications vary among different centers. Criteria include OI >40 for >4 hours, OI >20 with lack of improvement despite prolonged medical therapy for >24 hours, severe hypoxic respiratory failure with acute decompensation, PaO_2 <40 not responding to intervention, and severe pulmonary hypertension with ventricular dysfunction (Extracorporeal Life Support Organization [ELSO] guidelines). Other commonly used criteria

include single OI of 60 on high-frequency ventilation or single OI of 40 combined with cardiovascular instability. For infants hospitalized where ECMO is not available, an OI of 20 should prompt early outreach to an ECMO center for potential transfer because prolonged ventilation at high ventilator settings may worsen ventilator-induced lung injury and worsen the overall outcome. On a practical level, once ventilator support is maximally escalated, transport to an ECMO center may become impossible. Indications for respiratory ECMO include meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn (PPHN), and air leak syndrome.

2. Total anomalous pulmonary venous return (TAPVR) may mimic neonatal respiratory distress syndrome (RDS), resulting from lung congestion in the setting of inadequate drainage of the pulmonary veins in the left atrium. In any neonate with respiratory failure, hypoxia, and bilateral opacities on chest radiograph, TAPVR should be excluded prior to initiating ECMO support. Once venoarterial (VA) ECMO support is initiated, pulmonary blood flow is reduced and the diagnosis of TAPVR may be difficult to make using echocardiography alone; these patients may require cardiac catheterization on ECMO to demonstrate the presence or absence of pulmonary veins entering the left atrium.
3. Patient selection is a crucial step for the success of neonatal ECMO. In CDH, irreversible lung hypoplasia as evidenced by $PaCO_2$ of more than 80 for more than 6 hours is an independent predictor of poor outcome.

B. Cardiac failure. ECMO provides biventricular support for neonates with cardiac failure. General indications are low cardiac output (CO) syndrome despite maximal hemodynamic support or cardiac arrest with a potentially reversible underlying condition. ECMO for congenital heart defects can be offered as a bridge to definitive treatment until the newborn's condition has stabilized. Other cardiac indications are failure to wean from cardiopulmonary bypass, cardiogenic shock, cardiomyopathy, and myocarditis.

C. Rapid-response ECMO (ECMO-cardiopulmonary resuscitation [E-CPR]). In the setting of a witnessed cardiorespiratory arrest, ECMO can be offered in centers with a rapid response team. Response times from the arrest to cannulation are ideally 15 to 30 minutes. A readily "clear-primed circuit" (an ECMO circuit primed with normal saline rather than with blood products) and an ECMO team must be available 24 hours per day in order to offer E-CPR. Effective cardiopulmonary resuscitation (CPR) before cannulation is essential for a favorable outcome during rapid-response ECMO. Globally, around 5% of the neonatal ECMO runs are E-CPR.

D. *Ex utero* intrapartum treatment (EXIT) to ECMO procedure. The vessels are cannulated during a cesarean section while the newborn remains on placental support. Indications include severe CDH, lung tumors, and airway obstructing lesions such as large neck masses and mediastinal tumors.

E. Contraindications. ECMO should be offered only for reversible conditions. Contraindications are considered to be lethal chromosomal disorder (including Trisomies 13 and 18 but not 21), irreversible brain damage, and grade 3 or greater intraventricular hemorrhage (IVH) or intraparenchymal hemorrhage. Relative contraindications include weight <2,000 g due to cannula size limitations (except

for thoracic cannulations), gestational age <34 weeks due to increased risk of IVH, severe coagulopathy, progressive chronic lung disease, mechanical ventilation for more than 10 to 14 days, and continuous CPR for more than an hour before ECMO support.

III. TYPES OF ECMO SUPPORT

A. VA ECMO. VA ECMO supports the cardiac and the respiratory system and is indicated for primary cardiac failure or respiratory failure combined with secondary cardiac failure. However, in neonates, even for respiratory etiology, majority of the times VA ECMO is done due to logistic reasons. In VA ECMO, the blood is drained from a single vein (internal jugular vein [IJV]) and returned into the arterial system (internal carotid artery). Venovenous-arterial ECMO (VVA ECMO) indicates drainage from two different veins and returns to the arterial side. VVA ECMO is done only rarely in neonates. The patient's total cardiac output (CO) is the sum of the native pulsatile CO and the nonpulsatile pump flow generated by the circuit: $CO_{total} = CO_{native} + CO_{circuit}$.

B. Venovenous (VV) ECMO. VV ECMO supports only the respiratory system and is indicated for isolated respiratory failure. It refers to drainage to and fro through a single vein using a dual-lumen cannula or draining from one vein (IJV) and return through another vein (femoral vein). VV ECMO can also be considered in respiratory failure with hemodynamic instability, when hypotension and cardiovascular instability are likely due to hypoxemia. It spares accessing the carotid artery. Venovenous dual lumen (VVDL) refers to ECMO using specially designed double-lumen cannulas, providing drainage as well as return through different lumens of the same cannula. Some of the blood is immediately recirculated into the ECMO circuit. The rest of the oxygenated blood 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. As a requirement for VV ECMO, the IJV has to be large enough for a 14 French double-lumen cannula. The use of a dual-lumen cannula in neonates is limited in India due to lack of availability. Converting to VA ECMO is considered in the presence of additional hypotension, cardiac failure, or metabolic acidosis. Technical difficulties related to large recirculation in the venous cannula can also lead to the need to convert to VA ECMO. For conversion to VA ECMO, the venous cannula is left in place and an additional arterial cannula is inserted into the internal carotid artery.

IV. PARTS OF ECMO (Fig. 39.1)

A. Drainage (access) cannula. Cannula draining blood from one of the major veins or right atrium.

B. ECMO circuit. Specialized circuit for circulation of blood outside the body with a mechanism to minimize activation of clotting and systemic inflammatory responses. It is primed with crystalloid, colloid, or blood.

C. Pump. To drain blood via access cannula and pump it through the ECMO circuit and back to body via another cannula (return cannula). Pump can be a centrifugal pump (nonocclusive) or a roller pump (nonocclusive). The console unit controls the speed of the pump.

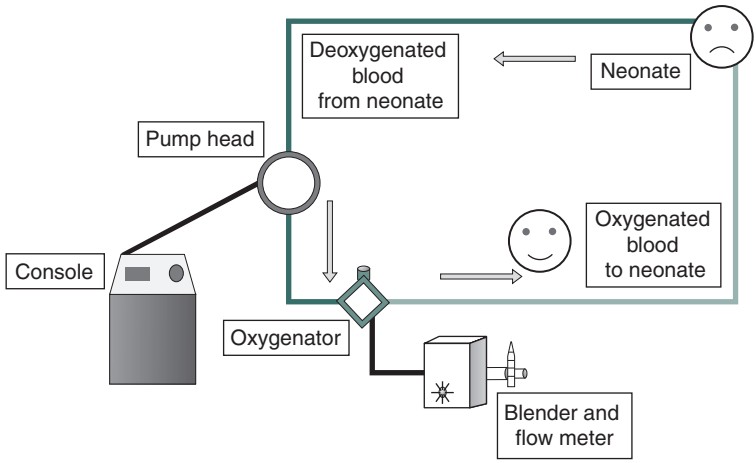

Figure 39.1. Parts of ECMO.

D. Membrane oxygenator (lung). A gas permeable membrane separating blood and gas flow, which adds oxygen to blood and also removes carbon dioxide from blood by diffusion. The most common type used now is a microporous membrane with hollow fibres.

E. Blender with air and oxygen supply and flow meter. To supply gas flow to the oxygenator. Flow set in the blender is termed as sweep gas flow.

F. Heater unit. This helps to maintain blood temperature to a set value of 37°C or lower (for therapeutic hypothermia) by heat exchange across the membrane.

G. Return cannula. To return blood to great vein or right atrium (VV ECMO) or any great artery (VA ECMO).

H. Monitoring devices. Help to detect any problems in circuit flow, membrane function, and mechanical kinks.

I. Flow. Flow is determined by the cannula size, intravascular volume, venous return, and ECMO pump. If intravascular volume is low (intravascular hypovolemia, cardiac tamponade, and pneumothorax), flow is reduced.

V. FACTORS DETERMINING EFFECTIVENESS OF ECMO

A. Factors determining oxygen delivery. Oxygen delivery is the product of CO and arterial oxygen content. During ECMO, many factors contribute to oxygen delivery. Arterial oxygen content is determined by the gas exchange in the membrane oxygenator and the gas exchange from the neonate's lung. CO is altered only during VA ECMO and is determined by the ECMO flow and the infant's native CO.

B. Factors determining 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 is dependent on the $PaCO_2$ of blood circulating through the membrane, the surface area of the membrane, and the gas flow through the membrane

lung ("sweep gas flow"). As physiologic pulmonary function and tidal volume improve, the $PaCO_2$ decreases further and ECMO settings have to be adjusted. CO_2 removal is extremely efficient during ECMO, to the point that additional CO_2 may have to be added into the circuit in order to prevent hypocarbia and respiratory alkalosis.

C. Factors determining cerebral perfusion. Cerebral perfusion during shock is rapidly restored after initiation of VA ECMO. Collateral circulation to the brain during VA ECMO in neonates is maintained through the circle of Willis. The carotid artery is frequently ligated after decannulation from ECMO, although reconstruction of the carotid artery has been successfully performed. Impairments to arterial reconstructions are an intimal flap, arterial thrombosis, infections, or excessive tension on attempt of reconstruction. Reconstructing the carotid artery may not have an impact on neurologic outcome, and arterial vascular stenosis post repair may be a significant problem.

VI. MANAGEMENT

A. Pre-ECMO. In preparation for cannulation, the following should be available: central venous access to the patient, postductal arterial catheter, cross-matched blood in the blood bank, complete blood count, coagulation profile, and head ultrasonographic examination. An echocardiogram should be done before ECMO in order to rule out structural cardiac abnormalities. Platelets should be transfused for a platelet count <100,000/mL.

B. Membrane. The appropriate membrane for a neonate is a silicone or polypropylene membrane oxygenator. The resulting total volume of a neonatal ECMO circuit ranges from 350 to 600 mL.

C. Blood priming. Patients who are placed on ECMO nonemergently are started on a blood-primed circuit. Orders for the initial prime of a neonatal circuit are as follows: 500 mL of packed red blood cell (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 and tris (hydroxymethyl) aminomethane (THAM, also "Tris") buffer and calcium gluconate can be added to the circuit to achieve target ranges as needed. Correction of blood parameters (blood gas and electrolytes) of the priming blood is optional and the practice varies widely among different units.

D. Saline priming. Patients who are placed on ECMO emergently can be started on a saline-primed circuit. Instead of blood products, the circuit is primed with normal saline. In centers with rapid-response ECMO, a saline-primed, sterile circuit is always available, minimizing the time to initiate ECMO therapy. The neonate's own blood volume is initially diluted with the normal saline from the ECMO circuit. This causes a drop in hematocrit and a transient decrease in oxygen-carrying capacity. The hematocrit is later restored by using ultrafiltration and transfusing PRBCs.

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. A surgical cutdown approach is preferred over transcutaneous cannulation. Semi-Seldinger technique can be done in which skin incision is made and

cannulation of the vessels is done instead of dissection. The infant is anesthetized and paralyzed with fentanyl, midazolam, and pancuronium. Heparin 50 to 100 units/kg is administered before cannulation. The following cannula sizes can be used: 10 to 14 French for the venous side, 8 to 10 French for the arterial side, or a 12- to 16- French VV double-lumen cannula. The vein is cannulated first. The catheter is introduced approximately 6.5 cm to the right atrium and sutured in place. In VA ECMO, the artery is cannulated in a similar manner. In full-term newborns, the arterial cannula is introduced 3.5 cm into the aortic arch. On initiation of ECMO, vasopressors can be rapidly weaned. The neonate may become markedly hypertensive on initiation of ECMO therapy. As hypertension in the setting of pre-ECMO acidosis and anticoagulation during ECMO is a significant risk factor for intracranial hemorrhage, any significant hypertension must be anticipated and treated without delay. Hydralazine 0.1 to 0.4 mg/kg/dose can be administered to treat hypertension. Other antihypertensive medications include sodium nitroprusside, nicardipine, and transdermal clonidine.

F. ECMO therapy. ECMO therapy and monitoring are depicted in Table 39.3.

G. Blood gas monitoring. Arterial blood gas targets are PaO_2 >60 mm Hg and $PaCO_2$ 40 to 45 mm Hg. 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.

H. Anticoagulation. Heparin is used in all patients to prevent clot formation. Point-of-care activated clotting time (ACT) is used for monitoring anticoagulation therapy. Heparin infusion is initiated at 20 to 50 units/kg/hour titrated according to ACT levels. Anti-Xa levels and activated partial thromboplastin time (aPTT) could also be monitored. Antithrombin (AT) III level monitoring and supplementation (recombinant AT III) should be limited to those with heparin resistance. Alternatively, FFP can be administered as a source of AT III. If heparin-induced thrombocytopenia (HIT) is confirmed, argatroban and bivalirudin, a synthetic direct thrombin inhibitor, can be used as an alternative anticoagulant during ECMO.

I. Blood products. FFP at a dose of 15 to 20 mL/kg can be administered as needed to maintain prothrombin time (PT), aPTT, and fibrinogen levels. Cryoprecipitate is administered if fibrinogen remains low (less than 100 mg/dL) in spite of FFP. Platelet count is maintained above 100,000 using platelet transfusion. The hematocrit is kept above 35% to facilitate oxygen delivery.

J. ε-Aminocaproic acid (Amicar), an antifibrinolytic, is often used to reduce bleeding in neonates who need surgical intervention while on ECMO. In neonates with CDH, aminocaproic acid has shown to reduce the perioperative bleeding and the need for re-exploration. However, usage is associated with an increased risk of circuit change. A loading dose of Amicar (100 mg/kg) is given followed by a 20- to 30-mg/kg/hour infusion. Topical tranexamic acid may be beneficial in mucosal bleeding. A surgical consult should be obtained in the setting of postoperative hemorrhage or bleeding from surgical sites. Factor VII at 90 μg/kg can be used in the setting of severe bleeding.

Table 39.3. ECMO Setting and Monitoring

ECMO blood flow	100–120 mL/kg/minute (adjust the revolution per minute accordingly in the console); 50%–80% of the flow may be enough; determines oxygenation in both VV and VA ECMO; hemodynamics in VA ECMO
Sweep gas flow	Usually 1:1 as ECMO flow; begin with 0.1 L/minute; increase if carbon dioxide retention and vice versa; PCO_2 target 35–45 mm Hg (except CDH)
ECMO blender FiO_2	50%–100% (as required to maintain SpO_2 >90 and PaO_2 60–80 mm Hg in VA ECMO, and SpO_2 80%–90% and PaO_2 40–60 mmHg in VV ECMO)
Heat exchange unit	Set temperature of 37°C (unless therapeutic hypothermia in hypoxic-ischemic encephalopathy)
Safety check in equipment	Blood clots and circuit inspection for leaks
ECMO monitoring	Clots in the circuit; ECMO blood flow, premembrane and postmembrane pressure, inlet pressure, and mixed venous saturation (65%–80% in VA ECMO)
Patient monitoring	SpO_2 (target as above), ECG, invasive BP (pulsatility dampened in VA ECMO; target mean BP), temperature, urine output; NIRS (optional)
Lab parameters	Complete blood count, electrolytes, lactate, calcium twice daily; blood gas q4h initially, and then as needed; liver function tests, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, albumin, prealbumin, and total protein every week
Hematologic monitoring	Platelets >100,000 for the first 48 hours, and then 50,000–80,000/μL Fibrinogen >150 mg/dL; hematocrit >35%–40%; plasma free hemoglobin daily (>50 mg/dL significant) to detect hemolysis
Anticoagulation	Keep target activated clotting time (ACT) 160–180 seconds, and during weaning 180–220 seconds; target anti-Xa levels 0.3–0.7 second; thromboelastogram (TEG) in the presence of bleeding

CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; NIRS, near infrared spectroscopy; VA, venoarterial; VV, venovenous.

K. Antibiotics. We routinely administer broad-spectrum antibiotics to lower the risk of infection while on ECMO therapy. According to the ELSO registry, infections during ECMO occur in about 5% to 8% of all ECMO runs. In India, nosocomial infections are common in the neonatal intensive care unit (NICU), although there is a lack of exact data in ECMO patients.

L. Analgesia and sedation. Patients are sedated with an opioid/benzodiazepine combination. Morphine 10 to 40 µg/kg/hour can be used for analgesia and sedation. Either midazolam (1 to 2 µg/kg/dose) or intermittent dose of lorazepam (0.05 to 0.1 mg/kg/dose every 4 to 6 hours) can be administered for sedation. Fentanyl can be used during ECMO cannulation but should not be used during ECMO procedure. It is absorbed in large quantities by the ECMO membrane, leading to suboptimal analgesia. Muscle relaxants are indicated at the times of cannulation, decannulation, and circuit change.

M. Fluids and nutrition. Nutrition is administered through the parenteral route initiated within 24 hours of ECMO. Lipid administration should not exceed 1 g/kg/day to prevent lipid accumulation and embolism in the circuit. Lipids should be administered directly to the patient and not to the circuit. Dextrose and amino acid solution (parenteral nutrition) are preferably given to the patients, although these can be administered through the circuit. Once the neonate is stable, enteral feeds are initiated and graded up. Generally, enteral feeding through a nasogastric tube is well tolerated. Fluid management should be aimed to maintain the dry weight and normalize the extracellular fluid. Due to the critical illness prior to ECMO and subsequently due to systemic inflammatory response during ECMO, there is capillary leak and shifting of fluid to the third space. When the neonate is hemodynamically stable (usually after 48 hours), diuretics can be initiated. If a negative balance is needed, to circumvent an earlier positive balance, ultrafiltration can be attached to the ECMO unit. In case of overt renal failure, hemofiltration is added to the extracorporeal circuit.

N. Ultrafiltration. An ultrafilter is placed in line with the ECMO circuit. The goal is to normalize fluid balance in patients who have excessive positive fluid balance. Indications are urine output of <0.5 mL/kg/hour, positive fluid balance >500 mL per 24 hours, and failed diuretic therapy.

O. Head imaging. Head ultrasonographic examinations are performed before ECMO, if possible, and serially during the ECMO run. Details on the neuromonitoring are depicted in Table 39.4.

P. Ventilatory setting. These are the neonatal setting-rule of 10-10-10. Typical settings are peak inspiratory pressure (PIP) of 15 to 22 cm H_2O, positive end-expiratory pressure (PEEP) of 5 to 10, rate of 10 to 20, inspiratory time 0.5 second, and FiO_2 of 0.21 to 0.3. This rest setting is commonly known as 10-10-10 (PEEP of 10; delta P:PIP above PEEP of 10; rate 10). With a patient on VA ECMO for pneumothorax and air leak, apneic oxygenation with $FiO_2 = 1$ should be considered starting at continuous positive airway pressure (CPAP) settings of 12 cm H_2O and decreasing until no further air leaks are present. Endotracheal suctioning is performed every 4 hours. During ECMO, lung function is assessed as follows: (i) as the lung function improves, CO_2 removal increases and oxygenation by the lung improves, resulting in better gas exchange (sweep gases can be adjusted based on the CO_2 level); (ii) chest radiographs show gradual resolution of pulmonary edema; and (iii) as pulmonary edema resolves, lung mechanics improves and expired tidal volumes increase.

Q. Recovery. In VV ECMO, lung recovery is indicated by a constant need to reduce ECMO settings and also by an improvement in the chest x-ray. Cardiac recovery on VA ECMO support is indicated by an improvement in cardiac contractility

Table 39.4. Neuromonitoring in ECMO

Neuromonitoring	When to Do	Findings	Advantages	Limitations
Cranial ultrasound (CUS)	Pre-ECMO as baseline After initiation: every day for the first 1 week, and then on alternate days	Intraventricular and cerebral intraparenchymal hemorrhage	Bedside availability and ease of usage	Can miss posterior fossa abnormality and infarction
CT scan	As clinically indicated—following abnormal CUS	Improved sensitivity to detect intracranial pathology	Can predict long-term outcome	Radiation; can be used only when portable CT is available
MRI	Post-ECMO	Sensitive to detect infarction, even small intracranial hemorrhage, white matter injury	Can predict long-term outcome; no radiation	Might need sedation; cannot be done during ECMO
NIRS	During ECMO; continuous monitoring	Measures regional oxygen saturation	No radiation	Limited availability
EEG	During ECMO; continuous monitoring	Detects seizure activities	Appropriate interventions can be done to improve the outcome	Limited availability

ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram.

assessed by echocardiography and an increase in pulse pressure. During the weaning process, inotropes and ventilator settings are increased and hemodynamic status is assessed clinically and by echocardiography.

R. Weaning.

VV ECMO - Improvement in chest x-ray and the constant need to reduce the ECMO settings (FiO_2 and sweep gas flow) indicates lung recovery. Weaning process is simple. Sweep gas flow is gradually reduced and turned off with increase in ventilator settings.

VA ECMO - Improvement in cardiac contractility on echocardiography indicates cardiac recovery. Weaning process is more complex. The ECMO flow is gradually decreased (or clamped). Ventilator settings are increased and hemodynamics assessed clinically and by echocardiography.

S. Decannulation. Once the patient's lung disease and the cardiac status have improved enough to tolerate moderate ventilator settings, decannulation is considered. In respiratory conditions, PaO_2 >60 mm Hg with FiO_2 of <0.50 and a PIP of 25 cm H_2O suggests the readiness for decannulation. If the neonate tolerates low ECMO flow or clamping with an acceptable ventilatory setting and good cardiac function, decannulation is indicated in cardiac conditions. At the time of decannulation from VA ECMO, the common carotid artery can be reconstructed or ligated. There is no significant difference in the long-term outcome whether the carotid artery had been repaired or ligated. The jugular vein is routinely ligated.

Discontinuation of ECMO support is also considered in the following situations: when the disease process becomes irreversible, failure to wean successfully, neurologic events (devastating neurologic examination, significant intracranial hemorrhage), or multiorgan system failure.

VII. SPECIAL SITUATIONS DURING EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT

A. ECMO circuit change. A change of the entire ECMO circuit is considered (i) if premembrane pressures exceed 350 mm Hg with no change in postmembrane pressure, or if the circuit is extensively thrombosed by visual inspection of the tubing; (ii) if CO_2 removal is impaired despite maximum sweep gas flow rate and the circuit is extensively clotted; (iii) if there is a gas-to-blood leak and the circuit is extensively clotted; and (iv) if 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 being taken to keep air out of the system and to maintain strict sterile barriers. Occasionally, partial circuit change or change in one of the components might need temporary clamping.

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 or cardiothoracic 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 can be 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.

VIII. COMPLICATIONS. Complications include mechanical and patient-related complications and the rate varies widely. Highest and lowest rates of complications of neonatal ECMO are depicted in Figure 39.2.

A. Mechanical. Common mechanical problems include clots in the circuit component (most common in oxygenator, pump, and bridge), cannula problems, oxygenator failure, clot in hemofilter, and air in the circuit. Rupture of tubing is a rare but potentially significant problem. Heat exchange malfunction is also rare. Poor venous return to the circuit causes the pump to shut down in order to avoid air entrainment. 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 catheter length, kinked tubing, and insufficient hydrostatic column length (height of the patient above the pump head). Initially, fluids are administered while other reasons for poor return are ruled out. Moderate to severe hemolysis can occur due to mechanical effects.

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. In the ECLS registry, 22.3% of newborns on ECMO received inotropic support and 12% received vasodilators for hypertension. According to the ECLS registry (January 2020), cardiac arrhythmia was reported in less than 5% of cases in

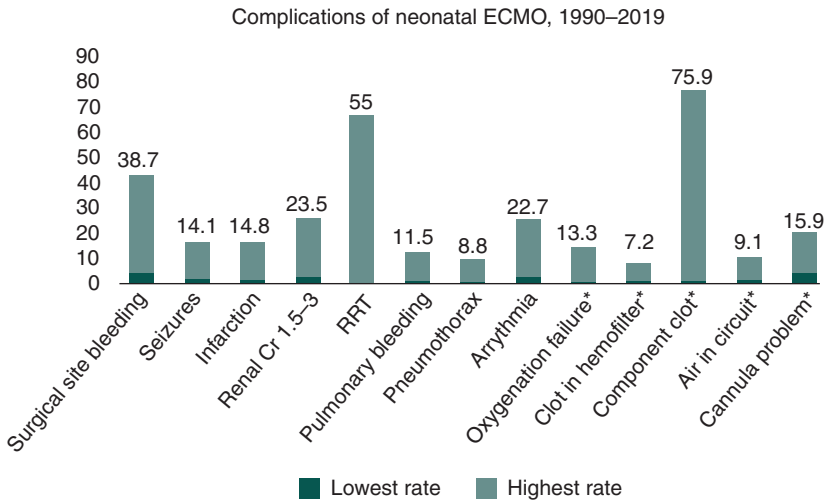

Figure 39.2. Complication rates of neonatal ECMO (respiratory/cardiac). (*) Mechanical complications. Cr, creatinine; RRT, renal replacement therapy. (*Source:* Extracorporeal Life Support Organization. *ECLS registry report. International Complication Trend Report*. https://www.elso.org/Portals/0/Files/Reports/2020_January/Complication%20Trend%20Report%20January%202020.pdf)

neonatal respiratory ECMO compared to in 10% to 20% of cases in neonatal cardiac ECMO.

C. **Hemorrhagic and thrombotic.** Hemorrhagic and thrombotic complications are very common. Apart from intracranial and pulmonary hemorrhage, other hemorrhages include surgical site (especially in CDH) and cannula site bleeding. Thrombosis results in cerebral infarction or leads to change in circuit in view of clots in the circuit or component (pump or oxygenator).

D. **Neurologic.** Sequelae resulting in neurologic damage often originate from acidosis and hypoxia before commencement of ECMO. Neurologic monitoring recommended during ECMO is depicted in Table 39.4. In 2019, the ELSO registry reported the occurrence of intraventricular and intraparenchymal hemorrhage as less than 4%, although the incidence was higher (11%) till 2015. A finer balance between prothrombotic and antithrombotic states helps in reducing the incidence of hemorrhage and thrombosis. Small intracranial hemorrhages are managed by optimizing clotting factors. Larger intracranial hemorrhages may force discontinuation of ECMO. IVH are commoner in preterm neonates. There is a higher incidence of ICH in the first week of ECMO. There is a higher rate of MRI abnormalities, ranging from 52% to 62%.

E. **Renal.** Some degree of renal impairment occurs in nearly all neonatal ECMO runs ranging from oliguria to progressive renal failure. Risk factors for renal failure include VA ECMO, need for E-CPR, and lower pre-ECMO pH. Renal failure may warrant continuous renal replacement therapy or hemodialysis, whereas concomitant fluid overload may require continuous venovenous hemodiafiltration during the ECMO run. Hemofiltration is common and was used in 15.6% of all neonatal ECMO runs (ECLS registry data). Long-term renal impairment is uncommon.

F. **Infection.** Neonates on ECMO are at an increased of infection due to multiple risk factors such as central line, poor nutritional status, prolonged ventilation, and general illness; longer duration of ECMO runs increases the risk of infection.

IX. OUTCOME

A. **Survival.** The ECLS database has reported the outcomes of ECMO therapies worldwide since 1985. A total of 32,385 ECMO runs (84% survival) for neonatal respiratory support were reported for neonatal respiratory disorders through January 2020 (see Table 39.1). In the recent years (since 2015), the most common indication for ECMO therapy was CDH, followed by MAS, PPHN, sepsis, and neonatal RDS. Survival rates for these conditions are shown in Table 39.2. Cardiac indication for initiating ECMO is increasing in the neonatal period. Mortality at 7 years of age after completion of the UK Collaborative ECMO trial was 33% in the ECMO group and 59% in the conventional group (Table 39.5).

B. **Neurodevelopment.** Neurologic follow-up was assessed 7 years after completion of the UK Collaborative ECMO trial (see Table 39.5). Both the ECMO and conventional therapy groups had developmental problems and impaired neurologic outcomes, but the ECMO group performed better in each task. Both groups had progressive sensorineural hearing loss and notable difficulties with learning

Table 39.5. UK Neonatal ECMO Trial; Overall Status by 7 Years of Age

Overall Status by 7 Years of Age	ECMO (*n* = 93) (%)	Conventional (*n* = 92) (%)
Deaths	31 (33)	54 (59)
Lost to follow-up	6 (6)	4 (4)
Children with		
Severe disability	3 (3)	0
Moderate disability	9 (10)	6 (7)
Mild disability	13 (14)	11 (12)
Children with		
Impairment only	21 (23)	15 (16)
No abnormal signs or disability	10 (11)	2 (2)
Survivors with no disability	31/56 (55)	17/34 (50)

ECMO, extracorporeal membrane oxygenation.
Source: McNally H, Bennett CC, Elbourne D, et al. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. *Pediatrics* 2006;117(5):e845–e854.

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 is still present after 7 years. As neonates initiated on ECMO are at an increased risk of neurologic disability including sensorineural deafness, they should be on a regular follow-up in a neurodevelopmental unit. ECMO survivors have an increased occurrence of deficits such as memory, executive function, and visuospatial functioning.

Suggested Readings

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40 Shock

Amir M. Khan

KEY POINTS

- Shock is a state of acute circulatory dysfunction resulting in insufficient oxygen and nutrient delivery, eventually causing cell death.
- Shock assessment includes *tissue and end-organ perfusion*, not just blood pressure.
- 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), inadequate oxygen delivery (dissociative shock), and intracardiac shunt (patent ductus arteriosus [PDA]).
- Outcomes of shock depend on severity and duration, timely and cause-specific treatment of shock should be supplemented with support of damaged end-organ.
- The choice of treatment modality (fluid bolus, inotropes, steroids, iNO, treatment of PDA) depends on the pathophysiology; echocardiography (ECHO) may be necessary adjunct to clinical assessment.

I. DEFINITION. Shock is defined as acute circulatory dysfunction resulting in insufficient oxygen and nutrient delivery to the tissues relative to their metabolic demand, leading to cellular dysfunction that may lead to lactic acidosis and if left uncorrected cause cell death. Shock is an important cause of neonatal mortality and morbidity. Its prognosis depends on the duration and severity of shock and the resultant extent of vital organ damage. Shock can lead to long-term morbidity including severe neurologic compromise because of cerebral ischemia and reperfusion injury. Therefore, recognizing shock promptly and initiating therapy to address the cause of shock and maintaining hemodynamic stability is essential. In the extremely premature newborn, the lowest acceptable blood pressures (BPs) that may be associated with end organ damage are not well established; treatment plan should include an assessment of tissue perfusion, end-organ function, and echocardiography (ECHO).

II. 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), inadequate oxygen delivery (dissociative shock) and intracardiac shunts (PDA). Distributive shock, with or without myocardial dysfunction, is the most frequent cause of shock, especially in preterm infants.

A. Distributive shock. Changes in vascular tone in neonates can be 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 hypoxic-ischemic injury 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 the 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 patent ductus arteriosus [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/asphyxia)
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. Large PDA in a premature infant diverting left ventricular output to pulmonary circulation (when uncompensated by an increase in left ventricular output)
2. Intrapartum asphyxia leading to myocardial depression
3. Bacterial or viral myocarditis. Congenital viral infections such as enterovirus are more likely to cause severe myocarditis.
4. Fetal or neonatal arrhythmias compromising cardiac output
5. Large arteriovenous malformations (AVMs) such as an intracranial AVM that diverts a considerable amount of cardiac output away from the systemic circulation
6. Metabolic abnormalities (e.g., hypoglycemia, hypocalcemia), or cardiomyopathy seen in infants of diabetic mothers
7. Persistent pulmonary hypertension of newborn (PPHN) can result in right ventricular (RV) failure. Inhaled NO (iNO) is the treatment of choice for shock due to RV dysfunction in PPHN.

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 (three atria), tricuspid atresia, and 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, 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 outflow

III. DIAGNOSIS.

At the onset of shock, normal compensatory mechanisms may be able to maintain 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 and is aptly named "compensated shock." During compensated shock, clinical findings may be subtle and include increased systemic vascular resistance (SVR) presenting as ***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. "Uncompensated shock" refers to the phase of shock when the patient develops hypotension, and its clinical presentation will reflect decreased perfusion to vital organs. 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 abnormalities. 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 may be the first signs of shock.

The objective diagnosis and management of shock centers around BP measurement in addition to early but nonspecific signs of poor peripheral perfusion.

Blood pressure.

A. Method of measurement of blood pressure. A standardized method for measuring noninvasive BP should be used, which is depicted as follows:

- Neonate position: Supine or prone
- Device type: Oscillometric device
- Cuff size: Cuff width to arm circumference ratio 0.45 to 0.55
- Cuff location: Right upper arm
- Timing
  - Neonate should be asleep, or should be quiet if awake.
  - Neonate should not be disturbed for at least 15 minutes after the cuff is placed.
  - BP measurement should be deferred after the baby has been disturbed by a procedure.
- Number of BP readings: At least three readings, 2 minutes apart

B. Normative values of BP. Normal range of BP values increases with an increase in the gestational age/birth weight and postnatal age. Figure 40.1 shows a population-based mean arterial pressure (MAP) nomogram for neonates with gestational ages between 23 and 43 weeks.

In clinical practice, hypotension is usually defined in one of the following three ways during the first postnatal days:

- MAP less than 30 mm Hg

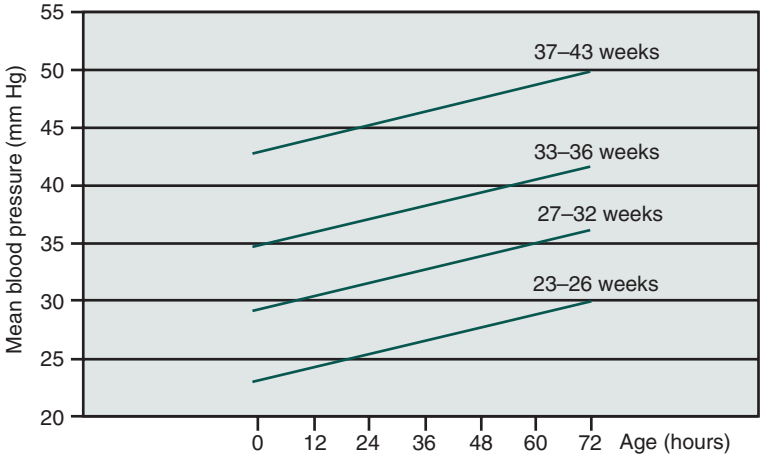

Figure 40.1. Nomogram for mean arterial pressure values based on postnatal and gestational age in neonates during the first 3 days of life. The nomogram is derived from 103 neonates with gestational ages between 23 and 43 weeks by continuous arterial blood pressure measurements. (From Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. *Clin Perinatol* 1999;26:981–996.)

- MAP below the neonate's gestational age in weeks at the time of birth
- Low BP value, accompanied by clinically detectable evidence of circulatory compromise, e.g., poor peripheral perfusion, decreased urine output, and/or lactic acidosis

IV. INVESTIGATIONS. Early signs of poor perfusion and indicators of organ dysfunction may be helpful in diagnosing and monitoring shock, and the initiation of treatment as described in the following text should not be delayed awaiting the laboratory indicators of shock. 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. Periodic serum lactate measurements may help predict outcome, and serial measurements may be helpful in assessing response to medical interventions.

Other investigations should focus on identifying the underlying etiology of shock based on clinical findings. Such evaluation may include an echocardiogram to assess cardiovascular anatomy and function, and appropriate laboratory studies to evaluate the presence of infection, anemia, dehydration, etc.

In addition to defining cardiac anatomy, functional ECHO may be used to assess the cardiac function over time. With the help of functional ECHO, we can assess cardiac output (CO) and volume status of a neonate. TnECHO (targeted neonatal ECHO or neonatologist preformed ECHO (NPE) allows objective evaluation of underlying pathophysiology and thus choosing the right therapies. TnECHO allows serial monitoring of response to therapy (or worsening of function). TnECHO also provides serial objective evaluation of cardiac status (cardiac function), this objective documentation allows research (evaluation of therapies) to be unbiased. Various ways of assessing the CO are by measuring the right ventricular output (RVO), left ventricular output (LVO), descending aorta (DAo) flow, and superior vena cava (SVC) flow. Fetal shunts such as PDA and patent foramen ovale can increase the LVO and RVO flows, respectively, thereby overestimating the CO. Therefore, SVC flow measurement is used in the presence of fetal shunts for the assessment of CO. Various studies have shown increased morbidity and mortality when ventricular output is <150 mL/kg/minute or SVC flow is <40 mL/kg/minute.

To assess hypovolemia, various subjective echocardiographic markers are used, such as left ventricular end-diastolic diameter, left atrial diameter, left atrium/aorta (LA/Ao) ratio, and collapsibility of the inferior vena cava.

Near-infrared spectroscopy (NIRS) may help with assessing the regional 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.

V. TREATMENT. 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 shock in the neonate.

A. Fluid therapy. The initial approach is usually to administer crystalloids such as normal saline. An infusion of 10 mL/kg 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 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. When managing shock, it is important to correct hypovolemia and improve cardiac output, before using inotropes or steroids.

In this regard, measurement of central venous pressure (CVP) may help in the management, especially in term or late preterm infants. In neonates, measurement of CVP is not commonly practiced. CVP in neonates is influenced by noncardiac factors such as mechanical ventilator pressures and high heart rates, and by cardiac factors such as tricuspid valve function. These affect the interpretation and usefulness of CVP measurements, besides technical challenges of placing a catheter in the right atrium in a sick baby.

B. Supportive treatment. Correction of negative inotropic factors such as hypoxia, acidosis, hypoglycemia, and anemia, and other metabolic derangements such as hypocalcemia must be addressed.

- **Correction of hypoxia.** Optimization of oxygenation and carbondioxide elimination, with least work of breathing is achieved by the right choice of respiratory support. Optimal PEEP is critical, too much PEEP can result in decreased venous return to heart and poor preload. Suboptimal PEEP causes increase in pulmonary vascular resistance (PVR) besides abnormal gas exchange. This causes significant decrease in cardiac output.
- **Correction of hypoglycemia.** Glucose is the substrate to myocardial cells and also to cells maintaining vascular tone, sick babies may have increased glucose needs and may tolerate lower fluid volumes. This may required higher concentration of dextrose administered through a central catheter.
- **Correction of hypocalcemia.** 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.
- **Correction of Anemia.** Packed red cell transfusion may be considered at PCV 40 in presence of severe/persistent shock as compared to lower values of PCV 30-21 in babies on respiratory support or anemia of prematurity with normal perfusion.
- **Correction of acidosis.** Acidosis causes cellular dysfunction and must be corrected by correction of underlying cause. Use of alkali therapy (sodium bicarbonate) is likely to be harmful than beneficial and is reserved for most severe and refractory shock.

C. Medications

1. **Inotropes** are used to improve cardiac function and include the following (Table 36.1):
   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. 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. The increase in myocardial contractility depends in part on myocardial norepinephrine stores. It *is an inotrope of choice in hypotensive shock.*

ii. **Dobutamine** is a synthetic catecholamine with relatively cardioselective inotropic effects. In doses of 5 to 15 μg/kg/minute, dobutamine increases cardiac output *with little effect on heart rate*. Dobutamine can decrease SVR and is often used with dopamine to improve cardiac output *in cases of decreased myocardial function.* Its inotropic effects, unlike those of dopamine, are independent of norepinephrine stores. However, because hypotension is a result of decreased SVR in the majority of nonasphyxiated newborns, *dopamine remains the first-line pressor therapy in newborns.*

iii. **Epinephrine** has potent inotropic and chronotropic effects in the 0.05- to 0.3-μg/kg/minute doses. At these doses, it has greater β_2-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 an increase in cardiac contractility. It improves diastolic myocardial function more readily than dobutamine. Milrinone also lowers *pulmonary vascular resistance (PVR) and SVR* by increasing cAMP levels in the vascular smooth muscle, and hence is a useful drug in left ventricular (LV) or RV dysfunction. Often there is a fall in BP due to vasodilatation necessitating the use of volume and dopamine (see Appendix A for dosage).

2. **Vasopressor therapy** is used to increase SVR and improve BP which will 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 SVR.

b. **Vasopressin** has primarily been studied in adults for the treatment of shock, with limited experience in neonates. It is a hormone that is primarily 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 are some data for

the use of vasopressin in PPHN and post-cardiac surgery in neonates. It is not routinely used to treat shock in the infants but may be a therapeutic option to consider in the setting of abnormal peripheral vasoregulation. A proposed benefit of vasopressin therapy may be its inhibitory action on NO-induced increases in the second messenger cyclic guanosine monophosphate (cGMP), a potent vasodilatory signal that predominates in the setting of sepsis from the increased endotoxin/inflammation-induced NO synthesis (usual dose of vasopressin is 0.0002 to 0.006 μg/kg/minute).

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 1 mg/kg. If efficacy is noted, the dose can be repeated every 8 hours for 2 to 3 days. Lower doses may be sufficient as maintenance dose once hypotension is corrected.

VI. TYPICAL CLINICAL SCENARIOS OF SHOCK IN THE NEONATE AND THEIR MANAGEMENT

A. Very low-birth-weight (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 is unclear. In general, a mean BP that equals the baby's gestational age in weeks is considered adequate if there is adequate perfusion and urine output. Pressor therapy has been associated with worse outcomes in ELBW infants (retrospective studies), but it remains uncertain whether this is due to the underlying cause of hypotension itself or its therapy.
3. Recommended initial therapy includes 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, especially in extreme preterm.

B. Perinatal depression in preterm or full-term neonate

1. Physiology involves the release of endogenous catecholamines leading to normal or increased SVR clinically manifested by pallor, mottled appearance, and poor perfusion and myocardial dysfunction. The baby is likely to be euvolemic and may have associated pulmonary hypertension.
2. Recommended therapy is dopamine with or without dobutamine up to 10 μg/kg/minute. Milrinone can be considered to provide afterload reduction

and inotropic effects without risk of further myocardial injury due to excess catecholamine exposure. Some infants may manifest vasodilatory shock and would benefit from increased doses of dopamine. ECHO (assessment of perfusion, in the absence of clinician-performed ECHO) can be used to guide therapy.

3. Timely management of shock following asphyxia is critical, delay can worsen the brain injury. Troponin T and muscle fraction creatinin kinase are markers of cardiac injury. Sinus bradycardia and prolonged QT are common with therapeutic hypothermia (TH, cooling), heart rates can be as low as 80 bpm. Hypotension or arrhythmia are not commoner in cooled babies with asphyxia. Volume resuscitation (boluses) must be carefully administered, as renal dysfunction and SIADH can significantly cause fluid retention.

   Cerebral autoregulation is significantly disturbed and the rise in blood pressure and brain perfusion following therapy can be harmful. Monitoring of cardiac output (SVC output) and regional brain circulation (NIRS) may be the future of optimizing shock management in asphyxia.

4. **Resuscitation with placental circulation** (before clamping the cord) has shown significant benefits in cerebral circulation in experimental studies. The placenta offers a low resistance circuit and mitigates the rebound hypertension and cerebrovascular injury.

C. Septic shock

1. Physiology involves relative hypovolemia, myocardial dysfunction, peripheral vasodilation, and increased pulmonary pressures secondary to acidosis and hypoxia.
2. Therapy includes volume resuscitation with crystalloid (10 to 30 mL/kg) which should be repeated as needed and administration of dopamine 5 to 20 μg/kg/minute with or without epinephrine 0.05 to 0.3 μg/kg/minute. An ECHO to evaluate cardiac function, superior vena cava flow, cardiac output, and intracardiac shunting will ensure appropriate choice of therapy. 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 with increased risk of pulmonary hemorrhage.
2. Recommended therapy includes dobutamine to enhance cardiac inotropy. Target ventilation management to increase PVR by increasing positive end-expiratory pressure (PEEP), maintaining permissive hypercarbia, and avoiding hyperoxygenation has not shown clear benefit. Medical/surgical closure of PDA may be necessary.
3. **Strategy for treatment of PDA in extreme preterm.** Extreme preterm babies are at high risk of intraventricular hemorrhage and pulmonary hemorrhage resulting in higher mortality and neurodisability. These complications are closely related to changes in circulation associated with hemodynamically significant PDA. Prophylaxis is associated with higher rates of PDA closure, but there are risks. Selective closure results in lower success. Current strategy may best

be early ECHO guided targeted group among babies <26 weeks, who are at higher risk of complications of PDA.

4. **Medical closure of PDA.** Oral brufen was more effective than IV brufen and indomethacin, there were no differences in mortality, NEC, or IVH rates. Paracetamol seems to be as effective as brufen and indomethacin, with no differences in development outcomes.

E. Preterm neonates with "pressor-resistant" hypotension

1. Late-onset glucocorticoid-responsive circulatory collapse (LGCC) in VLBW is resistant to volume expanders and inotropes but responds rapidly to intravenous steroids. LGCC is common after the first week of life. Adrenal insufficiency is most likely cause.
2. Consider low-dose hydrocortisone (1 to 3 mg/kg/day for 2 to 5 days in three 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. Increased incidence of intestinal perforation is reported in infants who have been treated with indomethacin and hydrocortisone concurrently.

F. PPHN. Choice of inotropes in PPHN may be guided by functional ECHO performed by neonatologist:

1. Normal BP/normal ventricular function: Sildenafil
2. Normal BP/ventricular dysfunction: Milrinone
3. Low BP/normal ventricular function: Fluid/adrenaline/vasopressin
4. Low BP/ventricular dysfunction: Milrinone plus adrenaline

G. Shock in congenital heart disease. Major congenital heart disease in neonates can present with acute circulatory failure or cardiogenic shock starting from day 1 of life. Treatment options, include diuretics, prostin, catecholamines, phosphodiesterase inhibitors, and occasionally ECMO.

Post surgery low cardiac output syndrome is dominantly due to severe pulmonary artery hypertension. Therapies include nitric oxide, slidenafil, and iloprost.

VII. OBJECTIVE CARDIOVASCULAR ASSESSMENT. Blood pressure, clinical assessment of perfusion, and ECHO currently guide cardiovascular and cerebral support. Objective tools likely to be used in future include NIRS, pulsatality index, continuous EEG, and bioimpedance derivatives singly or combined into decision support systems.

Suggested Readings

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41 Cardiac Disorders

John P. Breinholt

KEY POINTS

- The incidence of congenital heart defects (CHD) is 6 to 8 per 1,000 live births.
- The most critical CHD are usually symptomatic in the newborn period.
- Prompt recognition and treatment of critical congenital heart disease can be lifesaving.
- In the current era, most forms of critical CHD in the neonate can be offered an effective form of surgical or catheter-based treatment with excellent outcomes.
- Prenatal diagnosis and routine neonatal pulse oximetry screening before discharge permit early diagnosis of critical CHD and contribute to improved outcomes after treatment.

I. INTRODUCTION. Pediatric cardiology is a relatively young field. In an early 20th-century textbook of medicine, Dr William Osler dismissed congenital heart disease as "limited clinical interest as in a large proportion of cases the anomaly is not compatible with life, and in others, nothing can be done to remedy the defect or even relieve the symptoms." This would change dramatically in 1938, when Dr Robert Gross successfully ligated a patent ductus arteriosus (PDA) in a 7-year-old girl at Children's Hospital, Boston. In the current era, in the developed countries, most critical forms of congenital heart defects (CHD) are diagnosed by prenatal screening or in the early neonatal period by routine pulse oximetry screening. Improvements in surgical techniques and postoperative care have dramatically changed the outlook for most forms of critical CHD in the developed nations. Even in low- and middle-income countries, many centers have started performing neonatal cardiac surgeries with excellent outcomes in the current era.

In critical congenital heart disease, patient outcomes are dependent on (i) early and accurate identification of the cardiac lesion and (ii) initiation of specific cardiac care prior to the occurrence of secondary organ damage. Therefore, an important mantle of responsibility rests on the neonatologists and pediatricians who often first evaluate and manage these patients. Thereafter, a multidisciplinary team of several subspecialty services is frequently required to avoid the deleterious effects of the cardiac disease on the heart, lung, and brain. Such effects include failure to thrive, increased infection risk, pulmonary vascular disease, cognitive developmental delay, and neurologic deficits. 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. Additional details about specific heart defects and

conditions can be found in current textbooks of pediatric cardiology and pediatric cardiac surgery.

II. INCIDENCE AND SURVIVAL. The reported incidence of CHD in live born infants varies between 6 and 8 per 1,000 live births, resulting in 25,000 to 35,000 infants with congenital heart disease each year in the United States alone. In India, this number is estimated to be 200,000 per year, with one-fifth of them requiring intervention in the first year. This incidence has remained constant over the past several decades. Some reports indicate a higher incidence (1.2%), but this is likely to be due to inclusion of minor defects such as muscular ventricular septal defects (VSDs) that will resolve spontaneously or findings such as bicuspid aortic valve which may have an impact in later life. Data from large population studies suggest that approximately 1 per 110 live births has congenital heart disease, and approximately 25% of CHD are considered critical congenital heart disease, requiring intervention in the first year of life. Most of these infants with congenital heart disease are identified by the end of the neonatal period. The most common congenital heart lesions presenting in the first weeks of life are summarized in Table 41.1. 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 (<5%) in the past decade.

III. CLINICAL PRESENTATIONS OF CONGENITAL HEART DISEASE IN THE NEONATE. The timing of presentation is dependent on three primary elements: (i) the type and severity of the congenital defect; (ii) alterations in the cardiovascular physiology secondary to the effects of the transitional circulation, principally **closure of the ductus arteriosus and foramen ovale** (FO) and the decrease **in pulmonary vascular resistance**; and (iii) any *in utero* effects of the defect.

The first 72 hours after birth are particularly important because many of the most severe and acutely life-threatening lesions present in this time frame.

A. Parallel, nonmixing circulations. The primary diagnosis of this description is D-transposition of the great arteries (D-TGA). D-TGA is defined as the aorta arising from the morphologically right ventricle, wherein the systemic venous blood returns to the right cardiac chambers and returns to the systemic arterial system without passing through the pulmonary vasculature. The pulmonary artery arises from the morphologically left ventricle, leading to the fully oxygen-saturated blood from the pulmonary venous system returning to the left cardiac chambers, and then returning to the pulmonary vasculature. As such, the two circulations work in parallel, with oxygen-saturated blood not reaching the systemic circulation.

The two locations where the oxygen-saturated blood can enter the systemic circulation are (i) the FO and (ii) the ductus arteriosus (PDA). The intercirculatory mixing principally occurs at the level of the FO while the PDA contributes more to the pulmonary blood flow. With restriction of the FO and PDA as a part of the transitional circulation, the delivery of the oxygenated blood to the body dramatically decreases. Without intervention, the neonate will become increasingly cyanotic and develop metabolic acidosis and life-threatening circulatory changes.

Table 41.1. Top Five Diagnoses Presenting at Different Ages*

Diagnosis	Percentage of Patients
Age on admission: 0–6 days (n = 537)	
D-Transposition of great arteries	19
Hypoplastic left ventricle	14
Tetralogy of Fallot	8
Coarctation of aorta	7
Ventricular septal defect	3
Others	49
Age on admission: 7–13 days (n = 195)	
Coarctation of aorta	16
Ventricular septal defect	14
Hypoplastic left ventricle	8
D-Transposition of great arteries	7
Tetralogy of Fallot	7
Others	48
Age on admission: 14–28 days (n = 177)	
Ventricular septal defect	16
Coarctation of aorta	12
Tetralogy of Fallot	7
D-Transposition of great arteries	7
Patent ductus arteriosus	5
Others	53

*Reprinted with permission from Flanagan MF, Yeager SB, Weindling SN. Cardiac disease. In: MacDonald MG, Mullett MD, Seshia MMK, eds. *Avery's Neonatology: Pathophysiology and Management of the Newborn.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

Palliative interventions are urgently needed to prevent this clinical decompensation. These include initiation of a prostaglandin E_1 (PGE_1) infusion that maintains patency of the ductus arteriosus. Frequently, if this is insufficient, a balloon atrial septostomy is necessary, to improve the intercirculatory mixing. These interventions allow time to stabilize the patient in anticipation of neonatal reparative surgery (arterial switch operation).

B. Critically obstructed left heart lesions. This group of cardiac defects includes those in which patency of the ductus arteriosus is necessary to maintain systemic

blood flow (duct-dependent systemic circulation). As a result of the expected ductal constriction and closure, the neonate will become acidotic and develop cardiogenic shock. Some of these lesions can present later in life; however, those that present in the first 72 hours are of a more severe nature.

1. **Hypoplastic left heart syndrome.** This defect comprises underdevelopment of left heart structures including the mitral and aortic valve (either stenotic or atretic), small or absent left ventricular chamber, hypoplasia of the ascending aorta, and transverse aortic arch with coarctation.
2. **Critical aortic valve stenosis.** In its most severe form, systemic output is dependent on the PDA because sufficient blood flow does not cross the aortic valve to sustain the body. Less severe forms can be monitored beyond the neonatal period and may not require intervention for months or years.
3. **Coarctation of the aorta.** The most common site of coarctation is near the ductus arteriosus, and as the ductus arteriosus closes, the inadequate systemic output manifests. Again, less severe forms may not be discovered until months or years after the neonatal period. Those requiring early and urgent intervention are those with the most severe disease.
4. **Interrupted aortic arch.** In this lesion, there is absence of continuity between the ascending and the descending aorta. The different types are distinguished by the location of discontinuity relative to the head and neck vessels. Without the PDA, there is no blood flow to the lower body.

C. Critically obstructed right heart lesions. This group of cardiac defects includes those in which patency of the ductus arteriosus is necessary to maintain pulmonary blood flow. As a result, the neonate will become cyanotic without appropriate intervention. Milder forms of these lesions may present later in life; however, those that present in the first 72 hours are of a more severe nature.

1. **Pulmonary atresia (PA).** Here the pulmonary valve is completely closed with no antegrade flow from the right ventricle into the pulmonary artery. As a result, pulmonary blood flow is entirely dependent on the ductus arteriosus. This lesion presents in multiple forms:
   a. **PA with intact ventricular septum.** In this variant, blood flow in the right ventricle has no outlet other than via tricuspid regurgitation and subsequent right-to-left shunt across the FO. The high pressure generated in the right ventricle, in the absence of outflow, is correlated with coronary artery fistulas that can be dependent on the high pressure in the ventricle for coronary blood flow. This presents an independent risk factor for this disease.
   b. **PA with VSD.** This is often a severe form of tetralogy of Fallot. In this variant, systemic venous blood entering the right ventricle will mix with pulmonary venous blood entering the left ventricle and enter the systemic circulation via the aortic valve.
   c. **PA with complex forms of CHD such as tricuspid atresia, single ventricle, double outlet right ventricle, unbalanced atrioventricular (AV) septal defect, and similar complex lesions.** In most of these lesions, there will be complete admixture of systemic and pulmonary venous circulations.
2. **Critical pulmonary valve stenosis.** In its most severe form, pulmonary blood flow is dependent on the PDA because sufficient blood does not cross the

pulmonary valve to provide effective pulmonary blood flow. Less severe forms can be monitored beyond the neonatal period and may not require intervention for months or years.

3. **Ebstein's anomaly.** This disease is a product of distal displacement of the tricuspid valve into the right ventricle. The result is a large right atrium with an "atrialized" right ventricle and a limited, functional right ventricular (RV) chamber. In its severe form, due to severe tricuspid regurgitation, there will be very little forward flow of blood into the pulmonary artery (called functional PA), thus requiring the patency of the PDA to maintain pulmonary blood flow. Milder forms have been found incidentally in adulthood and may not require intervention.

D. Total anomalous pulmonary venous connection (TAPVC). The obstructed form of anomalous pulmonary venous connection has the initial clinical manifestation similar to pulmonary hypertension but should be considered when traditional pulmonary hypertension therapies are ineffective. Typical clues can be obtained by features of pulmonary edema in chest x-ray. The unobstructed form of TAPVC presents with milder clinical features, typically like a large left-to-right shunt, with cyanosis. Obstructed TAPVC is a surgical emergency and there is no medical management that will improve this condition.

Without acute intervention, many of the heart lesions described above can have significant morbidity and mortality. Hence, it is important for pediatricians and neonatologists to screen for these defects early and before discharge of the baby from the hospital. A combination of prenatal diagnosis and neonatal screening offers the best chance for early diagnosis of these life-threatening conditions. Important clinical findings should alert the clinician to the possibility of congenital heart disease. Key findings that require additional evaluation include (i) cyanosis, (ii) congestive heart failure (CHF), (iii) cardiovascular collapse or shock, (iv) heart murmur, and (v) arrhythmia.

IV. CLINICAL MANIFESTATIONS OF CONGENITAL HEART DISEASE

A. Cyanosis

1. **Clinical findings.** Cyanosis (bluish tinge of the skin and mucous membranes) is a common presenting sign of congenital heart disease in the neonate. In the setting of congenital heart disease, cyanosis is an indication of hypoxemia or decreased arterial oxygen saturation. However, depending on the underlying 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) and 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. Also, there are a few instances when cyanosis is associated with normal arterial oxygen saturation. True 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 determining cyanosis by visual inspection can be challenging for the reasons mentioned, adding routine preductal and postductal extremity pulse oximetry has been proposed as an additional screening test in the first 48 hours of life. Several studies from all over the world have demonstrated good sensitivity (around 60% to 70%) and very high specificity (>95%) for pulse oximetry screening for the detection of critical CHD in the newborn. Importantly, the combination of clinical examination and pulse oximetry screening has demonstrated better sensitivity than either form of screening alone. In 2011, the U.S. Secretary of Health and Human Services recommended that critical CHD be added to the U.S. Recommended Uniform Screening Panel for newborns. Current recommendations advocate routine screening of all neonates with a single lower extremity pulse oximetry screening, 24 hours after birth. Pulse oximetry reading of <95% requires a reassessment and careful clinical evaluation. If the repeat screen and/or clinical examination is positive, further cardiac evaluation with echocardiography is recommended. Multiple states have included it in their screening mandates, with additional studies to validate its clinical and cost-effectiveness underway.

2. **Differential diagnosis.** Differentiation of cardiac from respiratory causes of cyanosis in the neonatal intensive care unit (NICU) is a common problem. Pulmonary disorders are frequently the cause of cyanosis in the newborn due to intrapulmonary right-to-left shunting. Primary lung disease (pneumonia, hyaline membrane disease, pulmonary arteriovenous malformations, etc.), pneumothorax, airway obstruction, extrinsic compression of the lungs (congenital diaphragmatic hernia, pleural effusions, etc.), and central nervous system abnormalities may produce varying degrees of hypoxemia manifesting as cyanosis in the neonate. For a more complete differential diagnosis of pulmonary causes of cyanosis in the neonate, see Chapters 33 to 38. Finally, clinical cyanosis may occur in an infant without hypoxemia in the setting of methemoglobinemia or pronounced polycythemia. Table 41.2 summarizes the differential diagnosis of cyanosis in the neonate.

B. Congestive heart failure

1. **Clinical findings.** 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. Signs and symptoms of CHF occur when the heart is unable 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. Diaphoresis during feeding is a common scenario that this symptom manifests. Finally, CHF may present acutely with cardiorespiratory collapse, particularly in "left-sided" lesions (see section VI.A). *Hydrops fetalis* is an extreme form of intrauterine CHF (see Chapter 5).

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's 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
Extrinsic compression of the lungs
Pneumothorax
Pulmonary interstitial or lobar emphysema
Chylothorax or other pleural effusions

(continued)

Table 41.2. Differential Diagnosis of Cyanosis in the Neonate
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)

PO_2, partial pressure of oxygen.
*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).

2. **Differential diagnosis.** The age when CHF develops depends on the physiologic effects of the underlying lesion. 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.

C. Heart murmur. Heart murmurs are not uncommonly heard while examining neonates. It is estimated that >50% of children have a murmur at some point during childhood, with the majority presenting in the neonatal period. Murmurs heard in the newborn in the first days of life are often associated with structural heart disease of some type, and therefore may need further evaluation, particularly if there are any other associated clinical symptoms. Nevertheless, it is not uncommon for an innocent murmur to be heard during the transition from fetal circulation, specifically before the closing of the PDA. Other transient murmurs may be heard, including a very small muscular VSD that is closing or peripheral branch pulmonary artery stenosis that is due to blood flow turbulence at the pulmonary artery branches that disappears as the branches grow.

Pathologic murmurs tend to appear at characteristic ages. Semilunar valve stenosis (systolic ejection murmurs) and AV valvular insufficiency (systolic regurgitant murmurs) tend to be noted very shortly after birth, on the first day of life. 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

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
Secondary
Sustained tachyarrhythmias
Perinatal asphyxia
Sepsis
Severe intrauterine valvular obstruction (e.g., aortic stenosis)
Premature closure of the ductus arteriosus

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.

D. Arrhythmias. See section IX for a detailed description of the identification and management of the neonate with an arrhythmia.

E. Fetal echocardiography. In the modern era, with the widespread use of first trimester screening and midtrimester anomaly scans, a considerable proportion of major and complex forms of CHD are being diagnosed in the pregnancy period itself. Standard protocols have been laid down for the conduct of the fetal heart examination. Information from prenatal diagnosis may be quite valuable to the team of physicians caring for the mother and baby, guiding 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 12 to 14 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 to note, however, that most cases of prenatally diagnosed congenital heart disease occur in pregnancies without known risk factors. Some critical forms of CHD such as coarctation of the aorta, TAPVC, and coronary anomalies may be missed in fetal echocardiography. Minor CHDs such as small ventricular and atrial septal defects, mild aortic or pulmonary stenosis, and physiologic findings such as patent foramen ovale (PFO) and PDA cannot be diagnosed by fetal echocardiography.

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 and decide the need for transplacental therapy. Most forms of fetal tachycardias can be effectively controlled by maternal transplacental therapy with good neonatal outcomes. Fetal bradyarrythmias may be isolated (usually in association with maternal autoimmune disease) or associated with CHD. Fetal complete heart block (CHB) may need transplacental therapy, if it is hemodynamically significant, and in most cases, postnatal pacemaker implantation will be needed in the first year of life.

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. Several institutions have begun intervening in semilunar valve stenosis, as well as select other defects. Early data on the outcomes of these interventions (especially fetal aortic valvuloplasty) are encouraging with respect to prospects of a postnatal biventricular circulation. However, the selection criteria are evolving and most live-born babies need various forms of postnatal catheter or surgical interventions.

V. EVALUATION OF THE NEONATE WITH SUSPECTED CONGENITAL HEART DISEASE.

The most time-sensitive presentation of the neonate with congenital heart disease is circulatory collapse. In this scenario, emergency treatment of circulatory shock should precede cardiac diagnostic studies. Low cardiac output in a neonate should always generate a suspicion for congenital heart disease.

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

A. Initial evaluation

1. **Physical examination.** The physical examination should extend beyond the heart. Inexperienced examiners frequently focus solely on the presence or absence of cardiac murmurs, but many other findings can guide diagnostic decision making.

   a. **Inspection**. Cyanosis may first be apparent on inspection of the mucous membranes and/or nail beds (see section IV.A.1). Mottling of the skin and/or an ashen, gray color are important clues to severe cardiovascular compromise and incipient shock. While observing the infant, particular attention should be paid to the pattern of respiration including the work of breathing and use of accessory muscles.

   b. **Palpation.** Palpation of the **distal extremities** with attention to temperature and capillary refill is imperative. Although cool extremities with delayed capillary refill would indicate a suspicion of sepsis, it should also raise a suspicion of congenital heart disease. While palpating the distal extremities, note the presence and character of the distal pulses. Diminished or absent distal pulses are suggestive of aortic arch obstruction. Palpation of the *precordium* may provide important information suggesting congenital heart disease. A precordial thrill may be present in the setting of at least moderate pulmonary or aortic outflow obstruction. A restrictive VSD with low RV pressure could also generate a thrill; however, it is less likely in the early neonatal period. A hyperdynamic precordium suggests a significant left-to-right shunt or volume overload of the ventricles.

   c. **Auscultation.** This part of the examination should be performed systematically and not be rushed to identify heart murmurs. Many severe CHD will not have a murmur in the neonatal period. First, listen to the heart rate to determine whether it is regular. Second, listen carefully to the heart sounds. The second heart sound is important because its split indicates the presence of two semilunar valves. Hearing this can be difficult in neonates who have fast heart rates. Absence of normal S2 splitting (single S2 or fixed split) should immediately raise the suspicion of underlying CHD. However, the presence of a S3 or S4 is abnormal and should prompt further study and consultation. 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) AV valve regurgitation. Diastolic murmurs are **always** indicative of cardiovascular pathology. For a more complete description of auscultation of the heart, refer to the cardiology texts from the section "Suggested Readings."

      A careful search for other anomalies is essential because congenital heart disease is accompanied by at least one extracardiac malformation in 25% of these patients. Table 41.5 summarizes malformation and chromosomal syndromes commonly associated with congenital heart disease.

2. **Four-extremity blood pressure.** Measurement of blood pressure should be taken in bilateral upper and lower extremities. The lower extremities should

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 13 (Patau's 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's 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)
Trisomy 21 (Down's 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's 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
Single-gene defects			
Noonan's 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

(Continued)

Table 41.5. Chromosomal Anomalies, Syndromes, and Associations Commonly Associated with Congenital Heart Disease

	Approximate Incidence or Mode of Inheritance	Extracardiac Features	Cardiac Features
Holt's–Oram syndrome	AD	Spectrum of upper limb and shoulder girdle anomalies	≥50% have cardiac defect, usually ASD or VSD
Alagille's 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's 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's syndrome (deletion 22q11)	1/6,000	Thymic hypoplasia/aplasia; parathyroid hypoplasia/aplasia; cleft palate or velopharyngeal incompetence	IAA and conotruncal malformations including truncus, TOF
Associations			
VACTERL		Vertebral defects, anal atresia, cardiac defects, TE fistula, radial and renal anomalies, limb defects	Approximately 50% have cardiac defect, most commonly VSD

(Continued)

Table 41.5. Chromosomal Anomalies, Syndromes, and Associations Commonly Associated with Congenital Heart Disease

	Approximate Incidence or Mode of Inheritance	Extracardiac Features	Cardiac Features
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)

AD, autosomal dominant; ASD, atrial septal defect; CAVC, complete atrioventricular canal; CM, cardiomyopathy; CoA, coarctation of the aorta; DORV, double outlet right ventricle; FIT, failure to thrive; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PPS, peripheral pulmonary stenosis; SGA, small for gestational age; TE, tracheoesophageal; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

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 for an accurate measurement. A systolic pressure that is 10 to 15 mm Hg higher in the upper body compared to in 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.** Multiple studies indicate improved detection of congenital heart disease with the implementation of routine pulse oximetry screening. As such, many countries include this as part of the neonatal evaluation. The primary approach includes preductal and postductal extremity pulse oximetry measurement >24 hours after birth. Values <95% would result in further evaluation with echocardiography. A difference of >4% between the upper and the lower extremity pulse oximetry is significant and could indicate the presence of a critical aortic arch obstruction with right-to-left shunting across the ductus arteriosus. Some investigators suggest that the threshold may need to be adjusted for patients born at altitude.

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 suggest decreased pulmonary blood flow, whereas diffusely opaque lung fields may represent increased pulmonary blood flow or significant left atrial hypertension (like in an obstructed TAPVC).

5. **Electrocardiogram (ECG).** The neonatal ECG reflects the hemodynamic relations that existed *in utero*; therefore, the normal ECG is notable for RV predominance. As many forms of congenital heart disease have minimal prenatal hemodynamic effects, the ECG is frequently "normal for age" despite significant structural pathology (e.g., TGA, tetralogy of Fallot). Throughout the neonatal period, infancy, and childhood, the ECG will evolve due to the expected changes in physiology and the resulting changes in chamber size and thickness that occur. 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.

Table 41.6. ECG 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 (°)	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)
V1, 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)
V1, 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)
V6, 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)
V6, 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 (°)	127 (75–194)	121 (75–195)	117 (75–165)	80 (17–171)
PR interval (seconds)	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 (seconds)	0.04	0.04	0.04	0.04
V1, 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)
V1, 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)

(Continued)

Table 41.6. ECG Standards in Newborns

	Age (Days)			
Measure	**0–1**	**1–3**	**3–7**	**7–30**
V6, 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)
V6, 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)

ECG, electrocardiogram. *Source:* Davignon A, Rautaharja P, Boiselle E, et al. Normal ECG standards for infants and children. *Pediatr Cardiol* 1980;1(2):123–131; 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.

Table 41.7. ECG Findings in Premature Infants (Compared to in 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 second (longer than for term infants, QT_c <0.40 second)
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

ECG, electrocardiogram. *Source:* Reproduced with permission 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.

When interpreting an ECG, the following determinations should be made: (i) rate and rhythm; (ii) P and QRS axes; (iii) intracardiac conduction intervals; (iv) evidence for chamber enlargement or hypertrophy; (v) evidence for pericardial disease, ischemia, infarction, or electrolyte abnormalities; and (vi) whether 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 (Table 41.7).

6. **Hyperoxia test.** In neonates with suspected critical congenital heart disease (not just those who are cyanotic), a hyperoxia test may be considered. In the era of widespread availability of pulse oximetry screening and neonatal echocardiography, the hyperoxia test may find its value more in sick ventilated patients than in more stable neonates. This test is a sensitive and specific tool in the initial evaluation of the neonate with suspected disease.

   To investigate the possibility of 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 "hyperoxia test"). If possible, the arterial partial pressure of oxygen (PO_2) should be measured directly through arterial puncture, although properly applied transcutaneous oxygen monitor (TCOM) values for PO_2 are also acceptable. **Pulse oximetry cannot be used** for documentation; in a neonate given 100% inspired oxygen, a value of 100% oxygen saturation may be obtained with an arterial PO_2 ranging from 80 torr (abnormal) to 680 torr (normal, see section IV.A.1).

Measurements should be made (by arterial blood gas or TCOM) at both "preductal" and "postductal" sites and the exact site of PO_2 measurement must be recorded because some congenital malformations with desaturated blood flow entering the descending aorta through the ductus arteriosus may result in "differential cyanosis" (as seen in persistent pulmonary hypertension of the newborn). Markedly higher oxygen content in the upper than in the lower part of the body can be an important diagnostic clue to such lesions, including all forms of critical aortic arch obstruction or left ventricular outflow obstruction. There are also the rare cases of "reverse differential cyanosis" with elevated lower body saturation and lower upper body saturation. This occurs only in children with TGA with an abnormal pulmonary artery to aortic shunt due to coarctation, interruption of the aortic arch, or suprasystemic pulmonary vascular resistance ("persistent fetal circulation").

When a patient breathes 100% oxygen, an arterial PO_2 of >250 torr in both upper and lower extremities virtually eliminates critical structural cyanotic heart disease (a "passed" hyperoxia test). An arterial PO_2 of <100 in the absence of clear-cut lung disease (a "failed" hyperoxia test) is most likely due to intracardiac right-to-left shunting and is virtually diagnostic of cyanotic congenital heart disease. Patients who have an arterial PO_2 between 100 and 250 **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 immediately undergo a further evaluation with echocardiography. One may consider initiation of PGE_1 until anatomic definition can be accomplished** (see section V.B.2).

B. Stabilization and transport. On the basis of the initial evaluation, if an infant has been identified as likely to have congenital heart disease, further medical management must be planned as well as arrangements made for a definitive anatomic diagnosis. This may involve transport of the neonate to another medical center where a pediatric cardiologist is available.

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. In the neonate, this can most reliably be accomplished through the umbilical vessels. Volume resuscitation, inotropic support, and correction of metabolic acidosis are required with the goal of improving cardiac output and tissue perfusion (see Chapter 40).

2. **PGE_1.** The neonate who "fails" a hyperoxia test (or has an equivocal result in addition to other signs or symptoms of congenital heart disease), as well as the neonate who presents in shock within the first 3 weeks of life, is highly likely to have congenital heart disease. These neonates will most likely have congenital lesions resulting in ductal-dependent systemic or pulmonary blood flow or have a PDA that aids in intercirculatory mixing.

PGE_1, administered as a continuous intravenous (IV) infusion, has important side effects that must be anticipated. It 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 should be ideally intubated for the maintenance of a stable airway before leaving the referring hospital. In infants who will not require transport, intubation may not be required but continuous cardiorespiratory monitoring is essential. In addition, PGE_1 typically causes peripheral vasodilation and subsequent hypotension in many infants. A separate IV line should be secured for volume administration in any infant receiving PGE_1, especially those who require transport. Feeding may be withheld in neonates immediately after commencement of PGE_1 due to risk of necrotizing enterocolitis and may be resumed once we confirm stable gastrointestinal status.

Specific information regarding other adverse reactions, dose, and administration of PGE_1 is in section VIII.A.

The need to begin a PGE_1 infusion cannot be overemphasized in any neonate in whom congenital heart disease is strongly suspected (i.e., a failed hyperoxia test and/or severe, acute CHF with cardiogenic shock). In the neonate with ductal-dependent pulmonary blood flow, oxygen saturation will typically improve and the pulmonary blood flow will remain secure until an anatomic diagnosis and plans for surgery are made. In neonates with TGA, maintenance of a patent ductus improves pulmonary blood flow and enhances intercirculatory mixing. Most important, **neonates who present in shock in the first few weeks of life have duct-dependent systemic blood flow until proved otherwise**; resuscitation will not be successful unless the ductus arteriosus is opened. In these cases, it is appropriate to begin an infusion of PGE_1 even **before** a precise anatomic diagnosis can be made by echocardiography.

It is prudent to remeasure arterial blood gases and reassess perfusion, vital signs, and acid–base status within 15 to 30 minutes of starting a PGE_1 infusion. 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, obstructed forms of TAPVC, mitral atresia with a restrictive PFO, TGA with intact ventricular septum and a restrictive PFO, and some cases of Ebstein's 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. PGE_1 must be available at all neonatal facilities that manage sick newborn babies. Despite the small risk of apnea, a term neonate with shock or a newborn with cyanosis not responding to 100% oxygen (chest x-ray not suggestive of lung disease) must be started on PGE_1 before transfer. This may be lifesaving. The heart diseases that may worsen with PGE_1 are rare; far more babies will be saved by PGE_1 than a rare worsening. In right-sided obstructive lesions, the improvement in saturation will occur within 30 minutes (may not reach 90); the left-sided obstructive lesions present with multiple organs in shock—gut, kidney, and brain. Recovery of a left-sided obstruction is slow to PGE_1 (can take 24 hours) therapy and is often not complete. Also, the right-sided obstructive lesions are more likely to have good

prognosis following surgical repair as compared to the left-sided obstructive lesions (hypoplastic left heart).

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 β_1-adrenergic, 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. **Dobutamine** is an analog of dopamine, with predominantly β_1 effects and relatively weak β_2- and α-receptor-stimulating activity. In comparison with dopamine, dobutamine lacks renal vasodilating properties, has less chronotropic effect (in adult patients), and does not depend on norepinephrine release from peripheral nerves for its effect. There are limited data on the use of dobutamine in neonates, although our clinical experience has been favorable. A combination of low-dose dopamine (up to 5 μg/kg/minute) and dobutamine may be used to minimize the potential peripheral vasoconstriction induced by high doses of dopamine while maximizing the dopaminergic effects on the renal circulation. See section VIII.B for details of administration of inotropic agents and additional pharmacologic agents (see Chapter 40).

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 actually 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. The umbilical venous catheter should be at the inferior vena cava (IVC)–right atrial junction to ensure that access to the heart via this route is possible.

   Particular attention should be paid to the patient's airway and respiratory effort before transport. In general, all neonates receiving a PGE_1 infusion should be **intubated for transport** (see section V.B.2). Neonates with probable or definite congenital heart disease will most likely require surgical or interventional catheterization management during the hospitalization; therefore, it is likely that they will be intubated at some point. All intubated patients should have gastric decompression by nasogastric or orogastric tube.

   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 management decision for transport is particularly important for infants with duct-dependent systemic blood flow and complete intracardiac mixing with single-ventricle physiology and emphasizes the need to consult with a pediatric cardiologist before transport to achieve optimal intra-transport patient care.

Finally, it is important to remember in neonates that **hypotension** is a late finding in shock. 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. In recent era, online real-time transfer of critical data of the vital signs is possible using specialized apps for neonatal transport and this permits a three-way communication between the sender, transporter, and receiver during the actual process of transport.

C. Diagnosis confirmation

1. **Echocardiography.** Two-dimensional echocardiography, supplemented with Doppler and color Doppler, has become 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 is a time-consuming procedure 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 has changed a great deal in its focus. In the current era, cardiac catheterization is rarely necessary for anatomic definition of intracardiac structures (although catheterization is still necessary for definition of the distal pulmonary arteries, aortopulmonary collaterals, and certain types of coronary artery anomalies) or for physiologic assessment as Doppler technology has assumed an increasingly important role in this regard. Increasingly, catheterization is performed for catheter-directed therapy of congenital lesions. See Figure 41.1 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 valvular lesions, even extending to critical lesions in the neonate. Balloon valvuloplasty is considered the initial treatment of choice for both pulmonary and aortic stenoses, with >90%

Table 41.8. Indications for Neonatal Catheterization

Interventions
Therapeutic
Balloon atrial septostomy
Balloon pulmonary valvuloplasty
Balloon aortic valvuloplasty*
Balloon angioplasty of native coarctation of the aorta*
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*
Diagnostic
Endomyocardial biopsy
Anatomic definition (not visualized by echocardiography)
Coronary arteries
Pulmonary atresia/intact ventricular septum
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.

immediate success rate in the neonate. The application of balloon dilation of native coarctation of the aorta is controversial (see the subsequent text) and is typically utilized in select circumstances when surgery is contraindicated or high risk. The recent introduction of biodegradable stents for coronary artery applications may provide an attractive alternative to surgery for coarctation when these products become available in larger sizes. Other neonatal catheterization procedures include balloon atrial septostomy, radiofrequency (RF) perforation of the pulmonary valve in pulmonary atresia with intact ventricular septum, and stenting of the persistent ductus arteriosus in critical duct-dependent circulations such as PA.

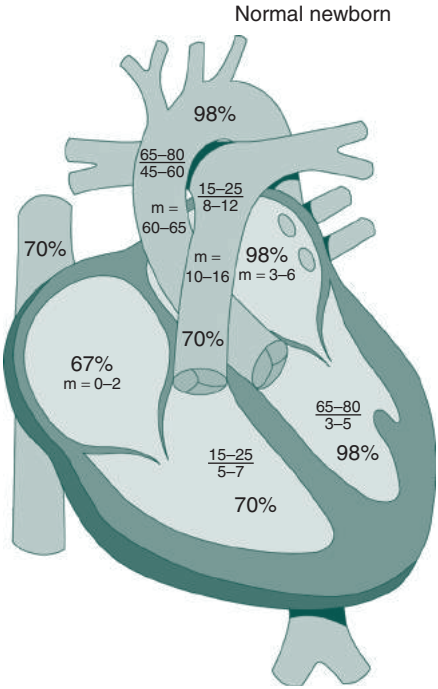

Figure 41.1. Typical hemodynamic measurements obtained during cardiac catheterization in a newborn, term infant without congenital or acquired heart disease. In this (and subsequent figures), oxygen saturations are shown as percentages, and typical hemodynamic pressure measurements are shown in mm Hg. 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.

c. Preparation for catheterization. Catheterization in the neonate is not without its attendant risks; young age, small size, and interventional procedures are risk factors for complications. With appropriate anticipatory care, complications can be minimized. In addition to basic medical stabilization (see section V.B), specific attention to airway management is crucial. Sedation and analgesia are necessary but will depress the respiratory drive in the neonate. In most centers, neonatal catheterization will utilize intubation and mechanical ventilation, especially if an intervention is contemplated.

Supervision of the neonate undergoing catheterization should also include periodic evaluation of the patient's body temperature, acid–base status, serum glucose, and monitoring of blood loss. All infants undergoing interventional catheterization should have 10 to 25 mL/kg packed red blood cells (PRBCs) typed and cross-matched **in the catheterization laboratory** during the procedure. IV lines are recommended in the upper extremities or head (because the lower body will be draped and inaccessible during the case) in order to provide unobstructed access for medications, volume infusions, etc. Finally, the neonate may have the catheterization

performed through umbilical vessels that were previously used for the administration of fluid, glucose, PGE_1, inotropic agents, or blood administration. Therefore, a peripheral line should be started and medications changed to that site before transfer of the neonate to the cardiac catheterization laboratory.

Consultation with the pediatric cardiologist who will be performing the case beforehand will help clarify these issues and allow the infant to be well prepared and monitored during the case.

VI. "LESION-SPECIFIC" CARE FOLLOWING ANATOMIC DIAGNOSIS

A. Duct-dependent systemic blood flow. Commonly referred to as **left-sided obstructive lesions**, this group of lesions includes a spectrum ranging from isolated coarctation of the aorta to hypoplastic left heart syndrome. These infants typically present in cardiovascular collapse as the ductus arteriosus closes, with resultant systemic hypoperfusion; they may also present more insidiously with symptoms of CHF (see section IV.B). Although all infants with significant left-sided lesions and duct-dependent systemic blood flow require prostaglandin-induced patency of the ductus arteriosus as part of the initial management, additional care varies somewhat with each lesion.

1. **Aortic stenosis** (Fig. 41.2). Morphologic 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 systemic cardiac output from the left ventricle. By convention, "severe" aortic stenosis is defined as a mean systolic gradient from the left ventricle to the 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 dysfunction and, frequently, endocardial fibroelastosis. Associated left-sided abnormalities such as mitral valve disease and coarctation are not uncommon. Following closure of the ductus, the left ventricle must supply all of the systemic cardiac output. In cases of severe myocardial dysfunction, clinical CHF or shock will become apparent.

   Initial management of the severely affected infant includes treatment of shock, stable vascular access, airway management and mechanical ventilation, sedation and muscle paralysis, inotropic support, and institution of PGE_1. Positive end-expiratory pressure (PEEP) is helpful to overcome pulmonary venous desaturation from pulmonary edema secondary to left atrial hypertension. For a patient with critical aortic stenosis to benefit from a PGE_1 infusion, there must be a small PFO to allow effective systemic blood flow (pulmonary venous return) to cross the atrial septum and ultimately enter the systemic vascular bed through the ductus. Inspired oxygen should be limited to a fractional concentration of inspired oxygen (FiO_2) of 0.5 to 0.6 unless severe hypoxemia is present.

   Following anatomic definition of left ventricular size, mitral valve, and aortic arch anatomy by echocardiography, cardiac catheterization or surgery

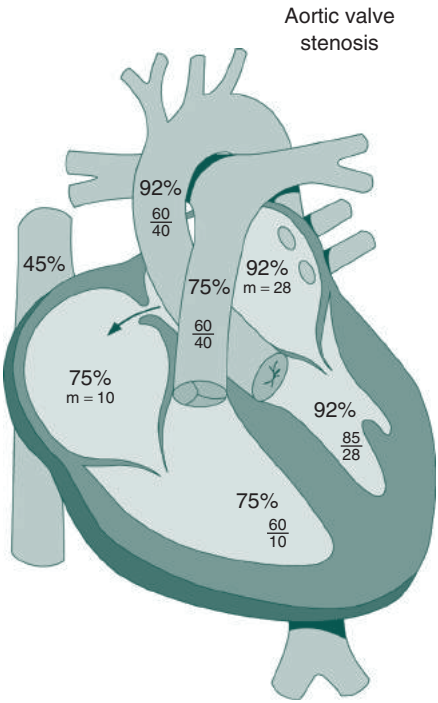

Figure 41.2. Critical aortic valve stenosis with a closed ductus arteriosus. Typical anatomic and hemodynamic findings include (i) a morphologically abnormal, stenotic valve; (ii) poststenotic dilatation of the ascending aorta; (iii) elevated left ventricular end-diastolic pressure and left atrial pressures 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.

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. Multiple procedures in childhood are likely in these cases.

In the modern era, several centers are attempting *in utero* balloon dilatation of the aortic valve in critical aortic stenosis in the fetus which is evolving into left heart hypoplasia. The results of these procedures depend on appropriate case selection and correct timing of the procedure during the pregnancy. Encouraging results on achieving postnatal biventricular circulation have been reported, although most of the patients will require multiple postnatal interventions or surgeries.

2. **Coarctation of the aorta** (Fig. 41.3) 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 is not uncommon and must be evaluated 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.

   As in critical aortic stenosis, initial management of the severely affected infant includes treatment of shock, stable vascular access, airway management and mechanical ventilation, moderate supplemental oxygen, sedation and

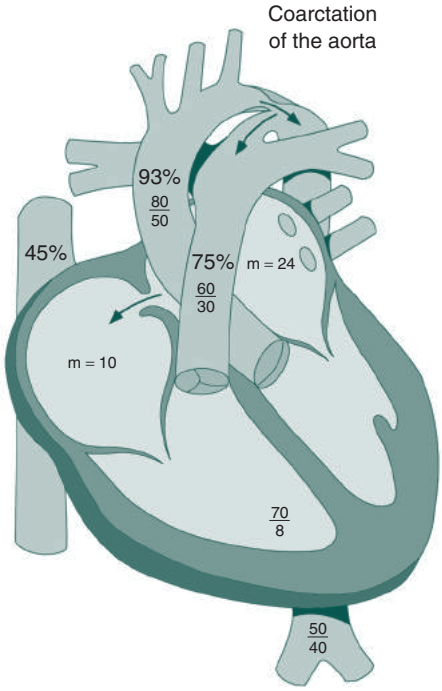

Figure 41.3. Coarctation of the aorta in a critically ill neonate with a nearly closed ductus arteriosus. Typical anatomic and hemodynamic findings include (i) "juxtaductal" site of the coarctation, (ii) a bicommissural aortic valve (seen in 80% of patients with coarctation), (iii) narrow pulse pressure in the descending aorta and lower body, and (iv) a bidirectional shunt at the ductus arteriosus. As in critical aortic stenosis (see Fig. 41.2), 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.

muscle paralysis, inotropic support, and institution of PGE_1. PEEP is helpful to overcome pulmonary venous desaturation from pulmonary edema secondary to left atrial hypertension. In some infants, PGE_1 is unsuccessful in opening the ductus arteriosus. Often, much higher initial doses of PGE_1 (up to 0.2 μg/kg/minute) may be needed to open up the PDA in these cases, compared to in neonates with duct-dependent pulmonary lesions. These neonates are at a higher risk of gut-related complications and hence frequent monitoring and withholding feeding may be appropriate.

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. In infants with symptomatic coarctation and a large, coexisting VSD, consideration is given to repair both defects in the initial procedure through a median sternotomy. 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. Balloon dilation of native coarctation in neonates is controversial because of the high incidence of restenosis and aneurysm formation, especially given the safe and effective surgical alternative. Balloon dilatation or stenting is reserved as a bailout procedure for critical cases where the surgical risks are very high due to multiple comorbidities or organ dysfunction.

3. **Interrupted aortic arch** (Fig. 41.4) 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. Many cases of type B interruption have associated genetic syndromes, especially 22q deletion syndrome.

   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. Oxygen saturations should be measured in the upper body; pulse oximetry readings in the lower body are reflective of the pulmonary artery oxygen saturation and are typically lower than that distributed to the central nervous system and coronary arteries. High concentrations of inspired oxygen may result in low pulmonary vascular resistance, a large left-to-right shunt, and a "runoff" 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 (if present) 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.

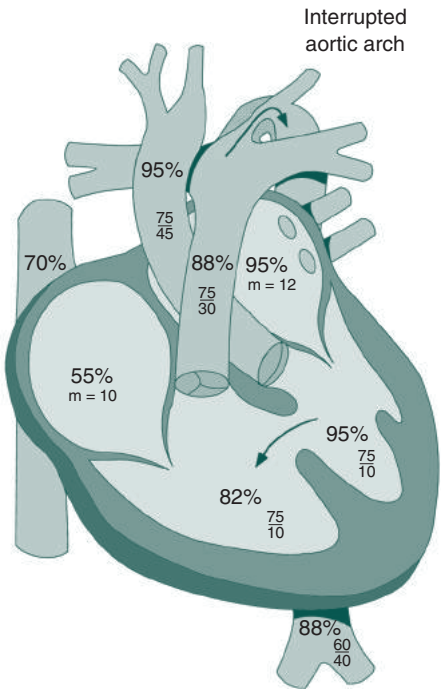

Figure 41.4. Interrupted aortic arch with restrictive patent ductus arteriosus. Typical anatomic and hemodynamic findings include (i) atresia of a segment of the aortic arch between the left subclavian artery and the left common carotid (the most common type of interrupted aortic arch—break "type B"), (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 which 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, and (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.

4. **Hypoplastic left heart syndrome** (Fig. 41.5A and B) 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 right ventricle 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. 41.5A), 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 right ventricle becomes progressively volume overloaded 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

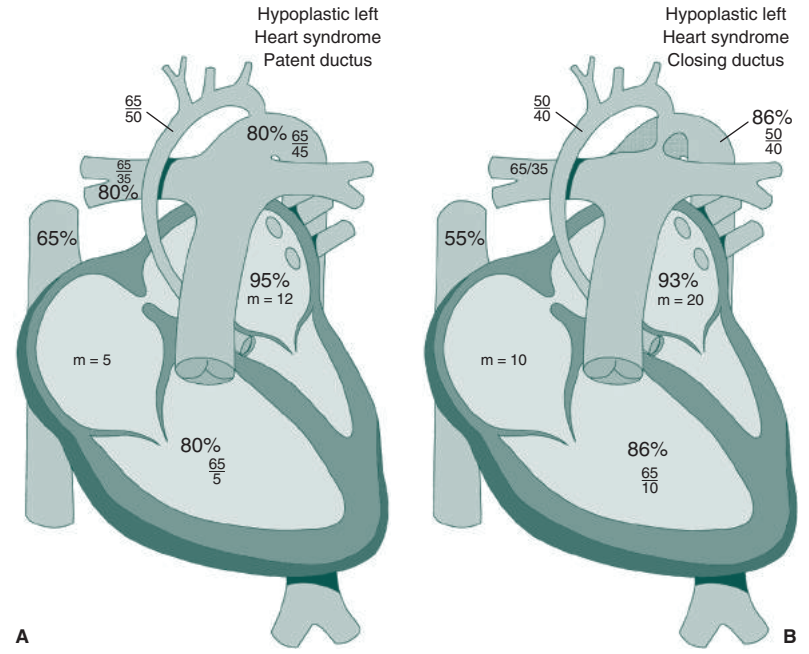

Figure 41.5. **A:** Hypoplastic left heart syndrome in a 24-hour-old patient with falling pulmonary vascular resistance and a nonrestrictive ductus arteriosus. Typical anatomic and hemodynamic findings include (i) atresia or hypoplasia of the left ventricle, mitral, and aortic valves; (ii) a diminutive ascending aorta and transverse aortic arch, usually with an associated coarctation; (iii) coronary blood flow being usually ***retrograde*** from the ductus arteriosus through the tiny ascending aorta; (iv) systemic arterial oxygen saturation (in 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, and acidosis, and in respiratory distress. The anatomic features are similar to those in "A," 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.

of pulmonary venous return in the mixed ventricular blood results in mildly decreased systemic arterial oxygen saturation (80%), 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 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. Arterial oxygen saturation approaches 90%.

Alternatively, a sudden deterioration takes place with rapidly progressive CHF and shock as the ductus arteriosus constricts (see Fig. 41.5B). 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, possibly resulting in acute tubular necrosis, necrotizing enterocolitis, or cerebral infarction or hemorrhage. A vicious cycle may also result from inadequate retrograde perfusion of the ascending aorta (coronary blood supply), with further myocardial dysfunction and continued compromise of coronary blood flow. Therefore, one has the paradoxical presentation of profound metabolic acidosis in the face of a relatively high PO_2 (70 to 100 mm Hg).

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 our experience, 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 of the atrial septum, or balloon atrial septostomy, may be necessary.** Medical therapy may be briefly palliative; however, surgical therapy is necessary for survival of infants with hypoplastic left heart syndrome. After a period of medical stabilization and support to allow for recovery of ischemic organ

system injury (particularly of the kidneys, liver, central nervous system, and heart), surgical relief of left-sided obstruction is required. Surgical intervention involves either staged reconstruction (with a neonatal Norwood procedure followed by the Glenn and Fontan operations later in infancy and childhood, respectively) or neonatal cardiac transplantation. Recent results from both reconstructive surgery and transplantation have vastly improved the outlook for infants born with this previously 100% fatal condition.

B. Duct-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 PA. Closure of the ductus arteriosus results in marked cyanosis.

1. **Pulmonary stenosis** (Fig. 41.6) with obstruction to pulmonary blood flow may occur at several levels: (i) within the body of the right ventricle, (ii) at the pulmonary valve (as pictured in Fig. 41.6), and (iii) in the peripheral pulmonary arteries. Pulmonary valve stenosis with an intact ventricular septum is the second most common form of congenital heart disease; "critical" obstruction occurs more rarely. Grading of the degree of pulmonary stenosis is similar to that of aortic stenosis (see section VI.A.1) with severe pulmonary stenosis defined as a peak systolic gradient from the right ventricle to the pulmonary artery of 60 mm Hg or more. By convention, "critical" pulmonary stenosis is defined as severe valvular obstruction with associated hypoxemia due to a right-to-left shunt at the FO. Critical pulmonary stenosis may be associated with hypoplasia of the right ventricle and/or tricuspid valve and significant RV hypertrophy. The pressure in the right ventricle is often higher than the left ventricular pressure (i.e., suprasystemic) in order to eject blood through the severe narrowing. Due to the long-standing (*in utero*) increased RV pressure, there is typically a hypertrophied, noncompliant right ventricle with a resultant increase in the right atrial filling pressure. When the right atrial pressure exceeds the left atrial pressure, a right-to-left shunt at the FO results in cyanosis and hypoxemia. There may be associated RV dysfunction and/or tricuspid regurgitation.

   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 right ventricle 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. **PA with intact ventricular septum** (Fig. 41.7) 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 artery–myocardial–RV sinusoidal connections. The coronary arteries may be very abnormal, including

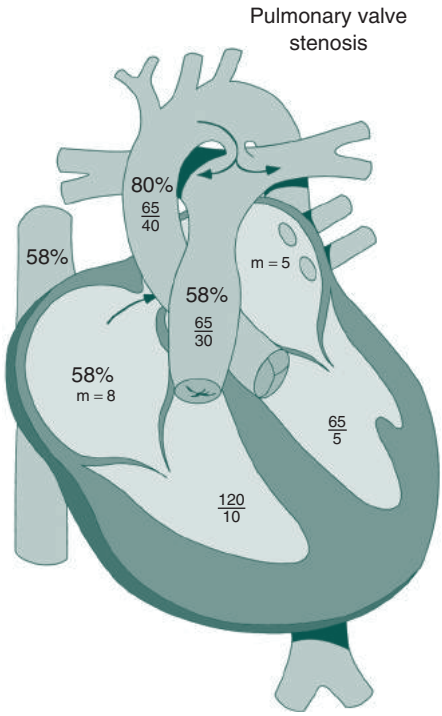

Figure 41.6. Critical pulmonary valve stenosis in a neonate with a nonrestrictive patent ductus arteriosus while receiving prostaglandin E_1 (PGE_1). Typical anatomic and hemodynamic findings include (i) thickened, stenotic pulmonary valve; (ii) poststenotic dilatation of the main pulmonary artery with normal-sized branch pulmonary arteries; (iii) right ventricular 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 right ventricular (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.

areas of stenoses or atresia. Myocardial perfusion therefore may be dependent on the hypertensive right ventricle to supply the distal coronary arteries (RV-dependent coronary circulation). Surgical relief of the PA in this patient subset (with a RV-to-pulmonary artery connection) could lead to myocardial infarction and death because blood would flow preferentially to the pulmonary arteries instead of the distal coronary segments that are dependent on the previously hypertensive right ventricle. The presence of sinusoidal connections between the right ventricle and the coronary arteries is associated with poorer long-term survival. Because there is no outlet of the right ventricle, there is typically suprasystemic pressure in the right ventricle 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 permanent and reliable form of pulmonary blood flow must be created for the infant to survive. Surgical management is

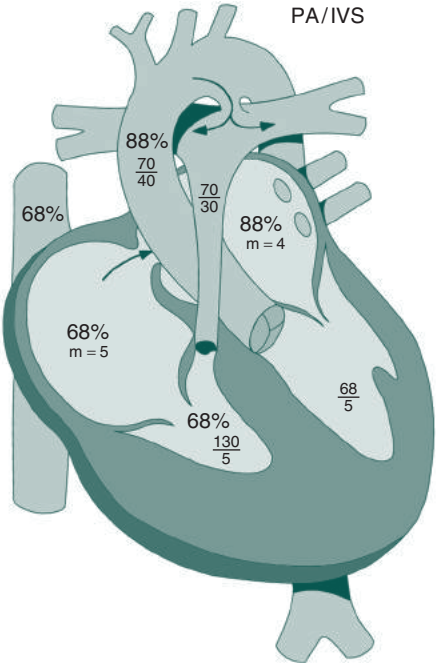

Figure 41.7. Pulmonary atresia (PA) with intact ventricular septum (IVS) in a neonate with a nonrestrictive patent ductus arteriosus while receiving prostaglandin E_1 (PGE_1). Typical anatomic and hemodynamic findings include (i) hypertrophied, hypoplastic right ventricle; (ii) hypoplastic tricuspid 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.

often preceded by catheterization to define the coronary artery anatomy. In patients without significant coronary abnormalities, pulmonary blood flow is established by creating an outflow for the right ventricle. In the setting of a "platelike" atresia where a well-formed outflow is present, with a mobile but imperforate valve plate, a catheter can be placed in the outflow tract and an RF wire can be used to perforate the 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 RV outflow tract augmentation can be performed. If additional patient growth is desired prior to surgical intervention, or if pulmonary valvotomy (catheter- or surgical-based) is insufficient, a systemic-to-pulmonary artery shunt (most often a Blalock–Taussig shunt) is constructed to augment pulmonary blood flow. In patients who undergo RF perforation of the valve and require additional pulmonary blood flow, stent implantation in the ductus arteriosus has been used to provide additional pulmonary blood flow. In patients with RV-dependent coronary arteries, a systemic-to-pulmonary artery shunt is the typical procedure performed.

3. **Tricuspid atresia** (Fig. 41.8) involves absence of the tricuspid valve and therefore no direct communication from the right atrium to the right ventricle. The right ventricle 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 RV 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 the blood to travel right to left because no source of right-sided inflow is present; right-sided outflow is derived from the left heart. In patients with normally related great arteries, pulmonary blood flow is derived from the right ventricle; if the right ventricle (or its connection with the left ventricle through a VSD) is severely diminutive, the pulmonary blood flow may be ductal-dependent; closure of the ductus arteriosus leads to profound hypoxemia and acidosis.

   Immediate medical management is primarily aimed at maintenance of adequate pulmonary blood flow. In the usual case of severe pulmonary stenosis and limited pulmonary blood flow, PGE_1 infusion maintains pulmonary blood flow

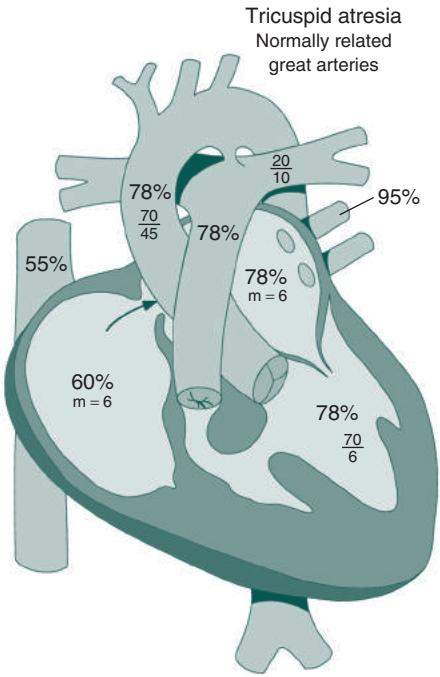

Figure 41.8. Tricuspid atresia with normally related great arteries and a small patent ductus arteriosus. Typical anatomic and hemodynamic findings include (i) atresia of the tricuspid valve; (ii) hypoplasia of the right ventricle; (iii) restriction to pulmonary blood flow at two levels: a (usually) small ventricular septal defect and a stenotic pulmonary valve; (iv) passage of all systemic venous return through the patent foramen ovale to reach the left ventricle; and (v) complete mixing at the left atrial level, with systemic oxygen saturation of 78% (in FiO_2 of 0.21), suggesting balanced systemic and pulmonary blood flow ("single ventricle physiology"—see text). m, mean value.

through the ductus arteriosus. Surgical creation of a more permanent source of pulmonary blood flow (usually a Blalock–Taussig shunt) is undertaken as soon as possible. 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.

4. **Tetralogy of Fallot** (Fig. 41.9) consists of RV outflow obstruction, a VSD (anterior malalignment type), "overriding" of the aorta over the ventricular septum, and hypertrophy of the right ventricle. There is a wide spectrum of anatomic variation encompassing these findings, depending particularly on the site and severity of the RV outflow obstruction. The severely cyanotic neonate with tetralogy of Fallot most likely has severe RV 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, although balloon dilation or stenting of the RV outflow tract has been used. Alternatively, a ductal stenting or surgical shunt replacement may be considered in a severely cyanotic neonate with

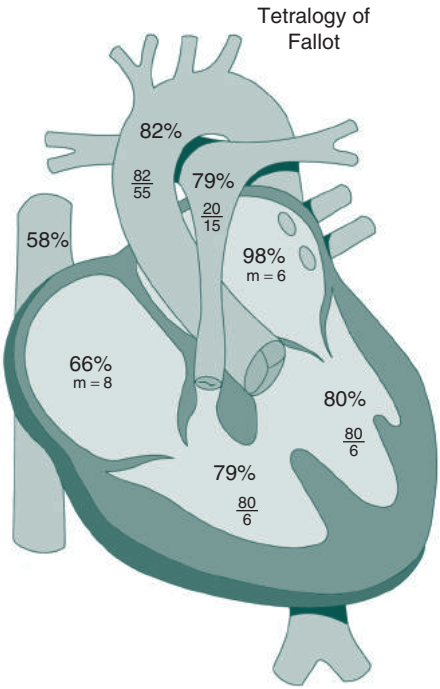

Figure 41.9. Tetralogy of Fallot. Typical anatomic and hemodynamic findings include (i) an anteriorly displaced infundibular septum, resulting in subpulmonary stenosis, a large ventricular septal defect, and overriding of the aorta over the muscular septum; (ii) hypoplasia of the pulmonary valve and 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%.

critical stenosis to the pulmonary blood flow. Detailed anatomic definition particularly regarding the coronary artery anatomy, the presence of additional VSDs, and the sources of pulmonary blood flow (systemic to pulmonary collateral vessels) is necessary before surgical intervention. If echocardiography is not able to fully show these details, then 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 intervention. The decision whether to perform complete repair versus some type of palliative intervention is dependent on the institution.

5. **Ebstein's anomaly** (Fig. 41.10A and B) 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 right ventricle. The tricuspid valve is frequently regurgitant resulting in marked right atrial

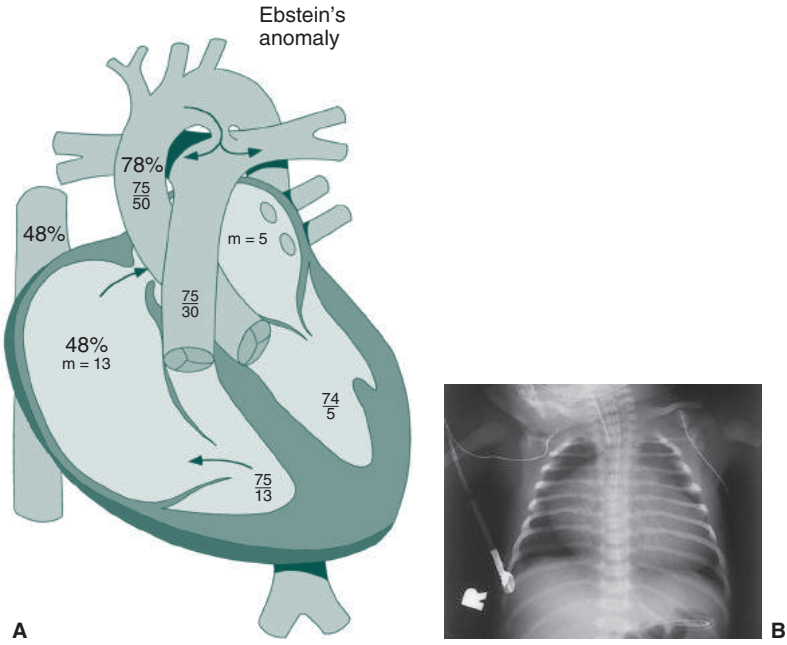

Figure 41.10. **A:** Ebstein's anomaly (with large nonrestrictive ductus arteriosus). Typical anatomic and hemodynamic findings include (i) inferior displacement of the tricuspid valve into the right ventricle, which may also cause subpulmonary obstruction; (ii) diminutive muscular right ventricle; (iii) 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's 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.

enlargement and a large right-to-left shunt at the atrial level; there is little forward flow out the RV outflow tract into the pulmonary circulation, often resulting in functional PA. The prognosis for neonates presenting with profound cyanosis due to Ebstein's anomaly is very poor. Surgical options are limited and generally reserved for the severely symptomatic child. Further complicating the medical condition, Ebstein's 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, alkalosis, and inhaled nitric oxide (iNO) (see Chapter 36). If there is total 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's anomaly is the associated pulmonary hypoplasia that is present (due to the massively enlarged right heart *in utero*; see Fig. 41.10B).

C. Parallel circulation/transposition of the great arteries (Fig. 41.11). **TGA** is defined as a condition where the aorta arises from the morphologic right ventricle and the pulmonary artery from the morphologic left ventricle. Approximately one-half of all patients with transposition have an associated VSD.

In the usual arrangement, this creates a situation of "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 separation from the placenta, neonates with transposition are dependent on mixing between the parallel systemic and pulmonary circulations in order for them to survive. In patients with an intact ventricular septum, this communication exists through the FO and the PDA. The major contributor to the intercirculatory mixing is the FO. These patients are usually clinically cyanotic within the first hours of life leading to their early diagnosis. Infants with an associated ventricular septal defect typically have somewhat improved mixing between the systemic and pulmonary circulations and may not be as severely cyanotic.

In neonates with TGA and an intact ventricular septum, a very low arterial PaO_2 (15 to 20 torr) with high $PaCO_2$ (despite adequate chest motion and ventilation) and metabolic acidosis are markers for severely decreased effective pulmonary blood flow and need urgent attention. The initial management of the severely hypoxemic patient with transposition includes the following: (i) **ensure adequate mixing** between the two parallel circuits and (ii) **maximize mixed venous oxygen saturation**.

In patients who do not respond with an increased arterial oxygen saturation by opening of the ductus arteriosus with PGE_1 infusion (usually these neonates have very restrictive atrial defects and/or pulmonary hypertension), **the FO should be**

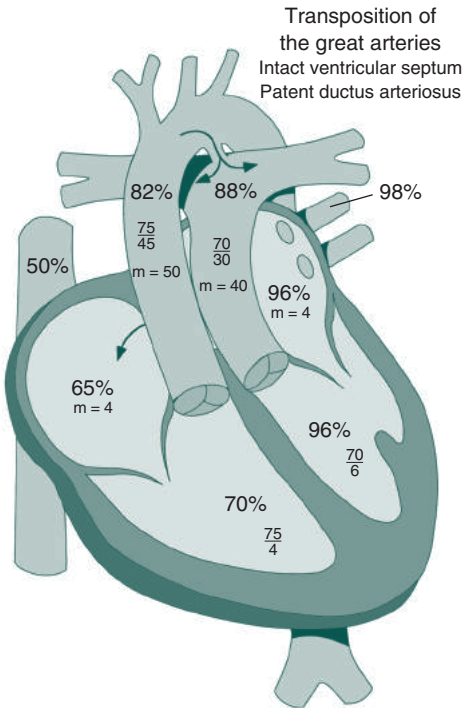

Figure 41.11. Transposition of the great arteries with an intact ventricular septum, a large patent ductus arteriosus (on prostaglandin E_1 [PGE_1]), and atrial septal defect (status post-balloon atrial septostomy). Note the following: (i) the aorta arises from the anatomic right ventricle and the pulmonary 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; and (vi) pulmonary hypertension due to a large ductus arteriosus. m, mean value.

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.

Coexisting causes of pulmonary venous desaturation (e.g., pneumothorax) should also be sought and treated. Increasing the FiO_2 to 100% will have little effect on the arterial PO_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. In the current era, arterial switch operation has a success rate of >98% in most centers and can be performed in the early neonatal period (<5 days) with no incremental risks.

D. Lesions with complete intracardiac mixing

1. **Truncus arteriosus** (Fig. 41.12) consists of a single great artery arising from the heart, which gives rise to (in order) the coronary arteries, the pulmonary arteries, and the brachiocephalic arteries. The truncal valve is often anatomically abnormal (only 50% are tricuspid) 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 such as hypoplasia, coarctation, and interruption are seen in 10% of cases. Extracardiac anomalies are present in 20% to 40% of cases. Thirty-five percent of patients with truncus arteriosus have a chromosome 22q11 deletion, detectable by fluorescence *in situ* hybridization (FISH) testing.

   The overwhelming majority of infants with truncus arteriosus present with symptoms of CHF in the first weeks of life. The infants may be somewhat cyanotic, but CHF symptoms and signs usually dominate. The pulmonary blood flow is increased, with significant pulmonary hypertension common. The natural history of truncus arteriosus is quite bleak. Left unrepaired, only 15% to 30% survive the first year of life. Furthermore, in survivors of the immediate

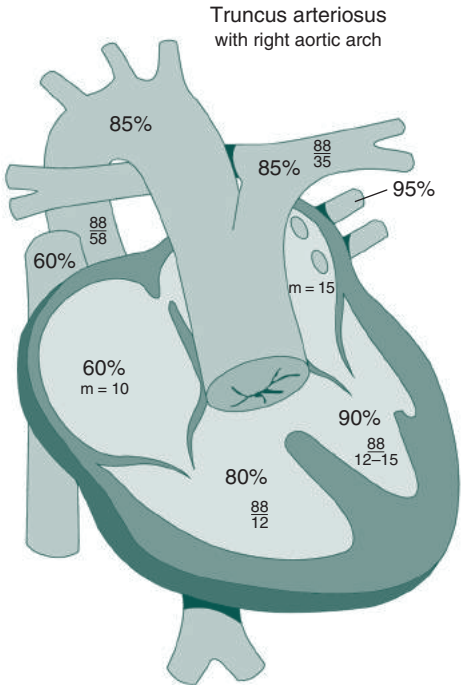

Figure 41.12. Truncus arteriosus (with right aortic arch). Typical anatomic and hemodynamic findings include (i) rise of a single artery from the conotruncus giving rise to coronary arteries (not shown), pulmonary arteries, and brachiocephalic vessels; (ii) abnormal truncal valve (quadricuspid shown) 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) at the great vessel level. m, mean value.

neonatal period, the occurrence of accelerated irreversible pulmonary vascular disease is common, making surgical repair in the neonatal period (or as soon as the diagnosis is made) the treatment of choice. "Medical management" of heart failure would be considered only a temporizing measure until surgical correction can be accomplished.

2. **TAPVC** (Fig. 41.13A and B) occurs when all pulmonary veins drain into the systemic venous system with complete mixing of pulmonary and systemic venous return, usually in the right atrium. The systemic blood flow is therefore dependent on an obligate shunt through the PFO into the left heart. 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

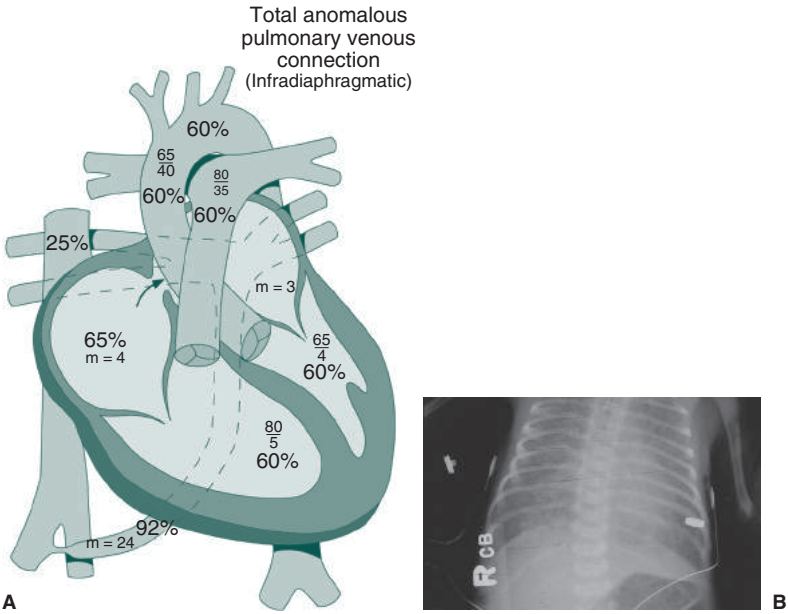

Figure 41.13. **A:** Infradiaphragmatic total anomalous pulmonary venous connection. Note the following: (i) pulmonary venous confluence does not connect with the left atrium but descends to connect with the portal circulation below the diaphragm (this connection is frequently severely obstructed); (ii) 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 an FiO_2 of 1, the arterial blood gas revealed a pH of 7.02, arterial carbon dioxide tension ($PaCO_2$) of 84, and arterial oxygen tension (PaO_2) of 23 torr. Emergent surgical management is indicated. m, mean value.

innominate vein and the superior vena cava), (ii) cardiac (usually to the right atrium or coronary sinus), (iii) infracardiac (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 connection is a surgical emergency, with minimal beneficial effects from medical management. PGE_1 can worsen the pulmonary venous hypertension and pulmonary edema in these cases and hence is typically contraindicated in obstructed forms of TAPVC. In the current era of prostaglandin, ventilatory support, and advanced medical intensive care, obstructed TAPVC represents one of the few remaining lesions that require emergent, "middle of the night" surgical intervention. Early recognition of the problem (see Fig. 41.13B) and prompt surgical intervention (surgical anastomosis of the pulmonary venous confluence to the left atrium) are necessary in order for the infant to survive. Patients with a mild degree of obstruction typically have minimal symptoms, with many neonates escaping recognition until later in infancy when they present with 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 frequently applied. Physiologically, systemic blood flow and pulmonary blood flow are 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). The management of these patients requires staged surgical palliative procedures. The initial procedure often involves optimizing the pulmonary blood flow by either a surgical aortopulmonary shunt (in cases where the pulmonary blood flow is low) or a pulmonary artery banding (in cases where the pulmonary blood flow is excessive). Any obstruction to the systemic blood flow also needs to be corrected in the initial palliative procedure. This is followed by staged separation of systemic and pulmonary circulations by bidirectional cavopulmonary shunt and an eventual Fontan procedure.

E. Left-to-right shunt lesions. For the most part, infants with pure 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 that of a PDA.

1. **PDA** is not particularly common in term newborns and rarely causes CHF. However, the frequency that a premature neonate will develop a hemodynamically significant left-to-right shunt through a PDA is inversely proportional to the advancing gestational age and weight (see Chapter 13).

   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). Generally, however, the clinical assessment of a premature infant with the typical findings of a hemodynamically significant ductus arteriosus is adequate to guide therapeutic decisions. If the diagnosis is in doubt, an echocardiogram will clarify the anatomic diagnosis.

   Initial medical management includes increased ventilatory support, fluid restriction, and diuretic therapy. In symptomatic patients, indomethacin or ibuprofen may be used for pharmacologic closure of PDA in the premature neonate 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 the 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 the 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).

2. **Complete AV canal** (Fig. 41.14) consists of a combination of defects in (i) the primum portion of the atrial septum; (ii) the inlet portion of the ventricular septum; and (iii) a common AV valve. Because of the large left-to-right shunt, which increases as the pulmonary vascular resistance falls, these infants typically present early in life with CHF. There may be some degree of cyanosis as well, particularly in the immediate neonatal period before the pulmonary vascular resistance has fallen. In the absence of associated RV outflow tract obstruction, pulmonary artery pressures are at systemic levels; pulmonary vascular resistance is frequently elevated, particularly in patients with trisomy 21.

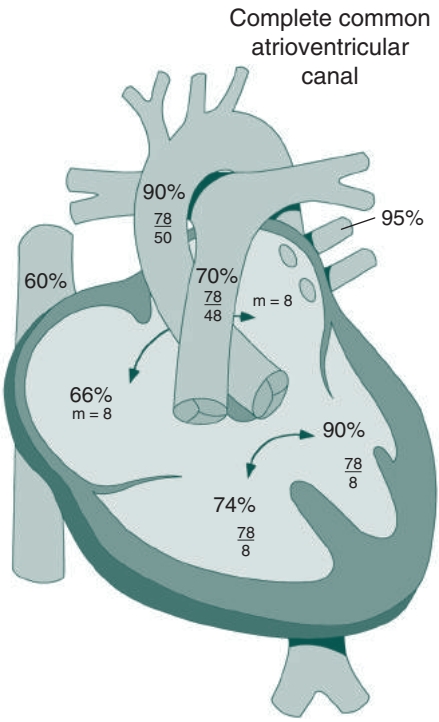

Figure 41.14. Complete common atrioventricular canal. Typical anatomic and hemodynamic findings include (i) large atrial and ventricular septal defects of the endocardial cushion type; (ii) single, atrioventricular valve; (iii) pulmonary artery hypertension (due to large ventricular septal defect); and (iv) bidirectional shunting (with mild hypoxemia) at atrial and ventricular levels 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.

Approximately 70% of infants with complete AV canal have trisomy 21; phenotypic findings of trisomy 21 often lead to evaluation of the patient for possible congenital heart disease (see Table 41.5). In the immediate neonatal period, these infants may have an equivocal hyperoxia test because there may be some right-to-left shunting through the large intracardiac connections. Symptoms of congestive failure 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°; see Fig. 41.15) which can be a useful clue for the presence of congenital heart disease in an infant with trisomy 21.

Most patients with complete AV canal will require medical treatment for symptomatic CHF, although prolonged medical therapy in patients with failure to thrive and symptomatic heart failure is not warranted. Complete surgical repair is undertaken electively at approximately 3 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 VSD become hemodynamically significant as the pulmonary

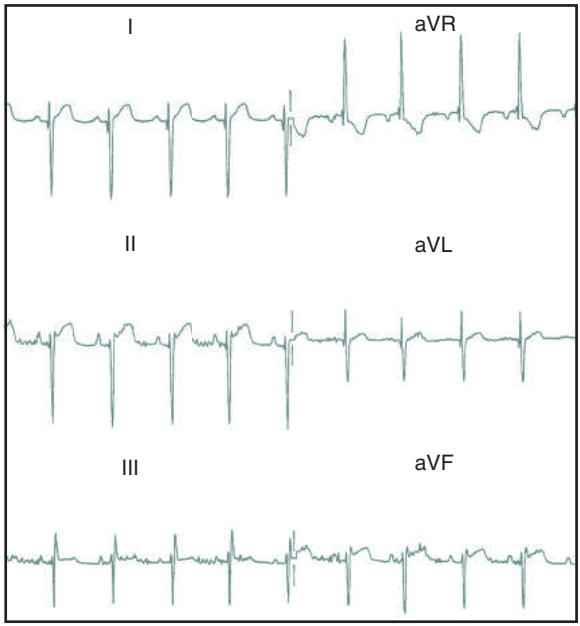

Figure 41.15. Superior ("northwest") axis as seen on the electrocardiogram (only frontal plane leads shown) in a newborn with complete atrioventricular canal. Note the initial upward deflection of the QRS complex (and subsequent predominantly negative deflection) in leads I and aVF. A superior axis (0–180°) is present in 95% of patients with endocardial cushion defects.

vascular resistance decreases and pulmonary blood flow increases due to a left-to-right shunt across the defect. Because this usually takes 2 to 4 weeks to develop, term neonates with VSD and symptoms of CHF should be investigated for coexisting anatomic abnormalities, such as left ventricular outflow tract obstruction and coarctation of the aorta. Premature infants, who have a lower initial pulmonary vascular resistance, may develop clinical symptoms of heart failure earlier or require longer mechanical ventilation compared with term infants.

VSD may occur anywhere in the ventricular septum and are usually classified by their location (Fig. 41.16). Defects in the membranous septum are the most common type. The diagnosis of VSD is usually initially suspected on physical examination of the infant; echocardiography confirms the diagnosis and localizes the defect in the ventricular septum. About 80% of the muscular VSD may become restrictive and eventually close in the first 2 years of life. However, large membranous, inlet or outlet VSDs typically need early surgical correction. Medical management of CHF typically includes diuretics and caloric supplementation. Digoxin is used in some institutions. Growth failure is the most common symptom of CHF not fully compensated by medical management. Typical indications for surgical correction in early infancy (<6 months) include significant CHF with growth failure associated with a large VSD. Several studies have shown that young age at repair and coexisting severe malnutrition are not incremental risk factors for an adverse outcome after surgical repair in VSD.

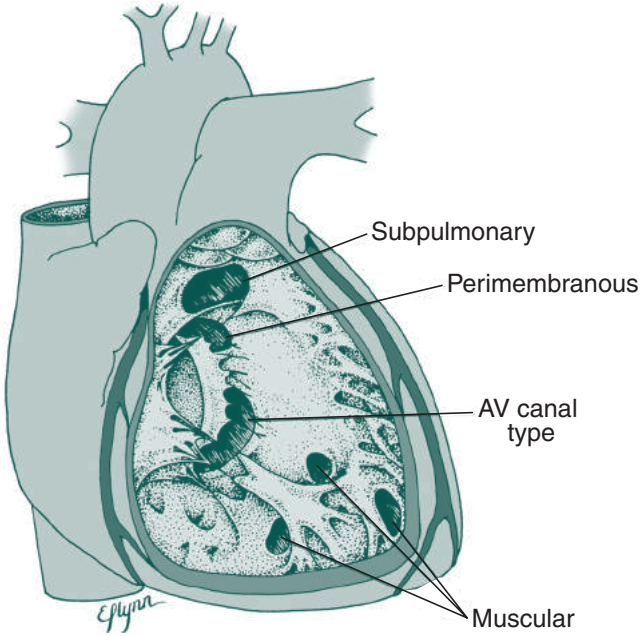

Figure 41.16. Types of ventricular septal defects as viewed from the right ventricle. AV, arteriovenous. (From Fyler DC, ed. *Nadas' Pediatric Cardiology*. St. Louis, MO: Mosby; 1992.)

F. Cardiac surgery in the neonate. In the past, because of the perceived high risk of open-heart surgery early in life, critically ill neonates were mostly subjected to palliative procedures or prolonged medical management. The unrepaired circulation and residual hemodynamic abnormalities frequently resulted in secondary problems of the heart, lungs, and brain, as well as more nonspecific problems of failure to thrive, frequent hospitalizations, and infections. In addition, there are difficult-to-quantitate psychologic burdens to the family of a chronically ill infant.

Recently, 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. Most centers are performing even complex forms of neonatal heart surgery with low in-hospital mortality (<5%). Prenatal diagnosis and planned peripartum care result in improved preoperative clinical status and permit earlier conduct of lifesaving surgical procedures with improved surgical outcomes. 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.

Low birth weight should not be considered an absolute contraindication for surgical repair. In one series, prolonged medical therapy in low-birth-weight infants to achieve further weight gain in the presence of a significant hemodynamic burden did not improve the survival rate, and prolonged intensive care management was associated with nosocomial complications. We believe that the symptomatic neonate with congenital heart disease should be repaired as early as possible to prevent the secondary sequelae of the congenital lesion on the heart, lungs, and brain.

Table 41.9. Common Neonatal Operations and Their Early Sequelae

Lesion	Surgical Repair (Eponym)	Early Postoperative Sequelae	
		Common	**Rare**
Corrective procedures TGA	Arterial switch procedure (Jatene) **1.** Division and reanastomosis of PA to RV and aorta to LV (anatomically correct ventricles) **2.** Pulmonary artery is brought up anteriorly (LeCompte maneuver) **3.** Translocation of coronary arteries **4.** Closure of septal defects if present	Transient decrease in cardiac output 6–12 hours after surgery	Coronary ostial stenosis or occlusion/sudden death
	Atrial switch procedure (Senning or Mustard) **1.** Intra-atrial baffling of systemic venous return to LV (to PA) and pulmonary venous return to RV (to AO) **2.** Closure of septal defects if present	Supraventricular tachycardia Sick sinus syndrome Tricuspid regurgitation	Pulmonary or systemic venous obstruction
TOF	**1.** Patch closure of VSD through ventriculotomy or right atrium **2.** Enlargement of RVOT with infundibular patch or muscle bundle resection **3.** ±Pulmonary valvotomy **4.** ±Transannular RV to PA patch **5.** ±RV to PA conduit	Pulmonary regurgitation (if transannular patch, valvotomy, or nonvalved conduit) Transient RV dysfunction Right-to-left shunt through PFO, usually resolves postoperatively as RV function improves	Residual left-to-right shunt at VSD patch Residual RVOT obstruction Junctional ectopic tachycardia Complete heart block
CoA	Resection with end-to-end anastomosis, or subclavian flap (Waldhausen), or patch augmentation	Systemic hypertension Absent left-arm pulse (if Waldhausen)	Ileus Hemidiaphragm paresis Vocal cord paresis Chylothorax

(Continued)

Table 41.9. Common Neonatal Operations and Their Early Sequelae *(Continued)*

Lesion	Surgical Repair (Eponym)	Early Postoperative Sequelae	
		Common	**Rare**
PDA	Ligation (±division) of PDA using open thoracotomy and direct visualization or video-assisted thoracoscopic visualization, or device occlusion via cardiac catheterization	—	Hemidiaphragm paresis Vocal cord paresis Chylothorax Interruption of left PA or descending aorta
TAPVC	**1.** Reanastomosis of pulmonary venous confluence to posterior aspect of left atrium **2.** Division of connecting vein	Pulmonary hypertension Transient low cardiac output	Residual pulmonary venous obstruction
Truncus arteriosus	**1.** Closure of VSD; baffling LV to truncus (neoaorta) **2.** Removal of PAs from truncus **3.** Conduit placement from RV to PAs	Reactive pulmonary hypertension Transient RV dysfunction with right-to-left shunt through PFO Hypocalcemia (DiGeorge's syndrome)	Truncal valve stenosis or regurgitation Residual VSD Complete heart block
Palliative procedure HLHS*	Stage I (Norwood) **1.** Connection of main PA to aorta with reconstruction of aortic arch **2.** Systemic-to-pulmonary shunt **3.** Atrial septectomy	Low systemic cardiac output due to excessive pulmonary blood flow	Aortic arch obstruction Restrictive atrial septal defect
Complex lesions with decreased pulmonary blood flow*	Systemic-to-pulmonary shunt (using prosthetic tube = modified Blalock–Taussig shunt; using subclavian artery = classic Blalock–Taussig shunt)	Excessive pulmonary blood flow and mild congestive heart failure	Hemidiaphragm paresis Vocal cord paralysis Chylothorax Seroma

(Continued)

Table 41.9. Common Neonatal Operations and Their Early Sequelae *(Continued)*

Lesion	Surgical Repair (Eponym)	Early Postoperative Sequelae	
		Common	Rare
Complex lesions with excessive pulmonary blood flow*	Ligation of main PA, creation of systemic-to-pulmonary shunt PA band (prosthetic or silastic constriction of main PA)	—	PA distortion Aneurysm of main PA

AO, aorta; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; LV, left ventricle; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RV, right ventricle; RVOT, right ventricular outflow tract; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
*In patients with a single ventricle, the goal is to separate pulmonary and systemic venous return, rerouting systemic venous blood directly to pulmonary arteries (Fontan operation), although this is done in late infancy or early childhood.
Source: Adapted 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. It is usually the result of a viral infection (coxsackievirus, adenovirus, parvovirus, and varicella 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.1) and/or arrhythmia (see section IX). The course of the illness is frequently fulminant and fatal; however, full recovery of ventricular function may occur if the infant can be supported and survive the acute illness. Supportive care including supplemental oxygen, diuretics, inotropic agents, afterload reduction, and mechanical ventilation is frequently used. In severe cases, mechanical support of the myocardium with ECMO or ventricular assist devices can be considered. Care should be used when administering digoxin due to the potential for the potentiation of arrhythmias or CHB.

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-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 diagnoses 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 the type seen in **infants born to diabetic mothers**. Echocardiographically and hemodynamically, these infants are indistinguishable from patients with other types of hypertrophic cardiomyopathy. However, in these cases, the ventricular hypertrophy typically resolves in 6 to 12 months. Presence of 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 duct-dependent systemic or pulmonary blood flow. It must be administered as a continuous parenteral infusion. The usual starting dose is 0.05 to 0.1 μg/kg/minute. Once a therapeutic effect has

been achieved, the dose may often be decreased to as low as 0.01 μg/kg/minute without loss of therapeutic effect. 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%), bradycardia (7%), seizures (4%), tachycardia (3%), cardiac arrest (1%), and edema (1%). See Table 41.10 for recommended mixing and dosing protocol for PGE_1.

B. Sympathomimetic amine 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) or synthetic (dobutamine, isoproterenol), achieve an effect by stimulating myocardial and vascular adrenergic receptors. These agents must be given as a continuous parenteral infusion, preferably through a central venous or umbilical catheter. 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 sympathomimetic amine 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 41.11 for recommended mixing and dosing of the sympathomimetic amines.

C. Afterload-reducing agents

1. **Phosphodiesterase inhibitors** such as **milrinone** are **bipyridine** compounds that 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.

Table 41.10. Suggested Preparation of Prostaglandin E_1

Add 1 Ampule (500 μg/1 mL) to	Concentration (μg/mL)	mL/hour × Weight (kg), Needed to Infuse 0.1 μg/kg/minute
200 mL	2.5	2.4
100 mL*	5.0	1.2
50 mL	10.0	0.6

*Usually the most convenient dilution, provides one-fourth of maintenance fluid requirement. Usually mix in dextrose-containing solution for newborns.
Source: Adapted from Warnovsky G, Erickson LC, Wessel DL. Cardiac emergencies. In: May HL, ed. *Emergency Medicine*. Boston, MA: Little, Brown and Company; 1992.

Table 41.11. Sympathomimetic Amines

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 (slightly), ↑ contractility, ↓ SVR
Epinephrine	0.05–0.50	↑ HR, ↑ contractility, ↑ SVR, ↑ BP
Isoproterenol	0.05–1.00	↑ HR, ↑ contractility, ↓ SVR, ↓ PVR

These infusions may be mixed in intravenous solutions containing dextrose and/or saline. For neonates, dextrose-containing solutions with or without salt should usually be chosen. Calculation for convenient preparation of intravenous infusions is as follows:

$$6 \times \frac{\text{desired dose (μg/kg/minute)}}{\text{desired rate (mL/hour)}} \times \text{weight (kg)} = \frac{\text{mg drug}}{\text{100 mL fluid}}$$

BP, blood pressure; HR, heart rate; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

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 the 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, with increased contractility and cardiac output as a result of cAMP-mediated increase in trans-sarcolemmal calcium flux; (ii) vasodilatation, with increase in arteriolar and venous capacitance as a result of cAMP-mediated increase in uptake of calcium and decrease in calcium available for contraction; and (iii) increased lusitropy, or improved relaxation properties 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 phosphodiesterase inhibitors 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. These agents are especially useful in the setting of management of low cardiac output in the postoperative period following arterial switch operation for TGA.

2. **Other vasodilators** 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.

Sodium nitroprusside is the most widely used afterload-reducing agent. It acts as a nitric oxide donor, increasing intracellular cyclic guanosine monophosphate (cGMP), which effects relaxation of vascular smooth muscle in both arterioles and veins. The overall effect is a decrease in atrial filling pressure and SVR with a concomitant increase in cardiac output. The vasodilatory effects of nitroprusside occur within minutes with IV administration. The principal metabolites of sodium nitroprusside are thiocyanate and cyanide; thiocyanate toxicity is unusual in children with normal hepatic and renal function, and monitoring of cyanide and thiocyanate concentrations in children may not be correlated with clinical signs of toxicity.

In neonates with low cardiac output, there may be an increase in urine output and improvement in perfusion with institution of nitroprusside, but there can also be a significant drop in blood pressure necessitating care in its use.

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 a 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; its relatively long half-life limits its use in postoperative patients with labile hemodynamics. The angiotensin-converting enzyme inhibitor **enalapril** similarly has a relatively long half-life (2 to 4 hours) that limits its use in the acute setting. β-Blockers (e.g., propranolol, esmolol, labetalol), although excellent in reducing blood pressure, may have deleterious effects on ventricular function. **Calcium channel blockers** (e.g., verapamil) may cause acute and severe hypotension and bradycardia in the neonate and should **rarely be used**. 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 used only for the 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 of one-fourth to one-third of the TDD (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). Infants with mild symptoms, primary myocardial disease, renal dysfunction, or the potential for AV block may be digitalized using only the maintenance dose (omitting the loading dose). The maintenance dose is divided into equal twice-daily doses, 12 hours apart.

Digoxin toxicity most commonly manifests with gastrointestinal upset, somnolence, and sinus bradycardia. More severe digoxin toxicity may cause high-grade AV 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. AV 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; Burroughs Wellcome Fund, Research Triangle Park, NC) is reserved for patients with evidence of severe digoxin intoxication and clinical symptoms of refractory arrhythmia and/or AV block; in these patients, it is quite effective. Calculation of the Digibind dose in milligrams is as follows: (serum digoxin concentration [ng/mL] × 5.6 × the body weight [kg]/1,000) × 64. The dose is given as a one-time IV infusion. A second dose of Digibind may be given to those patients who continue to have clinical evidence of residual toxicity.

E. Diuretics (see Appendix A) are frequently used in patients with CHF, often in combination with digoxin. **Furosemide**, 1 to 2 mg/kg/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 (3 to 4 mEq/kg/day) 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 arrhythmias in neonates and young infants.

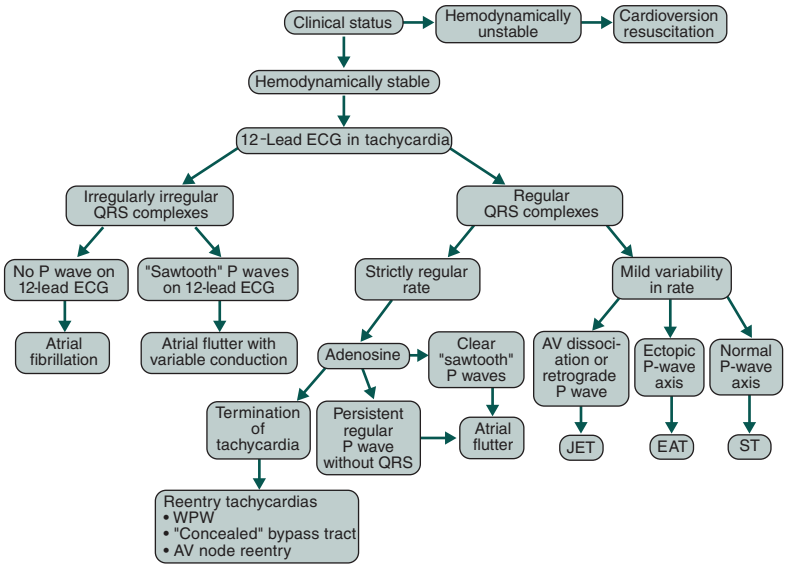

Figure 41.17. Algorithm for bedside differential diagnosis of narrow complex tachycardias, the most common type of arrhythmia in neonates. Note that, regardless of the mechanism of tachycardia, if the patient is hemodynamically unstable, immediate measures to resuscitate the infant including cardioversion 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. AV, atrioventricular; EAT, ectopic atrial tachycardia; ECG, electrocardiogram; JET, junctional ectopic tachycardia; ST, sinus tachycardia; WPW, Wolff–Parkinson–White syndrome.

In nearly all circumstances, 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. 41.17) 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. SVTs are the most common symptomatic arrhythmias in all children, including neonates. They usually have (i) a rate >200 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 later may become irritable and 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 AV pathway or the AV node, or occurs due to atrial flutter. Approximately half of these patients will manifest preexcitation (delta wave) on the ECG when not in tachycardia (WPW syndrome; see Fig. 41.18). Less commonly, the reentrant circuit may be within the atrium itself (atrial flutter) or within the AV node (AV node reentrant tachycardia). Patients with SVT may have associated structural heart disease (10% to 15%); evaluation for structural heart disease should be considered in all neonates with SVT. 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 significant variability in the overall rate.

Long-term medical therapy for SVT in the neonate is based on the underlying electrophysiologic diagnosis. β-Blocker therapy is the initial therapy of choice in patients with SVT. **Propranolol** is used as the initial and chronic drug therapy for patients with SVT due to WPW syndrome, to avoid the potential facilitation of antegrade (AV) conduction through the accessory pathway. Treatment with propranolol may be associated with apnea and hypoglycemia; therefore, neonates started on propranolol, especially premature infants, 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, it typically is continued for 6 to 12 months.

Digoxin is also commonly used in non-WPW syndrome SVT without CHF. It 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.

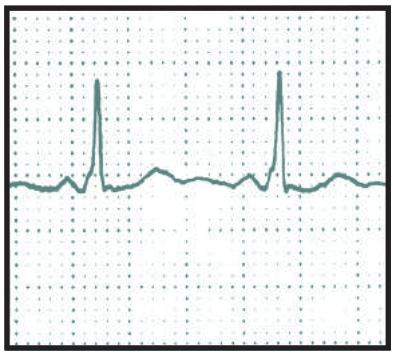

Figure 41.18. Wolff–Parkinson–White syndrome Note the characteristic "slurred" initial QRS deflection and short PR interval that can occur in any lead; only lead I pictured here.

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. In neonates, **verapamil should only rarely be used** because it has been associated with sudden death in this patient population.

***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. In resistant cases and in fetuses with hydrops, direct IM injection of digoxin to the fetus has been tried to control the tachycardia. 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, hypovolemia, and xanthine (e.g., aminophylline) toxicity. 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 QT_c 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 commonly with hemodynamic consequences. The underlying cause should be rapidly sought and treated. The hemodynamically stable patient should be treated with a lidocaine bolus, 1 to 2 mg/kg, followed by a lidocaine infusion, 20 to 50 μg/kg/minute. Direct current cardioversion (starting dose 1 to 2 J/kg) should be used if the patient is hemodynamically compromised, although it 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. Phenytoin, 2 to 4 mg/kg, may be effective if the arrhythmia is due to digoxin toxicity (see section VIII.D).

b. Ventricular fibrillation in the neonate is almost always an agonal (preterminal) 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. A bolus of lidocaine, 1 mg/kg, followed by a lidocaine infusion should be started. Once the infant has been resuscitated, the underlying problems should be evaluated and treated.

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 AV block** occurs when the PR interval is >0.16 second. In the neonate, first-degree AV block may be due to a nonspecific conduction disturbance, medications (e.g., digoxin), myocarditis, or hypothyroidism, or associated with certain types of congenital heart disease (e.g., complete AV canal or ventricular inversion). No specific treatment is generally indicated.

      ii. **Second-degree AV block.** Second-degree AV 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 AV block may occur with SVT, digitalis toxicity, or a nonspecific conduction disturbance. No specific treatment is usually necessary other than diagnosis and treatment of the underlying cause.

      iii. **Third-degree or 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. It 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 (left isomerism and congenital corrected TGA) and (ii) fetal exposure to maternal antibodies (anti-SSA/SSB) which may be isolated or as a part of maternal autoimmune disorders. The presence of CHB without structural heart disease should alert the clinician to investigate the mother for rheumatologic disease. In most cases, fetal CHB caused by maternal autoimmune disease is associated with favorable *in utero* survival. On the contrary, the prognosis of CHB associated with structural heart defects in the fetus is guarded.

      In high-risk cases with risk of hydrops fetalis and *in utero* death, transplacental therapy with dexamethasone and beta-agonists may be considered. In most cases, the pregnancy can be continued to near term by close monitoring of the fetal cardiovascular status. Indications for

neonatal pacemaker implantation depend on the hemodynamic status, heart rate, and presence of other high-risk features such as ventricular ectopy. Most infants with congenital CHB will require permanent pacemaker implantation in the first few months of life. The prognosis with pacemaker is excellent in most cases where the lesion is isolated and cardiac function is normal.

4. **Irregular rhythms**

   a. **Premature atrial contractions (PACs; see Fig. 41.19)** are common in neonates, are usually benign, and do not require specific therapy. Most PACs result in a normal QRS morphology (see Fig. 41.19A), distinguishing them from premature ventricular contractions (PVCs). If the PAC occurs

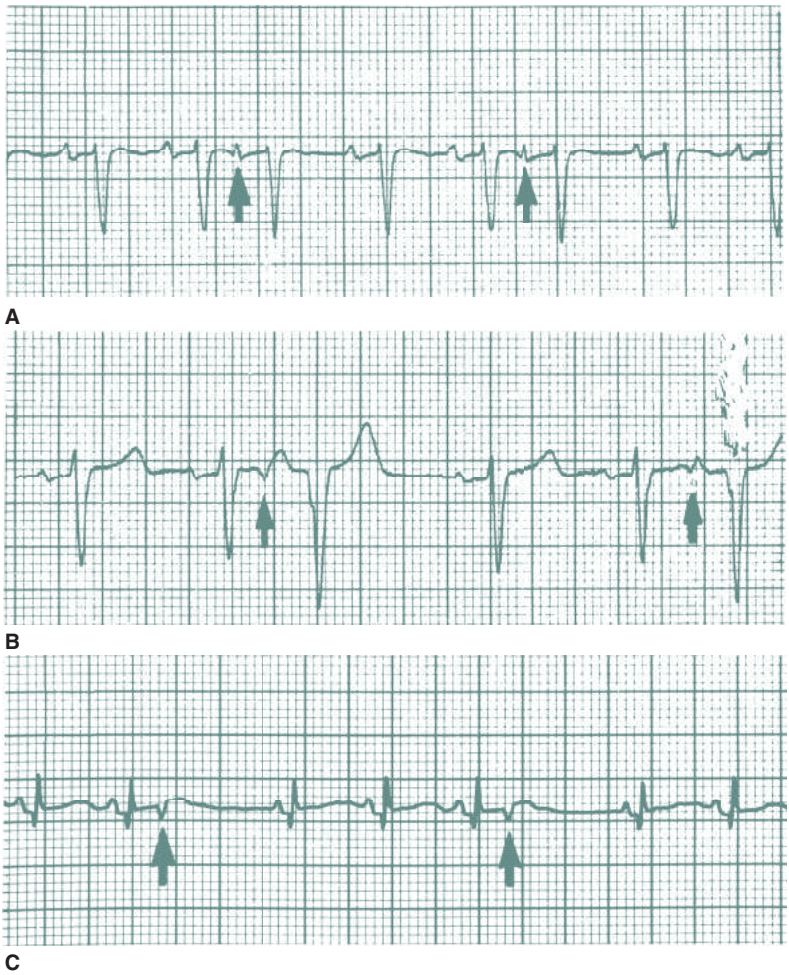

Figure 41.19. Premature atrial contractions (*arrows*) causing **A:** early ventricular depolarization with a normal QRS complex. **B:** Early ventricular depolarization with "aberration" of the QRS complex. **C:** Block at the atrioventricular node. (From Fyler DC, ed. *Nadas' Pediatric Cardiology.* St. Louis, MO: Mosby; 1992.)

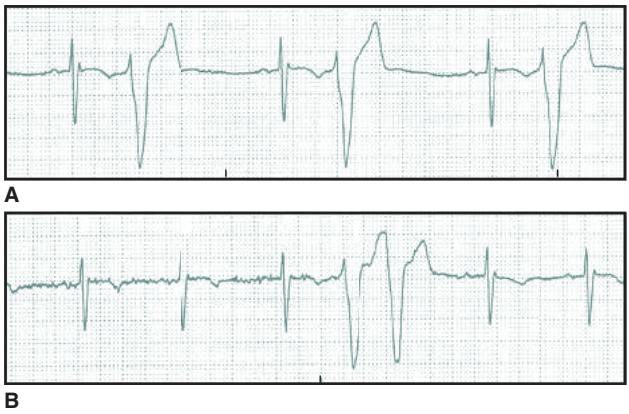

Figure 41.20. Premature ventricular contractions (PVCs). **A:** PVCs alternating with normal sinus beats (ventricular bigeminy) are usually not indicative of significant pathology. **B:** Paired PVCs ("couplet") are a potentially more serious rhythm and require further investigation.

while the AV node is partially repolarized, an aberrantly conducted ventricular depolarization pattern may be observed on the surface ECG (see Fig. 41.19B). If the premature beat occurs when the AV 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 a marked sinus bradycardia (see Fig. 41.19C).

b. PVCs (Fig. 41.20) 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. 41.20A) and every third beat (trigeminy). 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. 41.20B) are pathologic and "high grade"; they may be a marker for myocarditis or myocardial dysfunction, and further evaluation should be strongly considered.

C. Emergency treatment in the hemodynamically compromised patient. With all therapies described in the following text, it is important to have easily accessible resuscitation equipment available before proceeding with these antiarrhythmic interventions. It is important to have an ECG machine attached to the patient to document the conversion to sinus rhythm, where possible. Reliance on bedside monitors frequently loses the opportunity to provide important diagnostic information regarding the arrhythmia.

1. Tachycardia

a. Adenosine. Adenosine has become the drug of choice for acute management. It transiently blocks AV node 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; however, it has been reported to cause transient AV block severe enough to require pacing (albeit briefly), so it should be used with caution and in consultation with a pediatric cardiologist. 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 1 J/kg and be increased by a factor of 2 if unsuccessful. Care should be taken to avoid skin burns and arcing of the current outside the body by using only electrical transmission gel with the paddles. Paddle position should be anterior–posterior if possible.

c. Transesophageal pacing. When available, esophageal overdrive pacing is an effective maneuver for terminating tachyarrhythmias. The close proximity of the left atrium to the distal esophagus allows electrical impulses generated in the esophagus to be transmitted to the atrial tissue; burst pacing may then terminate reentrant tachyarrhythmias.

2. Bradycardia. Therapeutic options for treating a symptomatic bradyarrhythmia are more limited. A transvenous pacemaker 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 in an infant with CHF. The treatment of choice for sinus node dysfunction is transesophageal pacing at an appropriate rate, but this can be accomplished only with intact AV conduction and is not effective in patients with CHB. 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 only when indicated to promote oxygen delivery and coagulation.
- Very-low-weight infants are at risk for transfusion-associated graft-versus-host disease and require irradiated red blood cell (RBC) and platelet units.
- 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 is CMV safe.
- Risks of transfusion-transmitted infections are very low, with the highest current risks being due to 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, whole blood, usually in the form of reconstituted whole blood, is used. However, in most cases, blood components are preferred because each component has specific 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. Transfusion transmitted infection (TTI) risks (Table 42.1) have been hugely reduced by serologic testing in the past and recent nucleic-acid amplification technology (NAT). NAT reduces the window period significantly (when infection is present, but not detectable by test). Risk of HIV, HBV, and HCV transmission is less than 1 in 3 million in centers where NAT is used. NAT screening is also available for emerging infections like Zika, West Nile virus and Babesia Microti.

Pathogen-reduced blood components (platelet and RBC) are being used in a few centers and are possibly the future of blood transfusion safety.

Risk-based decision making, and cost effectiveness are considered in reaching consensus on testing.

Table 42.1. Infections Agents and Risk Associated with Transfusion–Transmitted Infections

Agents Proven to be Blood Safety Threats	Not Transfusion Transmitted
Bacteria*	Middle Eastern Respiratory Syndrome Corona virus
HIV	severe fever with thrombocytopenia virus
Hepatitis B virus	Chikungunya virus
Hepatitis C virus	Influenza
HTLV 1 and 2	Leishmania
Zika	Severe acute respiratory syndrome
Hepatitis E virus	Parvo virus 4
Babesia microti	
West Nile virus	
Trypanosoma cruzi	
variant Creutzfeldt-Jakob Disease (vCJD)	

Adapted from: Busch MP, Bloch EM, Kleinman S. Prevention of transfusion-transmitted infections. Blood. 2019 25;133(17):1854–1864.
*Septic transfusion reaction is high with platelets stored at room temperature; the risk is 1 in 100,000 transfusions, in contrast to 1 in 3 million with viral infections.

A balance will have to be maintained between risk of TTI and logistics of testing – both costs and availability of blood products. A level of tolerable risk approach was exercised during the Zika epidemic in 2017 to 2019.

COVID-19 and transfusion. The practice guidelines are still emerging on transfusion during this pandemic that hit the world in 2020. Currently, pragmatic suggestions are that potential donors be screened, that the blood products be used only after a period of 28 days (if the donor is asymptomatic for 28 days after donating, self-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 the 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 relative's 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. **Leukoreduction and irradiation.** Whole blood, platelets, and RBCs can be leukoreduced by filtration and/or irradiated to reduce the incidence of specific complications.

2.a. **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.** Potential to reduce a possible immunomodulatory effect of blood transfusions
- **c.** Decreased immunization to antigens on leukocytes such as HLA. This has been shown only for some oncology patients, and its importance for neonates is unknown.
- **d.** Neonates, especially premature infants, often receive leukoreduced blood components to decrease CMV transmission.

2.b. **Irradiation.** Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when transfused lymphocytes mount an immune response against the patient and the patient 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.

II. PACKED RED BLOOD CELLS

A. General principles

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.

1. **Types of RBC units.** 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 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 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. **CPD.** This contains 773 mg of dextrose and has a 21-day shelf life.

      ii. **CP2D.** This contains 1,546 mg of dextrose and has a 21-day shelf life.

      iii. **CPDA-1.** 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 for whole blood storage.

b. Additive solution units. RBC units are stored with additives (SAGM- saline, adenine, glucose, mannitol). The RBC 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 as this can significantly impact neonatal glucose homeostasis.

2. Effects of storage on RBC:

a. pH drops from 7.4–7.55 to 6.5–6.6 at the time of expiry.

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 to 45 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.

d. Although there are theoretical concerns that mannitol may cause a rapid diuresis and adenine may be a nephrotoxin in the premature infant, case reports and case series have found no risk associated with additive solution units. Although some hospitals still attempt to avoid additive solution units for neonates, the constituents of additives are not present in high enough concentrations to cause harm.

B. Transfusion guidelines. There has been a constant move toward restrictive thresholds for RBC transfusions. The concern for need of sufficient hemoglobin for oxygen transport, in acutely ill (cardiorespiratory instability) and long-term brain development in nonsick anemic babies, is counterbalanced by multiple serious complications such as transfusion-associated necrotizing enterocolitis (NEC), lung injury, CMV infections, GVHD, infections, and transfusion reactions. In extreme preterm infants, restrictive transfusion guidelines were associated with decrease in periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and NEC. British, Australian, Canadian, and Dutch guidelines were compared. The most recent Dutch guidelines (2019) recommend cutoffs of 11.5, 10, and 8.5 g for babies on respiratory support in the first, second, and third week, respectively, of life. For babies on no respiratory support, one may accept hemoglobin of 10, 8.5, and 7.5 g/dL.

Packed cell transfusions are often prescribed for apnea and intermittent hypoxia events. There seem to be some benefits in many babies.

C. Dosing and administration. The usual dose for a simple transfusion is 5 to 15 mL/kg transfused at a rate of approximately 5 mL/kg/hour. This may be adjusted depending on the severity of the anemia and/or the patient's ability to tolerate increases in intravascular volume.

D. Side effects

1. Acute transfusion reactions

a. 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 the kidneys. If necessary, treat hypotension with pressors and use hemostatic agents for bleeding; there may be a need to transfuse compatible RBCs.

b. **Allergic transfusion reactions.** These are unusual in neonates.

c. **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.

d. **Hypocalcemia.** Rapid infusion of components, especially FFP, can cause transient hypocalcemia secondary to transfusion of citrate.

e. **Hypothermia.** Cool blood can cause hypothermia. Transfusion through blood warmers can prevent this.

f. **Transfusion-associated acute lung injury (TRALI).** Worsening of respiratory distress (described as increased need of FiO_2 by 10 or mean airway pressure of 2) within 6 hours following transfusion, although not common, is a cause of serious morbidity and mortality. It may be difficult to differentiate from transfusion-associated cardiac overload (TACO). A two-hit hypothesis is used to explain TRALI. An underlying disease primes and activates neutrophils, and then the bioactive products in stored blood stimulate the primed neutrophils. It is difficult to recognize TRALI in preterm babies, and hence the actual incidence is not known.

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. Ideally, fresh (<3 -5 days old) RBC units can be provided for these transfusions. If fresh RBCs are unavailable, washing blood will reduce the extracellular potassium concentration.

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. TA-GVHD can be prevented by irradiation. Leukoreduction filters do not remove enough lymphocytes to prevent TA-GVHD. Several blood banks in developing countries do

not have processing technologies such as irradiation and leukoreduction. Premature neonates receiving nonirradiated blood products should be monitored for TA-GVHD. Clinicians following up these babies should be aware of symptomatology of GVHD (skin rashes, fever, jaundice, and abnormal liver function), which usually appears 2 to 4 weeks after transfusion.

k. Transfusion/anemia-associated NEC. There are multiple retrospective studies reporting association between NEC occurring within 24 to 48 hours of RBC transfusions in VLBW babies. Comparisons between units showed significantly lower NEC in units that used less RBC transfusions. The NEC was common in lower gestations and birth weight. Patent ductus arteriosus (PDA) was often present.

There are conflicting reports of RBC transfusion having protective effect. Prospective studies showed weak association between transfusion and NEC; in fact, severe anemia (<8 g/dL) itself, not transfusions, is likely in the causative pathway of NEC (transfusion/anemia associated NEC). Several studies have reported decreased incidence of NEC by withholding feeding around the time of transfusion, but good-quality evidence is lacking.

E. Special considerations. Donor exposures can be minimized by reserving a fresh unit of RBCs for a neonate at his or her 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.

F. Prevention. Strategies to decrease the need to transfuse include delayed cord clamping and decreasing blood losses in the neonatal intensive care unit (NICU) by careful planning of blood tests and microsampling techniques. Research is evaluating the possible use of erythropoietin.

III. FRESH FROZEN PLASMA, THAWED PLASMA

A. General principles. The two frozen plasma products that are most frequently available are FFP and thawed plasma. Both components are 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. FFP (yellow blood product) should be used only if there is active bleeding due to coagulopathy in a critically ill neonate or prior to major surgery. Generally, if international normalized ratio (INR) is ≤2, an invasive procedure can be safely done. FFP and thawed plasma are indicated to correct coagulopathies due to factor deficiencies. FFP may be used in known protein C or S deficiency and if specific factors products are not available. Although plasma contains proteins and albumins, these components are not indicated for intravascular volume expansion, prevention of intraventricular hemorrhage, or 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.

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. TRALI is more likely because plasma products contain more antibodies.
3. Acute hemolytic reactions involving hemolysis of transfused RBCs are 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.
4. 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.

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 5 days, there may be relatively low levels of the least stable coagulation factors V and VIII.

C. Indications. The cutoffs for platelet transfusions in stable preterm babies vary across guidelines from 25/L in Dutch to (10 to 20) $\times 10^9$/L in Australians; recent evidence suggests a cutoff of 20,000/mm^3 for stable preterms. For an unstable preterm (bleeding or invasive procedure), the cutoff values are similar across guidelines, 50,000/mm^3. NICU patients at an increased risk for intracranial hemorrhage or those with active bleeding should probably be maintained at a platelet count of 50,000.

D. Dosing and administration. A dose of approximately 5 mL/kg should raise the platelet count by approximately 30,000/mm^3.

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. 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. Granulocyte transfusions may benefit patients with severe neutropenia or dysfunctional neutrophils. Infants with chronic granulomatous disease also may benefit from granulocyte transfusions. Studies on neonatal sepsis do not support the use of granulocyte transfusion as an adjunct therapy.

B. Dosing and administration. The dosage is 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. Few units are stored as whole blood. 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°C 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 (exchange transfusion), 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 over 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. There is an inconclusive benefit of IVIG on use for hemolytic disease of the newborn.

IVIG can also be used to replace immunoglobulins for patients who are deficient in immunoglobulins as occurs with some congenital immunodeficiency syndromes.

IVIG has no proven benefit for prevention or treatment of neonatal 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. The availability in India is limited.

C. Dosing and administration. IVIG (non–disease-specific) is usually given at a dose of 500–1,000 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. In some neonates, NEC-like symptoms have been reported after IVIG. Live vaccines may be ineffective for a well-defined period after IVIG infusion.

VIII. UMBILICAL CORD BLOOD

A. General principles. It contains hematopoietic progenitor cells (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. There is better understanding of delayed cord clamping and its benefit to the baby; hence, the collection of cord blood should not be at the cost of the baby losing his or her own cord blood.

UCB can be collected for processing, freezing, and storage by UCB banks. It has a very low chance of being needed by the neonate because he or she would be able to use the UCB only 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, and two cord bloods or a single expanded cord blood may be used for transplants to larger patients. 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.

IX. EMERGENCY RELEASE BLOOD TRANSFUSION. Emergency release blood transfusion. Blood issued without cross-matching (type O RBC, AB plasma, and AB platelet) is needed occasionally in the delivery room (abruptio placentae, umbilical cord accident, congenital anemia, severe bleeding due to coagulopathy). Low-titer O blood is safer; large-volume transfusions may be given through blood warmers. An attempt to establish hemoglobin by ABG should be done pretransfusion, even in emergencies.

A case series on the safety of maternal blood, for transfusing neonates irrespective of ABO match, has been published in India.

Suggested Readings

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43 Bleeding

Stacy E. Croteau

KEY POINTS

- Normal levels of procoagulant and anticoagulant proteins are age-dependent. The physiologic balance of procoagulant and anticoagulant proteins and platelet function differs in neonates compared to older children or adult. Despite this "developmental hemostasis," 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 family history alone cannot exclude the diagnosis.
- Vitamin K is essential for normal production of several coagulation factors. Lack of administration to neonates increases their risk for severe bleeding in the neonatal period.

I. ETIOLOGY

A. Deficient clotting factors

1. **Transient deficiencies** of the procoagulant vitamin K–dependent factors II, VII, IX, and X and anticoagulant proteins C and S are characteristic of the newborn period and may be accentuated by the following:
   - **a.** The administration of total parenteral alimentation or antibiotics
   - **b.** Term infants may develop vitamin K deficiency by day 2 or 3 if they are not supplemented with vitamin K parenterally because of negligible stores and inadequate intake.
   - **c.** Liver disease may interfere with the production of clotting factors
   - **d. Transplacental exposure to certain drugs can cause bleeding in the first 24 hours of life.**
     - **i.** Phenytoin (Dilantin), phenobarbital, and salicylates interfere with the effect of vitamin K on clotting factor synthesis.
     - **ii.** Warfarin and related compounds given to the mother interfere with the synthesis of vitamin K–dependent clotting factors by both the maternal and fetal livers; bleeding may not be immediately reversed by administration of vitamin K.

2. **Disturbances of clotting**
   a. Disseminated intravascular coagulation (DIC) 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 the consumption of clotting factors in the bypass circuit in addition to therapeutic anticoagulation (see Chapter 39).
3. **Inherited abnormalities of clotting factors**
   a. **X-linked** recessive (expressed predominantly in males; Turner's syndrome, partial X deletions, or nonrandom X chromosome inactivation). **One-third of patients with severe hemophilia have "new mutations," so family history alone cannot exclude the diagnosis.**
      i. Factor VIII levels are decreased in the newborn with hemophilia A (1 in 5,000 males).
      ii. Hemophilia B, or Christmas disease, is due to a deficiency of factor IX (1 in 25,000 males).
   b. **Autosomal dominant** (expressed in boys and girls with one parent affected)
      i. von Willebrand disease (VWD) is caused by decreased levels or functional activity of von Willebrand factor (VWF), which acts as a carrier for factor VIII and plays a role in platelet aggregation. VWD is the most common inherited coagulation defect (up to 1% of the population as assayed by levels). VWF levels are elevated in neonates compared to older children and nonpregnant adults because of maternal estrogen.
      ii. Dysfibrinogenemia (very rare) is due to fibrinogen structural mutations.
   c. **Autosomal recessive** (occurs in both boys and girls born to carrier parents). In order of frequency, deficiencies of factors XI, VII, V, X, II, fibrinogen, and factor XIII are all encoded by autosomal genes. In factor XII deficiency, there is a prolonged partial thromboplastin time with no bleeding. Combined factor V and VIII deficiency is caused by a transport gene mutation, not mutations of the factor V and factor VIII genes.
      i. Severe factor VII or factor XIII deficiency can present as intracranial hemorrhage in neonates. Bleeding from the umbilical stump is also a feature of factor XIII deficiency.
      ii. Factor XI deficiency is incompletely recessive because heterozygotes may have unpredictable bleeding problems with surgery or trauma.
      iii. VWD type III (rare, complete absence of VWF)

B. Platelet problems (see Chapter 47)

1. **Qualitative disorders** include hereditary conditions (e.g., storage pool defects, Glanzmann thrombasthenia, Bernard–Soulier syndrome, platelet-type VWD) and transient disorders that result from maternal use of antiplatelet agents.
2. **Quantitative disorders** include the following:
   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) from kaposiform hemangioendothelioma or tufted angioma

h. Heparin-induced thrombocytopenia (HIT) results from antibody development to the complex of heparin with platelet factor IV. It is probably rare in neonates, although the antibody can be detected by enzyme-linked immunosorbent assay (ELISA) after cardiac surgery.

C. Other potential causes of bleeding

1. **Vascular** anomalies may cause central nervous system, 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 INFANT

A. History

1. Family history of excessive bleeding or clotting
2. Maternal medications (e.g., aspirin, phenytoin)
3. Pregnancy and birth history
4. Maternal history of 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. Swallowed maternal blood during labor or delivery or from a bleeding breast will not cause symptoms in the infant.

Clinical clues

a. **Petechiae, small superficial ecchymosis, or mucosal bleeding** suggests a platelet problem or VWD.

b. **Large bruises** suggest deficiency of clotting factors, DIC, liver disease, or vitamin K deficiency.

c. **Enlarged spleen** suggests possible congenital infection or erythroblastosis.

d. **Jaundice** suggests infection, liver disease, or resorption of a large hematoma.

e. **Abnormal retinal findings** suggest infection (see Chapter 48).

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 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 infant 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.

Table 43.1. Differential Diagnosis of Bleeding in the Neonate

Clinical Evaluation	Laboratory Studies			Likely Diagnosis
	Platelets	PT	PTT	
"Sick"	D–	I+	I+	DIC
	D–	N	N	Platelet consumption (infection, necrotizing enterocolitis, renal vein thrombosis, KMP)
	N	I+	I+	Liver disease
	N	N	N	Compromised vascular integrity associated with hypoxia, prematurity, acidosis, hyperosmolality
"Healthy"	D–	N	N	Immune thrombocytopenia, occult infection, thrombosis, bone marrow hypoplasia (rare), or bone marrow infiltrative disease
	N	I+	I+	Hemorrhagic disease of newborn (vitamin K deficiency)
	N	N	I+	Hereditary clotting factor deficiencies
	N	N	N	Bleeding due to local factors (trauma, anatomic abnormalities), qualitative platelet abnormalities (rare), factor XIII deficiency (rare), von Willebrand disease

D–, decreased; DIC, disseminated intravascular coagulation; I+, increased; KMP, Kasabach–Merritt phenomenon; N, normal; PT, prothrombin time; PTT, partial thromboplastin time.
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.

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.** Platelet counts of 20 to 30,000/mm^3 are considered safe and may not be associated with bleeding, however in NAIT platelet counts must be maintained above 50,000/mm^3. 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. 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 infancy or in affected family members is preferable to testing neonates.

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	Infant 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

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.
*Normal values may vary from laboratory to laboratory, depending on the particular reagents employed. 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 (under 1,500 g) tend to have prolonged 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. A 3-day-old full-term neonate not receiving vitamin K has levels similar to a premature neonate. Factor XI and XII levels are lower in preterm infants than in term infants and account for prolonged PTT. Fibrinogen, factor V, and factor VIII are normal in premature and term infants. Factor XIII is variable.

5. **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.
6. **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).
7. **Fibrinogen** can be measured on the same sample used for PT and PTT. It may be decreased in liver disease and consumptive states. The usual functional assay is low in dysfibrinogenemia.
8. **D-Dimer assays** measure degradation products of fibrin found in the plasma. D-Dimers are derivatives of cross-linked fibrin generated by the action of plasmin on fibrin clot. Normal levels vary by specific assay used (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 are common in the intensive care unit setting because trivial clotting from catheter tips and other causes gives positive results in this sensitive assay.
9. **Specific factor assays and von Willebrand panel** for patients with positive family history **can be measured in cord blood or by venipuncture after birth**. Age-specific norms must be used.
10. Bleeding time is not recommended in 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 42). 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 <50,000/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 NEONATES WITH CLINICAL BLEEDING

A. Replacement therapies

1. **Vitamin K_1 (AquaMEPHYTON).** An intravenous (IV) or intramuscular (IM) dose of 1 mg is administered if the neonate has not received 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 IV or IM 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 is 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 approximately to 20% of adult control, so specific factor deficiencies should be treated with factor concentrate when available. Cryoprecipitate contains only factor VIII, VWF, fibrinogen, and factor XIII. It is the most practical source of fibrinogen or factor XIII for neonates until a specific diagnosis is made.

3. **Platelets** (see Chapter 47). In the absence of platelet 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 factors VIII, IX, VII, and XIII. When there is a known deficiency of factor VIII or IX, the plasma concentration should be raised to normal adult levels (50% to 100% of pooled normal control plasma, or 0.5 to 1.0 unit/mL) to stop serious bleeding. Factor VIII or IX concentrates should be used if the diagnosis is clear. 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.

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 the 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. Continued transfusion with platelets, PRBCs, and FFP as needed
      ii. Administration of 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 unit/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. Anticoagulation is generally contraindicated in the presence of intracranial hemorrhage. When DIC manifests as both bleeding and thrombosis concurrently, heparinization is complicated; consult an expert immediately (see Chapter 44).

2. **Hemorrhagic disease of the newborn (HDN)** occurs in 1 out of every 200 to 400 neonates not given vitamin K prophylaxis.
   a. In the healthy infant, **HDN may occur when the infant is not given vitamin K**. The infant may have been born in a busy delivery room or at home, or transferred from elsewhere. Bleeding and bruising may occur after the infant is 48 hours old. The platelet level is normal, and PT and PTT are prolonged. If there is active bleeding, 10 mL/kg of FFP and an IV dose of 1 mg of vitamin K are given.
   b. **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 10 mg of vitamin K_1 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. The newborn should have PT, PTT, and platelet counts monitored if any signs of bleeding occur. Infuse FFP for bleeding.
   c. **Delayed HDN** from vitamin K deficiency can occur at 4 to 12 weeks of age. Although blood tests show that breastfed infants are at potential risk for HDN, HDN has not been reported in infants who received IM vitamin K at birth. Vitamin K_1, 1 mg/week orally for the first 3 months of life for breastfed infants, may prevent late HDN. Infants receiving broad-spectrum antibiotics or infants with malabsorption (liver disease, cystic fibrosis) are at a greater risk for vitamin K deficiency and hemorrhagic disease.

Suggested Readings

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44 Neonatal Thrombosis

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KEY POINTS

- Neonatal thrombosis is a rare but 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 most thrombotic events.
- Monitor for clinical signs of thrombosis if an umbilical arterial catheterization (UAC) is present.
- Renal vein thrombosis is the most common cause of non-catheter-associated thrombosis in neonates and can result in long-term renal impairment.
- Although recurrence risk is low, it is generally recommended that neonates with clinically significant thrombosis should undergo a thrombophilia evaluation. The frequency and contribution of inherited and acquired prothrombotic states to thromboembolic events in neonates remain poorly understood.
- Data are limited on the efficacy and safety of therapeutic agents in neonates. But treatment should be directed toward preventing clot extension and thereby end-organ damage.
- Unfractionated heparin and low-molecular-weight heparin (e.g., enoxaparin) are first-line therapies for the treatment of neonates with clinically significant thrombosis.
- 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 pathways of the coagulation cascade result in the formation of active thrombin from prothrombin.
2. **Inhibitors of coagulation** include antithrombin, heparin cofactors, protein C, protein S, α_2-macroglobulin, and tissue factor pathway inhibitor. Antithrombin activity is potentiated by 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 hemostasis 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. Both thrombogenic and fibrinolytic pathways are altered in the neonate compared with in the older child and adult, resulting in increased vulnerability to both hemorrhage and pathologic thrombosis. Under normal physiologic conditions, however, the hemostatic system in preterm and term newborns is in balance, and healthy neonates do not clinically demonstrate hypercoagulable or bleeding tendencies.
3. Concentrations of most procoagulant proteins, particularly vitamin K–dependent coagulation factors, are reduced in neonates compared with in adults; levels of some procoagulant factors such as factor VIII and fibrinogen are typically normal or even increased. Compared to adults, neonates have a decreased ability to generate thrombin, and values for the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) are prolonged.
4. Concentrations of most antithrombotic and fibrinolytic proteins are also reduced, including protein C, protein S, plasminogen, and antithrombin, although α_2-macroglobulin concentration is increased. Thrombin inhibition by plasmin is diminished compared with adult plasma.
5. Platelet number and life span appear to be like that of adults. The bleeding time, an overall assessment of platelet function and interaction with vascular endothelium, is shorter in neonates than in adults, suggesting more rapid platelet adhesion and aggregation.

II. EPIDEMIOLOGY AND RISK FACTORS

A. Epidemiology

1. Thrombosis occurs more frequently in the neonatal period than at any other age in childhood.
2. The presence of an **indwelling vascular catheter** is the single greatest risk factor for arterial or venous thrombosis. Indwelling catheters are responsible for more than 80% of venous and 90% of arterial thrombotic complications.
3. Autopsy studies show that 20% to 65% of infants who expire with an umbilical venous catheter (UVC) in place are found to have a thrombus associated with the catheter. Venography suggests that asymptomatic thrombi are present in 30% of newborns with a UVC.
4. Umbilical arterial catheterization (UAC) appears to result in severe symptomatic vessel obstruction requiring intervention in approximately 1% of patients. Asymptomatic catheter-associated thrombi have been found in 3% to 59% of cases by autopsy and 10% to 90% of cases by angiography or ultrasound.
5. Multiple maternal, perinatal, and neonatal risk factors are thought to contribute to thrombotic events 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.

6. Infants undergoing surgery involving the vascular system, including repair of congenital heart disease, are at an increased risk for thrombotic complications. Diagnostic or interventional catheterizations also increase the risk of thrombosis.
7. **Renal vein thrombosis** is the most common type of non-catheter-related pathologic thrombosis in newborns.
8. Registries from Canada, Germany, The Netherlands, and Italy have described series of cases of neonatal thrombosis.
   a. Incidence of clinically significant thrombosis among infants in neonatal intensive care units (NICUs) was reported as 2.4 per 1,000 NICU admissions in Canada, 6.8 per 1,000 NICU admissions in The Netherlands, and 5.8 and 6.6 per 1,000 NICU admissions at two large centers in Italy. Incidence among live births was estimated at 5.1 per 100,000 births in Germany, 14.5 per 10,000 neonates in The Netherlands, and 3.4 and 6.5 per 10,000 live births at the Italian centers.
   b. Three series examined both venous and arterial thromboses. Among all thrombotic events, the percentage of renal vein thrombosis ranged from 19% to 44%, other venous thrombosis ranged from 33% to 40%, and arterial thrombosis from 24% to 34%.
   c. Excluding cases of renal vein thrombosis, 67%, 89%, and 94% of venous thromboses were found to be associated with indwelling central lines in three series.
   d. Mortality was rare and generally restricted to very premature infants or infants with large arterial or intracardiac thromboses.

B. Inherited hypercoagulable states

1. Inherited prothrombotic disorders are characterized by a positive family history, early age of onset, recurrent disease, and unusual or multiple locations of thromboembolic events. Although it is estimated that a genetic risk factor can be identified in 10% to 50% of children with thrombosis, the incidence of these disorders in newborns with thrombosis is not well known.
2. Important inherited prothrombotic disorders include the following:
   a. Deficiencies of protein C, protein S, and antithrombin appear to have the largest increase in relative risk for thromboembolic disease but are relatively rare.
   b. Activated protein C resistance, including factor V Leiden mutation and prothrombin G20210A mutation, have a high incidence, particularly in certain populations, but appear to have a low risk of thrombosis in neonates.

c. Hyperhomocysteinemia, increased lipoprotein(a) levels, and polymorphism in the methylene tetrahydrofolate reductase (MTHFR) gene are relatively common, but their significance in neonatal thrombosis is still poorly understood.

3. Multiple other defects in the anticoagulation, fibrinolytic, and antifibrinolytic pathways have been identified, including abnormalities in thrombomodulin, tissue factor pathway inhibitor, fibrinogen, plasminogen, tPA, and plasminogen activator inhibitors. The frequency and importance of these defects in neonatal thrombosis are poorly understood.

4. The incidence of thrombosis in patients heterozygous for most inherited thrombophilias is small; however, increasing evidence suggests that the presence of a second risk factor substantially increases the risk for thrombosis. This second risk factor can be an acquired clinical condition or another inherited defect. Patients with single defects for inherited prothrombotic disorders rarely present in the neonatal period, unless another pathologic event occurs.

5. 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. The classic presentation of homozygous prothrombotic disorders is **purpura fulminans** associated with homozygous protein C or S deficiency, which presents within hours or days of birth, often with evidence of *in utero* cerebral damage.

6. Overall, the importance of inherited thrombophilias as independent risk factors for neonatal thrombosis is still undetermined. It appears that the absolute risk of thrombosis in the neonatal period in all patients with an inherited nonhomozygous thrombophilia is low. Among neonates with thrombotic disease, however, the incidence of an inherited thrombophilia appears to be substantially increased compared to that among the general population, and evaluation for thrombophilia should be considered.

C. Acquired thrombophilias

1. Newborns can acquire significant coagulation factor deficiencies due to placental transfer of maternal antiphospholipid antibodies, including lupus anticoagulant and anticardiolipin antibodies.

2. These neonates can present with significant thrombosis, including purpura fulminans.

3. Mothers should potentially be screened for the presence of autoimmune antibodies as part of a thrombophilia evaluation for neonates presenting with clinically significant thrombosis.

III. SPECIFIC CLINICAL CONDITIONS

A. Venous thromboembolic disorders

1. General considerations

a. Most venous thromboses occur secondary to **central venous lines (CVLs)**. Spontaneous (i.e., non-catheter-related) venous thrombosis can occur in renal veins, adrenal veins, superior or inferior vena cava (IVC), portal vein, hepatic veins, and the venous system of the brain.

b. Spontaneous venous thrombi usually occur in the presence of another risk factor. Less than 1% of clinically significant venous thromboembolic events in neonates are idiopathic.

c. Thrombosis of the **sinovenous system of the brain** is an important cause of neonatal cerebral infarction.

d. Surgical repair of complex congenital heart disease has been associated with an increased risk of thrombosis, particularly of the superior vena cava.

e. It is likely that the frequency of pulmonary embolism in sick neonates is underestimated because signs and symptoms would be similar to those of other common neonatal pulmonary diseases.

f. Short-term complications of venous catheter–associated thrombosis include loss of access, pulmonary embolism, superior vena cava syndrome, and specific organ impairment.

g. Long-term complications of venous thrombosis are poorly understood. IVC 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 CVL also raises the suspicion of thrombosis.

b. Diagnosis

i. Ultrasound with Doppler is diagnostic in most cases of significant venous thrombosis. In smaller infants or low-flow states, however, ultrasound may not provide sufficient information about the size of the thrombus, and a significant false-negative rate has been documented.

ii. Contrast studies, including a radiographic line study or venography through peripheral vessels, may assist with the diagnosis of catheter-associated thrombosis. However, these studies are rarely performed secondary to improvements in ultrasound technology and associated risks in neonates.

c. Prevention of catheter-associated venous thrombosis

i. Unfractionated heparin (UFH) 0.5 unit/mL is added to all compatible infusions through CVLs at a rate of 0.5 to 1 mL/hour.

ii. Also, heparinized normal saline fluid to maintain the patency of peripheral arterial catheters in neonates can be used.

iii. Both UVCs and peripherally inserted central catheters (PICCs) can be intermittently flushed or infused with low-dose heparin to maintain patency. Continuous heparin infusion reduces the risk of catheter occlusion but does not reduce rates of thrombosis or catheter-related sepsis.

iv. UVCs should be removed as soon as clinically feasible and should not remain in place for longer than 10 to 14 days. A PICC line is typically placed if the anticipated need for central access is >7 days.

d. Management of catheter-associated venous thrombosis

i. **Nonfunctioning CVL.** If fluid can no longer be easily infused through the catheter, remove the catheter unless the CVL is absolutely necessary. If continued central access through the catheter is judged to be clinically necessary, however, clearance of the blockage with thrombolytic agents (e.g., tPA) can be considered. Subsequently, prophylactic doses of low-molecular-weight heparin (LMWH) can be given until the device is removed.

ii. **Local obstruction.** If a small occlusive catheter-related thrombosis is documented, a low-dose infusion of thrombolytic agent through the catheter can be considered for localized site-directed thrombolytic therapy. If infusion through the catheter is not possible, the CVL should be removed and heparin therapy considered.

iii. **Extensive venous thrombosis.** It is currently recommended that UVCs and CVLs associated with confirmed extensive thrombosis by ultrasound be left in place for 3 to 5 days of therapeutic anticoagulation and subsequently removed in order to reduce the risk of paradoxical emboli. Systemic thrombolytic therapy should be reserved for extensive non-catheter-related organ-, limb-, or life-threatening venous thrombosis.

3. Renal vein thrombosis

a. Renal vein thrombosis occurs primarily in newborns and young infants and most often presents in the first week of life. A significant proportion of cases appear to result from *in utero* thrombus formation.

b. Affected neonates are usually term and often large for gestational age. There is an increased incidence among infants of diabetic mothers, and males are more often affected than females. A recent review demonstrated bilateral renal vein thrombus formation in up to 30% of cases.

c. Additional risk factors include perinatal asphyxia, hypotension, polycythemia, increased blood viscosity, and cyanotic congenital heart disease.

d. Presenting symptoms in the neonatal period include flank mass, hematuria, proteinuria, thrombocytopenia, and renal dysfunction. The diagnosis is made by ultrasound with Doppler interrogation. Coagulation studies may be prolonged, and fibrin degradation products are usually increased.

e. Complications can include hypertension, renal failure, adrenal hemorrhage, extension of the thrombus into the IVC, and death.

f. Retrospective studies have demonstrated that 43% to 67% of neonates with renal vein thrombosis had at least one or more prothrombotic risk factors. A thrombophilia evaluation of infants with renal vein thrombosis is warranted.

g. Management is generally based on the extent of thrombosis.

4. Management of renal vein thrombosis

a. Unilateral renal vein thrombosis without significant renal dysfunction or extension into the IVC is often managed with supportive care and close

radiologic monitoring. Any central venous catheter (CVC) or UVC in place in the IVC should be preferably removed. If the thrombosis progresses or there is extension into the IVC, anticoagulation should be initiated.

b. Unilateral renal vein thrombosis with renal dysfunction or extension into the IVC and bilateral renal vein thrombosis should be considered for therapeutic anticoagulation with UFH or LMWH for a total duration of 6 weeks to 3 months. Note that the dosing of LMWH may need to be reduced in patients with renal insufficiency.

c. Bilateral renal vein thrombosis with significant renal dysfunction should be considered for thrombolysis with tPA followed by anticoagulation with UFH or LMWH. However, in severe renal failure, UFH should be used instead of LMWH.

5. 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, and 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. UVC should be removed soon as possible.

e. If the thrombus extends into the main portal vein, anticoagulation should be initiated (typically with LMWH). There are currently no data to suggest that anticoagulation decreases the time to resolution or the risk of developing portal hypertension.

6. Right atrial thrombosis

a. Right atrial thrombi can occur with the use of CVC and can lead to pulmonary embolism and also affect heart function.

b. The catheter should be removed. Anticoagulation therapy (with LMWH) is recommended. If cardiac function is compromised, thrombolytic therapy is instituted.

c. In neonates, even smaller thrombi may be "high risk." If conservative management is chosen, the thrombus should be monitored closely and anticoagulation should be started if the thrombus increases in size.

7. Cerebral sinovenous thrombosis

a. Thrombosis of the sinovenous system of the brain 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 cerebral sinovenous thrombosis 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 sinovenous thrombosis and noted in 50% to 60% of cases on initial imaging.

e. The majority of cases of neonatal sinovenous thrombosis are associated with maternal conditions including preeclampsia, diabetes, autoimmune illnesses, and chorioamnionitis as well as acute systemic illness in the neonate.

f. Inherited thrombophilias have been reported in 15% to 20% of neonates with sinovenous thrombosis.

g. Ultrasound and computed tomography (CT) scan can identify cranial sinovenous thrombosis (CSVT), but magnetic resonance imaging (MRI) with venography is the imaging modality of choice for optimal detection of sinovenous thrombosis and associated cerebral injury.

h. Data on management remain limited. In general, neonates with cerebral sinovenous thrombosis without associated hemorrhage should be considered for anticoagulation therapy initially with UFH or LMWH and subsequently LMWH for a total of 6 weeks to 3 months. Recanalization is looked for after 6 weeks and anticoagulants stopped if recanalization is complete. But if there is incomplete recanalization, anticoagulation should continue for 6 weeks more and then stopped. If significant hemorrhage is present, anticoagulation should be reserved for cases with clinical deterioration or radiologic propagation of the thrombus.

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 catheter-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 the 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 all cases of suspected aortic thrombosis. If signs of thrombosis are mild and resolve promptly after removal of the arterial catheter, an ultrasound may not be necessary. Ultrasound is diagnostic in most cases, although a significant false-negative rate has been documented.

ii. Historically, radiographic contrast studies were performed if ultrasound was inconclusive. These studies are generally no longer recommended in neonates because of the associated risks.

iii. 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 unit/mL is added to all compatible infusions through arterial catheters in order to prolong patency. This has not been shown to decrease the risk of associated thrombosis.

ii. A review of the literature suggests that **"high" umbilical arterial lines** (tip in the descending aorta below the left subclavian artery and above the 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 is generally not indicated with the exception of life- or limb-threatening thrombosis because the associated mortality and morbidity in neonates are considered to exceed those of current medical management. Some recent experience suggests that thrombectomy and subsequent vascular reconstruction may have utility in significant peripheral arterial thrombosis, although experience is limited.

3. Peripheral arterial thrombosis

a. Although rare, congenital occlusions of large peripheral arteries are seen and can present with symptoms ranging 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 can often be made by 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 unit/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 heparin 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 commonly used diagnostic modality. Advantages include relative ease of performance, noninvasiveness, and ability to perform sequential scans to assess the 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 the 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. Evaluation for thrombophilia

1. Consider evaluating for congenital or acquired thrombophilias in neonates with severe or unusual manifestations of thrombosis or with positive family

histories of thrombosis. The benefit of evaluation in infants with known risk factors such as indwelling central catheters is uncertain.

2. Initial evaluation should include consideration of deficiencies of protein C, protein S, and antithrombin, presence of activated protein C resistance, factor V Leiden mutation, prothrombin G20210A mutation, and passage of maternal antiphospholipid antibodies.
   a. **Protein C, protein S, and antithrombin deficiencies** can be evaluated by measurement of antigen or activity levels. Results of testing of neonates should be compared with standard gestational age–based reference ranges because normal physiologic values can be as low as 15% to 20% of adult values. In addition, levels will be physiologically depressed in the presence of active thrombosis and may be difficult to interpret. It is generally recommended that levels be rechecked 2 to 3 months after the acute thrombotic episode. As an alternative to or in conjunction with testing of the neonate, parents can be tested for carrier status by measurement of protein C, protein S, and antithrombin levels.
   b. **Factor V Leiden, prothrombin G20210A, and MTHFR mutations** can be assayed by specific genetic tests in the neonate. Parents can be tested for carrier status.
   c. **Autoimmune antibodies**, including an antiphospholipid antibody panel, anticardiolipin, and lupus anticoagulant levels, can be checked in the mother.
3. If the given testing is negative, subsequent specialized laboratory evaluation includes abnormalities or deficiencies of homocysteine, lipoprotein(a), plasminogen, and fibrinogen. Very rarely seen are abnormalities or deficiencies of heparin cofactor II, thrombomodulin, plasminogen activator inhibitor-1, platelet aggregation, and tPA.

B. 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. 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 should 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 active bleeding.

b. In general, **relative contraindications** include platelet count <50,000/μL or <100,000/μL in critically ill neonates, fibrinogen level <100 mg/dL, international normalized ratio (INR) >2, severe coagulopathy, and hypertension.

C. Unfractionated heparin

1. General considerations

a. Term newborns generally have a faster clearance of heparin and lower antithrombin levels compared with adults. These factors generally result in a relative increase in the heparin dose required to achieve therapeutic levels in neonates. There is also significant variability in heparin dosage requirements between patients.

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 heparin therapy, a baseline complete blood count (CBC), PT, and partial thromboplastin time (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.

e. Use of PTT to monitor heparin effect is problematic in neonates due to significant variability of coagulation factor concentrations and baseline prolongation of the PTT. **Heparin activity level** is generally considered to be a more reliable marker. Therapeutic heparin activity for treatment of most thromboembolic events is considered to be an anti–factor Xa level of 0.35 to 0.7 unit/mL or a heparin level by protamine titration of 0.2 to 0.4 unit/mL. Most laboratories report heparin activity levels as an anti–factor Xa level.

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.

ii. Note that measurement of heparin activity levels, unlike measurement of PTT, is independent of the presence of antithrombin. Therefore, measured heparin activity levels may be therapeutic even though effective anticoagulation has not been achieved due to antithrombin deficiency.

2. **Dosing guidelines**
   a. Standard UFH is given as an initial bolus of 75 unit/kg IV, followed by a continuous infusion that is begun at 28 unit/kg/hour. In premature infants under 37 weeks' gestation, lower dosing of 25 to 50 unit/kg bolus followed by 15 to 20 unit/kg/hour can be considered.
   b. Heparin activity levels and/or PTT should be measured 4 hours after the initial bolus and 4 hours after each change in the 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. 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 the anticoagulation effects of heparin therapy and is usually sufficient.
   b. If a 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 exceed 5 mg/minute. Hypersensitivity can occur in patients who have received protamine-containing insulin or previous protamine therapy.
   c. Dosing is based on the total amount of heparin received in the last 2 hours as shown in Table 44.2.

Table 44.1. Unfractionated Heparin Dosage Monitoring and Adjustment

PTT (seconds)*	Heparin Activity (unit/mL)	Bolus (unit/kg)	Hold (minutes)	Rate (%)	Recheck (hours)
<50	0–0.2	50	—	+10	4
50–59	0.21–0.34	0	—	+10	4
60–85	0.35–0.7	0	—	—	24
86–95	0.71–0.8	0	—	−10	4
96–120	0.81–1.0	0	30	−10	4
>120	>1	0	60	−15	4

*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 unit/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 units 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.

D. Low-molecular-weight heparin

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 LMWHs** 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 dosage of LMWH is titrated to anti–factor Xa levels. **Target anti–factor Xa levels** for the treatment of most thromboembolic events are 0.50 to 1.0 unit/mL, measured 4 to 6 hours after a subcutaneous injection. In patients at particularly high risk for bleeding, target levels of 0.4 to 0.6 unit/mL can be considered. When used for prophylaxis, target levels are 0.1 to 0.4 unit/mL. After therapeutic levels have been achieved for 24 to 48 hours, levels should be followed at least weekly along with a CBC as thrombocytopenia can occur.

d. The therapeutic range for neonates has not been well established. Infants younger than 2 months have a higher dose requirement than older children. In addition, some studies suggest higher initial doses for preterm infants. Dosage requirements to maintain target levels in preterm infants may be quite variable. The safety and efficacy data related to the use of LMWH or UFH are based on the data on aPTT or anti–factor Xa levels in older children.

e. Several different LMWHs are available, and the dosages are not interchangeable. **Enoxaparin (Lovenox)** has the most widespread pediatric usage.

f. 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.

Table 44.3. Initial Dosing of Enoxaparin, Age-Dependent (in mg/kg/dose SQ)

Age (months)	Initial Treatment Dose	Initial Prophylactic Dose
<2	1.5 q12h	0.75 q12h
>2	1.0 q12h	0.5 q12h

Initial dose of 2 mg/kg every 12 hours can be considered in preterm infants. SQ, subcutaneous.
Source: Adapted from Truven Health Analytics. *Micromedex NeoFax essentials*. https://itunes.apple.com/us/app/thomson-reuters-neofax-essentials/id460060130?mt=8; and 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 44.4. Monitoring and Dosage Adjustment of Enoxaparin Based on Anti–Factor Xa Level Measured 4 Hours after Dose of Enoxaparin

Anti–Factor Xa Level (units/mL)	Hold Dose	Dose Change (%)	Repeat Anti–Factor Xa Level
<0.35	—	+25	4 hours after next dose
0.35–0.49	—	+10	4 hours after next dose
0.5–1.0	—	—	24 hours
1.1–1.5	—	–20	Before next dose
1.6–2.0	3 hours	–30	Before next dose and then 4 hours after next dose
>2.0	Until level is 0.5 unit/mL	–40	Before next dose; if level not <0.5 unit/mL, repeat q12h

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.

2. **Dosing guidelines** (Tables 44.3 and 44.4)
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 the last injection, although protamine may not completely reverse anticoagulant effects. Administer 1 mg protamine sulfate per 1 mg LMWH given in the last injection.

E. Thrombolysis

1. General considerations

a. Thrombolytic agents act by converting endogenous plasminogen to plasmin. Plasminogen levels in neonates are reduced compared with in adults,

and thus, the effectiveness of the thrombolytic agents may be diminished. Cotreatment with plasminogen with the 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 the 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 a sign at the head of the bed indicating thrombolytic therapy.

ii. Have topical thrombin available in the unit refrigerator.

iii. Notify the blood bank to ensure the availability of cryoprecipitate.

iv. Notify the pharmacy to ensure the availability of aminocaproic acid (Amicar).

v. Obtain good venous access. Consider the need for a mode of access to allow frequent blood draws to minimize the 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. Obtaining also a baseline cranial ultrasound is especially important for preterms who are inclined to have an increased risk of intracranial hemorrhage.

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 above 100 mg/dL** and **platelet count above 50,000 to 100,000** to minimize the risks of clinical bleeding. Administer cryoprecipitate 10 mL/kg (or 1 unit/5 kg) or platelets 10 mL/kg as needed. If fibrinogen level drops below 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 the 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.

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 units/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. For severe bleeding, stop the infusion and administer cryoprecipitate (1 unit/5 kg).

c. In the setting of life-threatening bleeding, stop the infusion, give cryoprecipitate, and infuse aminocaproic acid (Amicar) (at the usual dose of 100 mg/kg IV every 6 hours) after consulting hematology.

5. Post thrombolytic therapy. Consider initiating UFH without the initial loading dose or LMWH. Consider discontinuing heparin if no reaccumulation of the thrombus occurs after 24 to 48 hours.

F. Treatment of central catheter obstruction

1. Treatment guidelines

a. Central catheters may become occluded because of thrombus or chemical precipitate often secondary to parenteral nutrition.

b. Nonfunctioning central catheters should be removed whenever possible, unless continued access through the catheter is absolutely medically necessary.

c. tPA may be used for thrombosis, and hydrochloric acid (HCl) may be attempted for chemical blockage.

d. General procedure

i. Instill the chosen agent at the volume needed to fill the catheter (up to 1 to 2 mL) with gentle pressure. The 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 the catheter, 10-mL empty syringe, and a 1-mL syringe containing the agent to the stopcock. Create a 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 the stopcock off to the 10-mL syringe and allow vacuum in the catheter to draw in the infusate from the 1-mL syringe.

ii. The 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 to 1 mL of 0.1 M 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 the fluid through the catheter.

iv. If unsuccessful, the previous steps can be repeated once.

v. If clearance of the catheter is not successful after two attempts, the catheter should be removed.

e. Low-dose continuous infusion of thrombolytic agents can be considered for local thrombosis occluding the catheter tip (see the preceding text).

2. Dosing guidelines (Table 44.7)

Table 44.7. Local Instillation of Agents for Catheter Blockage

Agent	Dosing
tPA	0.5 mg/lumen diluted in NS to volume needed to fill line, to maximum 3 mL
HCl	0.1 M, 0.1–1 mL/lumen

HCl, hydrochloric acid; NS, normal saline; tPA, tissue plasminogen activator.

Suggested Readings

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45 Anemia

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KEY POINTS

- A postnatal fall in hemoglobin is physiologically expected in all infants, due to suppression of erythropoietin production in the relatively hyperoxic extrauterine environment, reaching nadir between 8 and 12 weeks of age. The degree of anemia, as well as the nadir period, is more dramatic in preterm infants.
- Infant growth and development are likely affected by hemoglobin levels, but current evidence is inconclusive regarding optimal hematocrit (Hct)/hemoglobin target levels.
- Iron supplemented to preterm babies before 10 to 14 weeks does not decrease the fall (nadir) in hemoglobin, but the iron is stored and available for synthesis later.
- Enteral iron supplementation of 2 to 4 mg/kg/day in the preterm infant improves iron stores, and lowers the risk of iron deficiency anemia in infancy (after 6 months of age), but its effect on neurodevelopment remains unclear.
- Erythropoiesis-stimulating agents are not routinely recommended in preterm infants.
- An association between red blood cell (RBC) transfusions and necrotizing enterocolitis (transfusion-associated necrotizing enterocolitis [TANEC]), and respiratory distress (transfusion related lung injury [TRALI]) has been reported; there is variability in practice on holding enteral feeding during transfusion.

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 take into account this developmental process as well as the infant's physiologic needs.

A. Normal development: the physiologic anemia of infancy

1. *In utero*, the fetal aortic oxygen saturation is low at 45%, erythropoietin levels are high, and RBC production is rapid. The fetal liver is the major site of erythropoietin production.
2. After birth, the oxygen saturation is much higher at 95%, and hence, erythropoietin is undetectable. RBC production by day 7 is <1/10th the level *in utero*. Reticulocyte counts are low, and the hemoglobin level falls (Table 45.1).
3. Although hemoglobin levels fall, oxygen availability to tissues remains good. The ratio of hemoglobin A to hemoglobin F increases, and the levels of 2,3-diphosphoglycerate (2,3-DPG) are high (2,3-DPG interacts with hemoglobin A to decrease its affinity for oxygen, thereby enhancing oxygen release to

the tissues). As a result, oxygen delivery to the tissues actually increases. This physiologic "anemia" is not a functional anemia in that oxygen delivery to the tissues is adequate.

4. At 8 to 12 weeks, hemoglobin levels reach their nadir (Table 45.2), oxygen delivery to the tissues decreases, renal erythropoietin production is stimulated, and RBC production increases.
5. Infants who have received transfusions in the neonatal period have lower nadirs than normal because of their higher percentage of hemoglobin A.
6. During this period of active erythropoiesis, iron stores are rapidly utilized. Iron is available from degraded RBC. Iron stores are sufficient for 15 to 20 weeks in term infants. After this time, the hemoglobin level decreases if iron is not supplied.

B. Anemia of prematurity is an exaggeration of the normal physiologic anemia (see Tables 45.1 and 45.2).

Table 45.1. Hemoglobin Changes in Babies in the First Year of Life

Week	Hemoglobin Level		
	Term Babies	Premature Babies (1,200–2,500 g)	Small Premature Babies (<1,200 g)
0	17.0	16.4	16.0
1	18.8	16.0	14.8
3	15.9	13.5	13.4
6	12.7	10.7	9.7
10	11.4	9.8	8.5
20	12.0	10.4	9.0
50	12.0	11.5	11.0

Source: From Glader B, Naiman JL. Erythrocyte disorders in infancy. In: Taeusch HW, Ballard RA, Avery ME, eds. *Diseases of the Newborn*. Philadelphia, PA: WB Saunders; 1991.

Table 45.2. Hemoglobin Nadir in Babies in the First Year of Life

Maturity of Baby at Birth	Hemoglobin Level at Nadir	Time of Nadir (week)
Term babies	9.5–11.0	6–12
Premature babies (1,200–2,500 g)	8.0–10.0	5–10
Small premature babies (<1,200 g)	6.5–9.0	4–8

Source: From Glader B, Naiman JL. Erythrocyte disorders in infancy. In: Taeusch HW, Ballard RA, Avery ME, eds. *Diseases of the Newborn*. Philadelphia, PA: WB Saunders; 1991.

1. RBC mass and iron stores are decreased because of low birth weight; however, hemoglobin concentrations are similar in preterm and term infants.
2. The hemoglobin nadir is reached earlier than in the term infant because of the following:
   a. RBC survival is decreased in comparison with that in the term infant.
   b. There is a relatively more rapid rate of growth in premature babies than in term infants. For example, a premature infant gaining 150 g/week requires approximately a 12 mL/week increase in total blood volume.
   c. Many preterm infants have reduced red cell mass and iron stores because of iatrogenic phlebotomy for laboratory tests. This has been somewhat ameliorated with the use of microtechniques.
   d. Vitamin E deficiency is common in small premature infants, unless the vitamin is supplied exogenously.
3. The hemoglobin nadir in premature babies is lower than in term infants because erythropoietin 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.
4. Iron administration *before the age of 10 to 14 weeks does not increase the nadir of the hemoglobin level or diminish its rate of reduction*. However, this iron is stored for later use.
5. Once the nadir is reached, RBC production is stimulated, and iron stores are rapidly depleted because less iron is stored in the premature infant than in the term infant.

II. ETIOLOGY OF ANEMIA IN THE NEONATE

A. Anemia due to blood loss is characterized by a *normal bilirubin level* (unless the hemorrhage is retained). If blood loss is recent (e.g., at delivery), the hematocrit (Hct) and reticulocyte count may be normal, and the infant may be in shock. The Hct will fall later because of hemodilution. If the bleeding is chronic, the Hct will be low, the reticulocyte count up, and the baby normovolemic.

1. **Obstetric causes of blood loss**, including the following malformations of the placenta and cord:
   a. Incision of the placenta at the time of cesarean section
   b. Rupture of anomalous vessels (e.g., vasa previa, velamentous insertion of the cord, or rupture of communicating vessels in a multilobed placenta)
   c. Hematoma of the cord caused by varices or aneurysm
   d. Rupture of the cord (more common in short cords and in dysmature cords)
   e. Abruptio placentae
   f. Placenta previa (uncommon to have fetal blood loss)
2. **Occult blood loss**
   a. **Fetomaternal bleeding** may be chronic or acute. It occurs in 8% of all pregnancies, and in 1% of pregnancies, the volume may be as large as 40 mL. The diagnosis of this problem is by Kleihauer–Betke stain of maternal

smear for fetal cells. 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. Bleeding in the neonatal period may be due to the following causes:

a. Intracranial bleeding associated with the following:

i. Prematurity

ii. Traumatic assisted delivery (especially vacuum extraction)

iii. Underlying coagulation disorder

b. Massive cephalohematoma, subgaleal hemorrhage, or hemorrhagic caput succedaneum

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. Necrotizing enterocolitis (NEC)

ii. Nasogastric catheter

g. Bleeding from the umbilicus

i. Slipped ligature or cord clamp

ii. Loss from an indwelling umbilical artery or venous catheter

4. Iatrogenic causes. Excessive blood loss may result from blood sampling with inadequate replacement.

B. Hemolysis is manifested by a decreased Hct, an increased reticulocyte count, and an *increased bilirubin level*.

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 (Direct Coomb's Test [DCT] will be positive in the mother and newborn) 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 usually seen only in Mediterranean or Asian G6PD-deficient men; blacks in the United States have a 10% incidence of G6PD deficiency but rarely have significant neonatal problems unless an infection or drug is operative), 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. Diminished RBC production is manifested by a decreased Hct, decreased reticulocyte count, and normal bilirubin level.

1. Physiologic anemia or anemia of prematurity (see sections I.A and I.B)

2. Diamond–Blackfan syndrome

3. Congenital leukemia (very rare)

4. Infections, especially rubella and parvovirus (see Chapters 48 and 49)

5. Osteopetrosis, leading to inadequate erythropoiesis, presents in infancy.

III. DIAGNOSTIC APPROACH TO ANEMIA IN THE NEWBORN (TABLE 45.3)

A. The family history should include questions about anemia, jaundice, gallstones, and splenectomy.

B. The obstetric history should be evaluated for severe abdominal pain (abruptio) or intrapartum blood loss.

C. The physical examination may reveal an associated abnormality and provide clues to the origin of the anemia.

1. Acute blood loss leads to shock, with cyanosis, poor perfusion, and acidosis.

2. Chronic blood loss produces pallor, but the infant may look well and exhibit only mild symptoms of respiratory distress or irritability.

3. Chronic hemolysis is associated with pallor, jaundice, and hepatosplenomegaly.

D. Capillary blood Hct is 3.7% to 2.7% higher than venous Hct. Warming the foot reduces the difference.

E. Complete blood cell count

F. Reticulocyte count (elevated with chronic blood loss and hemolysis, depressed with infection and production defect)

Table 45.3. Classification of Anemia in the Newborn

Reticulocytes	Bilirubin	Coomb's 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 from the work of Dr Glader Bertil, director of Division of Hematology-Oncology, Children's Hospital at Stanford, California, 1991.

G. Peripheral blood smear (see Table 45.3)

H. Coomb's test and bilirubin level

I. Apt test (see Chapter 43) on gastrointestinal blood of uncertain origin

J. Kleihauer–Betke preparation of the mother's blood. A 50-mL loss of fetal blood into the maternal circulation will show up as 1% fetal cells in the maternal circulation.

K. Ultrasound of the abdomen and head

L. 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.

M. Studies for infection (toxoplasmosis, other, rubella, cytomegalovirus [CMV], and herpes simplex), if physical examination has stigmata such as hepatosplenomegaly, cataract, rash, or severe fetal growth restriction (FGR)

N. Bone marrow (rarely used except in cases of bone marrow failure from hypoplasia or tumor)

IV. THERAPY

A. Transfusion (see Chapter 42). Neonatal transfusion practices have changed dramatically in the last 30 years. According to the Premature Infants in Need of Transfusion (PINT) study published in 2006 by Kirpalani et al., a liberal practice using higher hemoglobin thresholds to transfuse extremely low-birthweight (ELBW) infants resulted in more infants receiving transfusions but conferred little benefit, whereas a restrictive transfusion strategy was not associated with adverse outcomes. A follow-up study in 2009, the PINT Outcome Study (PINTOS), addressing neurodevelopmental outcomes at 18 to 21 month's corrected gestational age, showed that all adverse outcomes (death or serious neurodevelopmental disability, cerebral palsy, cognitive delay, severe hearing, or visual deficit) were more frequent in the restrictive group, but the difference did not reach statistical significance. We must also consider the possible adverse effects of transfusion on neurodevelopment which may result from circulation of proinflammatory mediators from stored red cells or the resulting depression of erythropoietin. It still remains unclear at which physiologic threshold hemoglobin levels become low enough to threaten the growth and development of the infant brain in chronic anemia of prematurity. Table 45.4 summarizes the transfusion thresholds described in a 2011 Cochrane Review.

1. **Indications for transfusion.** The decision to transfuse must be made in consideration of the infant's condition and physiologic needs and not based on hemoglobin/Hct values alone.

   a. Infants with significant respiratory disease or congenital heart disease (e.g., large left-to-right shunt) may need their Hct maintained above 40%. Transfusion with adult RBCs provides the added benefit of lowered

Table 45.4. Suggested Hemoglobin Levels and Hematocrit Thresholds for Transfusing Infants with Anemia of Prematurity

Postnatal Age	Respiratory Support	No Respiratory Support
Week 1	11.5 (35)	10.0 (30)
Week 2	10.0 (30)	8.5 (25)
Week 3 and older	8.5 (25)	7.5 (23)

Data presented as hemoglobin (g/dL) (hematocrit [%]). Respiratory support is defined as FiO_2 >25% or the need for mechanical increase in airway pressure

Source: Adapted from Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *Cochrane Database Syst Rev* 2011;(11):CD000512.

hemoglobin oxygen affinity, which augments oxygen delivery to tissues. Blood should be fresh (3 to 7 days old) to ensure adequate 2,3-DPG levels.

b. 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).

c. Premature babies may be quite comfortable with hemoglobin levels of 6.5 to 7.0 mg/dL. The level itself is not an indication for transfusion. Growing premature infants may manifest a need for transfusion by exhibiting poor weight gain, apnea, tachypnea, or poor feeding. Sick infants (e.g., with sepsis, pneumonia, or bronchopulmonary dysplasia) may require increased oxygen-carrying capacities and therefore need transfusion. Transfusion guidelines are shown in Table 45.5. Despite efforts to adopt uniform transfusion criteria, significant variation in transfusion practices among neonatal intensive care units (NICUs) has been reported.

Table 45.5. Transfusion Guidelines for Premature Infants

1. Asymptomatic infants with Hct ≤18% (hemoglobin ≤6 g/dL) and reticulocytes <100,000 cells/μL (<2%)
2. Infants with Hct ≤20% (hemoglobin ≤7 g/dL) on supplemental oxygen who are not requiring mechanical ventilation but have one or more of the following:
a. ≥24 hours of tachycardia (heart rate >180 bpm) or tachypnea (respiratory rate >80 breaths per minute)
b. A doubling oxygen requirement from the previous 48 hours
c. Acute metabolic acidosis (pH <7.20) or lactate ≥2.5 mEq/L
d. Weight gain of <10 g/kg/day for 4 days while receiving ≥120 kcal/kg/day
e. If the infant will undergo major surgery within 72 hours
3. Infants with Hct ≤25% (hemoglobin ≤8 g/dL) requiring minimal mechanical ventilation, defined as MAP ≤8 cm H_2O by CPAP or conventional ventilation, or MAP <14 cm H_2O on high-frequency ventilation, and/or FiO_2 ≤0.40
4. Infants with Hct ≤30% (hemoglobin ≤10 g/dL) requiring moderate or significant mechanical ventilation, defined as MAP >8 cm H_2O on conventional ventilation, or MAP >14 cm H_2O on high-frequency ventilation, and/or FiO_2 >0.40
5. A transfusion should be considered if acute blood loss of ≥10% associated with symptoms of decreased oxygen delivery occurs, or if significant hemorrhage of ≥20% total blood volume occurs

CPAP, continuous positive airway pressure; Hct, hematocrit; MAP, mean airway pressure;
Source: Data from Bishara N, Ohls RK. Current controversies in the management of the anemia of prematurity. *Semin Perinatol* 2009;33(1):29–34.

An association between RBC transfusions and transfusion-associated NEC (TANEC), also referred to as transfusion-related acute gut injury (TRAGI), has been reported in observational studies. Randomized controlled trials (RCTs) do not support a clear causal relationship between RBC transfusions and NEC, and it has been suggested that significant anemia and the pretransfusion Hct may play a role. There are some data to suggest that withholding feeding during transfusion may reduce the incidence of NEC.

Transfusion-related lung injury (TRALI) has been described in some preterm babies. The neonates present with a sudden and severe respiratory distress within 6 hours of a transfusion in a previously well neonate.

The cause may be related to endogenous neutrophil priming due to cytokines and chemokines in transfused blood. The neutrophils induce pulmonary endothelial damage leading to capillary leakage and pulmonary edema. Washing the blood components has been proposed to reduce TRALI.

Top-up transfusions in excess of 20 mL/kg are not recommended because of risk of transfusion-associated circulatory overload (TACO).

2. **Blood products and methods of transfusion** (see Chapter 42)
   a. **Packed RBCs.** We generally transfuse 15 to 20 mL/kg. The blood has to be used within 35 days of donation, while for exchange transfusion it needs to be used within less than 5 days from donation.
   b. **Whole blood** is rarely used these days; even for exchange transfusion, packed RBCs reconstituted with plasma are preferred. Whole blood may be required for ECMO.
   c. **Partial exchange** with high Hct-packed RBCs may be required for severely anemic infants, when routine transfusion of the volume of packed RBCs necessary to correct the anemia would result in circulatory overload (see Chapter 26).
   d. Irradiated RBCs are recommended in premature infants weighing <1,200 g. Premature infants may be unable to reject foreign lymphocytes in transfused blood. We use irradiated blood for all neonatal transfusions. Leukocyte depletion with third-generation transfusion filters has substantially reduced the risk of exposure to foreign lymphocytes and CMV. However, blood from CMV-negative donors for neonatal transfusion is preferable. The other option is to include CMV DNA–negative blood products or provision of blood products from long-term seropositive donors.
   e. Directed-donor transfusion from related donors is requested by many families. This is not an acceptable practice in modern blood banking. 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. Decreasing donor exposure. 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.

B. Prophylaxis

1. **Premature infants** (preventing or ameliorating the anemia of prematurity). The following is a description of our usual nutritional management of

premature infants from the point of view of providing RBC substrates and preventing additional destruction:

a. Delayed cord clamping

b. Iron supplementation in the preterm infant introduced between 4 and 6 weeks improves iron stores, and lowers the risk of iron deficiency anemia after the first 6 months of life. Early (up to 3 weeks of age) versus late (4 weeks to 60 days) commencement of iron supplementation did not result in differences in cognitive outcome, but a marginally increased rate of behavioral concerns at 5 years of age was noted in the late iron group. It remains unclear whether iron supplementation in preterm and low-birth-weight infants has long-term benefits in terms of neurodevelopmental outcome and growth. There is no discernible hematologic benefit in exceeding "standard" doses of iron; in fact, excess exogenous iron can contribute to oxidative injury in preterm babies.

c. Erythropoiesis-stimulating agents. Recombinant human erythropoietin (**rh-EPO**) or Darbepoietin has been evaluated as a promising measure in ameliorating anemia of prematurity. Studies show that rh-EPO stimulates red cell production and may decrease the frequency and volume of RBC transfusions if administered to premature infants early (before the neonate reaches 8 days of age). However, overall there is limited benefit in reducing the number or volume of transfusions or donor exposure once strict transfusion criteria are instituted. A trend for increased risk for retinopathy of prematurity (ROP) with both early (first week of life) and late (beyond first week of life) erythropoietin (EPO) use was reported in some studies, but recent meta-analyses found no statistically significant differences in stage 3 or greater ROP between EPO and placebo groups. However, early use of EPO may decrease the risk of neurologic damage (intraventricular hemorrhage and periventricular leukomalacia) and NEC but further studies are needed. Currently, we do not routinely use EPO prophylaxis for anemia, although there may be utility in exploring this option for families who withhold consent to transfusion of blood products. Complementary strategies to reduce phlebotomy losses and the use of conservative standardized transfusion criteria have contributed to significant reductions in transfusions.

Beyond erythropoiesis, there seems to be a beneficial effect of erythropoiesis-stimulating agents in neurodevelopmental outcomes of preterm infants. An RCT comparing erythropoiesis-stimulating agents with placebo showed improvement in cognitive outcomes at 18 to 22 month's corrected age in the treated preterm infants. Ongoing randomized controlled studies are evaluating this approach further. The use of darbepoetin requires further study.

Suggested Readings

Bishara N, Ohls RK. Current controversies in the management of the anemia of prematurity. *Semin Perinatol* 2009;33(1):29–34.

Kirpalani H, Whyte RK, Andersen C, et al. The premature infants in need of transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr* 2006;149(3):301–307.

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46 Polycythemia

Deirdre O'Reilly

KEY POINTS

- Polycythemia and hyperviscosity of the blood in newborns may be associated with symptoms such as hypoglycemia, poor feeding, and irritability; yet, most newborns with polycythemia are asymptomatic.
- Partial exchange transfusion may be considered only in severely symptomatic neonates with peripheral venous hematocrit >65% and perhaps in asymptomatic neonates with hematocrit >75%.
- Partial exchange transfusion will likely treat symptoms, but has not been shown to affect the neurodevelopmental outcome.
- Intravenous fluid supplementation does not decrease the need for partial exchange transfusion (for polycythemia). However, it may be considered in neonates with evidence of dehydration.

I. INTRODUCTION. As the central venous hematocrit rises, there is increased viscosity and decreased blood flow. When the hematocrit increases to >60%, there may be decreased oxygen delivery (Fig. 46.1). Newborns have larger, irregularly shaped red blood cells (RBCs) with different membrane characteristics than the RBCs of adults. As viscosity increases, there may be impairment of tissue oxygenation and decreased glucose in plasma, leading to an increased risk of microthrombus formation. If these events

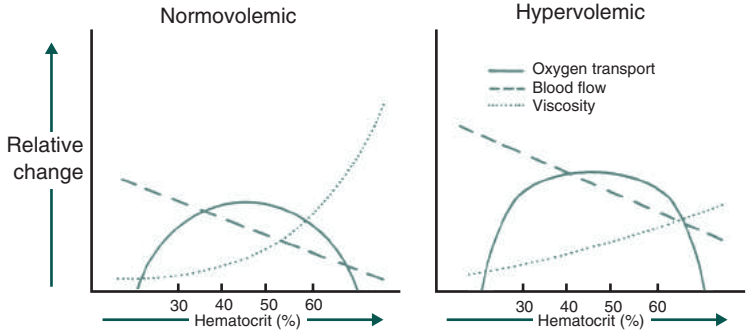

Figure 46.1. Effect of hematocrit on viscosity, blood flow, and oxygen transport. (Adapted from Glader B, Naiman JL. Erythrocyte disorders in infancy. In: Taeusch HW, Ballard RA, Avery ME, eds. *Diseases of the Newborn*. Philadelphia, PA: WB Saunders; 1991.)

occur in the cerebral cortex, kidneys, or adrenal glands, significant damage may result. Hypoxia and acidosis increase viscosity and deformity further. Poor perfusion associated with polycythemia may increase the possibility of peripheral vascular thrombosis.

II. DEFINITIONS

A. Polycythemia is defined as venous hematocrit of at least 65%. Hematocrit initially rises after birth from placental transfer of RBCs and then decreases to baseline by approximately 24 hours. The mean venous hematocrit of term infants is 53% in cord blood, 60% at 2 hours of age, 57% at 6 hours of age, and 52% at 12 to 18 hours of age.

B. Hyperviscosity is defined as viscosity >2 standard deviations greater than the mean. The hyperviscosity syndrome is usually seen only in infants with venous hematocrit above 60%. The relationship between hematocrit and viscosity is nearly linear below a hematocrit of 60%, but viscosity increases exponentially at a hematocrit of 70% or greater (Fig. 46.1). Factors affecting blood viscosity include plasma proteins such as fibrinogen, local blood flow, and pH. Blood viscosity is dependent on factors such as the pressure gradient along the vessel, radius, length, and flow.

III. INCIDENCE. The incidence of polycythemia is 1% to 5% in term newborns.

IV. CAUSES OF POLYCYTHEMIA. There are three possible settings for polycythemia: (i) hypervolemia—placental transfusion; (ii) normovolemia placental insufficiency (fetal growth restriction [FGR]); and (iii) hypovolemia—dehydration.

They may differ in the risk to the neonate's health and approach to management, but there is no systematic research.

A. Placental red cell transfusion

1. **Delayed cord clamping** (DCC) is recognized to have significant health benefits and is now standard of care. Practices include clamping of the cord only after pulsations stop or clamping after a minimum time (60 seconds or more). DCC is associated with higher hematocrit and risk of polycythemia. However, no difference was observed in symptomatic polycythemia or need for partial exchange transfusion (PET).

   Studies have shown that a delay of 60 to 180 seconds would result in an additional transfer of blood of 20 to 30 mL/kg equivalent of the infant's body weight.
2. **Umbilical cord stripping/milking** achieves transfer of placental blood in a shorter time; this also increases the hematocrit.
3. **Holding the baby at a level below the mother** before the cord is cut increases transfer of placental blood—the distance below the vaginal introitus promotes gravity-assisted transfusion.
4. **Twin-to-twin transfusion** is an uncommon phenomenon in monochorionic twins; this is associated with polycythemia in one twin and anemia in the other (see Chapter 11).

B. Placental insufficiency (increased fetal erythropoiesis secondary to chronic intrauterine hypoxia)

1. FGR infants
2. Maternal hypertension syndromes (preeclampsia, renal disease, etc.)

3. Post-term infants
4. Infants born to mothers with chronic hypoxia (heart disease, pulmonary disease)
5. Pregnancy at high altitude
6. Maternal smoking

C. Other conditions

1. Infants of diabetic mothers (increased erythropoiesis)
2. Some large-for-gestational-age (LGA) babies
3. Infants with congenital adrenal hyperplasia, Beckwith–Wiedemann syndrome, neonatal thyrotoxicosis, congenital hypothyroidism, trisomy 21, trisomy 13, and trisomy 18
4. Drugs (maternal use of propranolol)
5. Dehydration of an infant causing hemoconcentration
6. Sepsis increases hyperviscosity in the setting of polycythemia (increase in fibrinogen, reduced RBC deformability).

V. CLINICAL FINDINGS. Most infants with polycythemia are asymptomatic. Clinical symptoms, syndromes, and laboratory abnormalities that have been described in association with polycythemia include the following:

A. Central nervous system (CNS). Poor feeding, lethargy, hypotonia, apnea, tremors, jitteriness, seizures, and cerebral venous thrombosis

B. Cardiorespiratory. Cyanosis, tachypnea, heart murmur, congestive heart failure, cardiomegaly, elevated pulmonary vascular resistance, and prominent vascular markings on chest x-ray

C. Renal. Decreased glomerular filtration, decreased sodium excretion, renal vein thrombosis, hematuria, and proteinuria

D. Other. Other thrombosis, thrombocytopenia, poor feeding, increased jaundice, persistent hypoglycemia, hypocalcemia, testicular infarcts, necrotizing enterocolitis (NEC), priapism, and disseminated intravascular coagulation

All of these symptoms may be associated with polycythemia and hyperviscosity but may not be caused by it. They are common symptoms in many neonatal disorders.

VI. SCREENING. Hematocrit level should be determined in any baby who appears plethoric, who has risk factors for, or **who has symptoms suggestive of polycythemia**.

We do not routinely screen asymptomatic newborns for this syndrome because there are few data showing that treatment of asymptomatic patients with partial exchange transfusion (PET) is beneficial in the long term.

VII. DIAGNOSIS. Peripheral venous hematocrit sample is preferred to measure polycythemia. Arterial blood sample is not acceptable for hematocrit estimation as it would underestimate the hematocrit; capillary sample would overestimate the hematocrit by 5% to 15%. However, capillary hematocrit can be used for initial screening, which should always be confirmed with a venous hematocrit if greater than 65%. Warming

the heel (arterializing the capillary) before drawing blood for a capillary hematocrit determination will give a better correlation with the venous or central hematocrit.

VIII. MANAGEMENT

A. Observe closely. **Asymptomatic infants** with a peripheral venous hematocrit between 65% and 75% may be merely observed and one may repeat the hematocrit in 4 to 6 hours.

B. Fluid management. In neonates with hematocrit >65% and **mild symptoms and with evidence of dehydration**, increasing the daily maintenance fluids by 10 to 20 mL/kg and re-evaluating after 4 to 6 hours might be a reasonable alternative option. A recent clinical trial that compared supplemental intravenous fluids with no supplementation in **asymptomatic** late preterm and term neonates with venous hematocrit between 65 and 75 did not find any evidence of clinical benefit with fluid supplementation.

C. Partial exchange transfusion. There seems to be no short- or long-term benefits of PET in polycythemic newborn infants who are **asymptomatic or who have mild symptoms**. PET may increase the risk of NEC. The developmental outcomes are reported to be variable.

Partial exchange must be performed with crystalloid solutions; they are equally effective. The use of colloids is associated with a risk of infections and anaphylaxis.

Partial exchange transfusion should be performed with a crystalloid solution such as 0.9% saline. Available evidence shows that both crystalloids and colloids are equally effective and use of colloids is associated with higher risk of infection and anaphylaxis.

The following formula can be used to calculate the volume of normal saline for partial exchange. The blood volume varies inversely with the birth weight (Fig. 46.2). Usually, we take the blood from the peripheral artery and replace it with normal saline through a peripheral vein. Wherever possible, the umbilical vein should be avoided for pulling blood for PET due to the increased incidence of NEC when this vein is used. There are many methods of exchange (see Chapter 26).

$$\text{Volume of exchange [mL]} = \frac{(\text{blood volume/kg} \times \text{weight in [kg]}) \times ([\text{observed hematocrit}] - [\text{desired hematocrit}])}{\text{observed hematocrit}}$$

The total volume exchanged is usually 15 to 20 mL/kg of body weight.

One small clinical trial from India (n = 22) which compared a novel continuous arteriovenous exchange (CAVE) versus standard pull–push method in polycythemic preterm neonates reported significantly lesser Neonatal Pain, Agitation and Sedation scores in the CAVE group with comparable complications rate as well as reduction in hematocrit.

IX. OUTCOMES OF TREATING POLYCYTHEMIA

A. Short term benefits of PET. PET will lower hematocrit, decrease viscosity, and reverse many of the physiologic abnormalities associated with polycythemia/

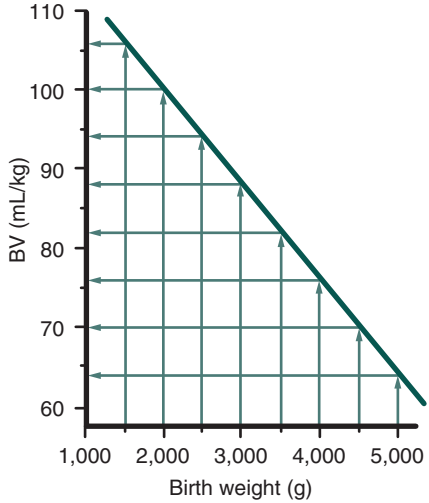

Figure 46.2. Nomogram designed for clinical use, correlating blood volume per kilogram with birth weight in polycythemic neonates. BV, blood volume. (From Rawlings JS, Pettett G, Wiswell T, et al. Estimated blood volumes in polycythemic neonates as a function of birth weight. *J Pediatr* 1982;101:594–599.)

hyperviscosity but has not been shown to significantly change the long-term outcome of these infants. Infants with polycythemia and hyperviscosity who have decreased cerebral blood flow velocity have been shown to have normal cerebral blood flow following PET. They also have improvement in systemic blood flow and oxygen transport.

B. The symptoms associated with polycythemia (hypoglycemia, hyperbilirubinemia, lethargy, thrombocytopenia) reversed rapidly (within 24 hours) in a cohort study. PET was done in asymptomatic neonates with hematocrit >70 or symptomatic neonates with hematocrit >70.

C. There is no evidence for improvement in long-term neurologic outcome in infants with asymptomatic polycythemia/hyperviscosity .

1. One trial with small numbers of randomized patients showed decreased IQ scores in school-age children who had neonatal hyperviscosity syndrome, in both treated and untreated newborns.
2. Another retrospective study, with small numbers of patients, showed no difference in the neurologic outcome of patients with asymptomatic neonatal polycythemia, including both treated and untreated newborns.
3. A small prospective study showed no difference at follow-up between control infants and those with hyperviscosity, between those with symptomatic and those with asymptomatic hyperviscosity, and between asymptomatic infants treated with PET and those who were observed. Analysis revealed that other perinatal risk factors and race, rather than polycythemia or PET, significantly influenced the long-term outcome.
4. An increased incidence of NEC following PETs by the umbilical vein has been reported. NEC was not seen in one retrospective analysis of 185 term

polycythemia babies given PETs with removal of blood from the umbilical vein and reinfusion of a commercial plasma substitute through peripheral veins.

A larger prospective, randomized clinical trial comparing PET with symptomatic care (increased fluid intake, etc.) equally balanced for risk factors and the etiologies of the polycythemia with a planned subgroup analysis of symptomatic neonates will be necessary to give guidelines for treatment of the asymptomatic newborn with polycythemia/hyperviscosity.

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47 Thrombocytopenia

Emöke Deschmann, Matthew Saxonhouse, and Martha Sola-Visner

KEY POINTS

- Common cause of mild-to-moderate, early onset thrombocytopenia in well-appearing neonates is placental insufficiency. Prognosis is good.
- Sepsis, NEC should be excluded in sick neonates with low platelet count.
- Severe thrombocytopenia in a well-looking baby on day 1 could be due to NAIT; random-donor platelets may be transfused to prevent IVH.
- Maternal ITP is not associated with increased risk of IVH.
- Platelets as low as 25×10^3 may be safe and transfusion may not be necessary, unless there is clinical coagulopathy.
- Gestation <28 weeks, age <10 days postnatal and NEC are associated with bleeding events, these risk factors predict bleeding better than platelet counts.
- Platelets are stored at room temperature, risk of bacterial infection is higher than other viral infections.

I. INTRODUCTION. Neonatal thrombocytopenia is traditionally defined as a platelet count of $<150 \times 10^3/\mu L$ and is classified as mild (100 to $149 \times 10^3/\mu L$), moderate (50 to $99 \times 10^3/\mu L$), or severe ($<50 \times 10^3/\mu L$). Platelet counts in the 100 to $149 \times 10^3/\mu L$ range are more common among neonates than among adults. The most recent and largest study on neonatal platelet counts demonstrated that platelet counts at birth increase with advancing gestational age. Importantly, while the mean platelet count was $\geq 200 \times 10^3/\mu L$ even in the most preterm infants, the fifth 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 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, while 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 to narrow 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 at 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 placental insufficiency, as occurs in infants born to mothers with pregnancy-induced hypertension/preeclampsia or diabetes, or in those with fetal growth restriction (FGR). There may be transient neutropenia and increased number of nucleated

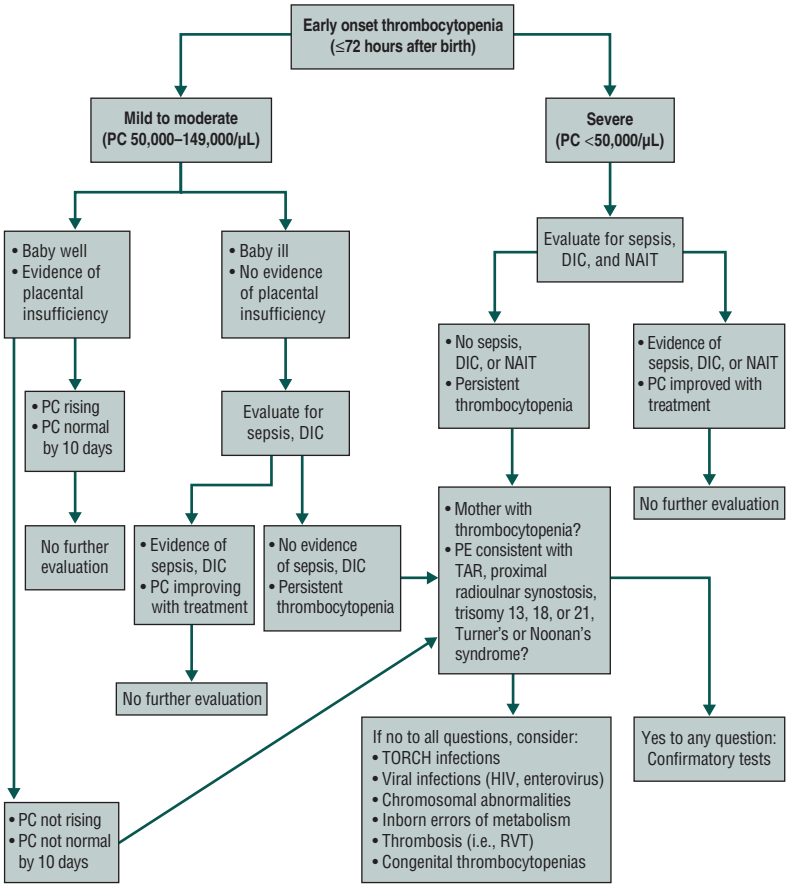

Figure 47.1. Guidelines for the evaluation of neonates with early onset thrombocytopenia (≤72 hours of life). DIC, disseminated intravascular coagulation; NAIT, neonatal alloimmune thrombocytopenia; PC, platelet count; PE, physical examination; RVT, renal vein thrombosis; TAR, thrombocytopenia-absent radius; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex;

cells in this setting. This thrombocytopenia is always mild to moderate, presents immediately or shortly after birth, 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 for >10 days, further investigation is necessary.

***Severe* early onset thrombocytopenia in a well-appearing infant** should trigger suspicion for an immune-mediated thrombocytopenia, either autoimmune (i.e., the mother is also thrombocytopenic) or alloimmune (i.e., 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 disseminated intravascular coagulation (DIC). DIC is most frequently associated with sepsis but can also be secondary to birth asphyxia.

Uncommon causes. 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 thrombocytopenia associated with Fanconi almost always presents later (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 earlyonset 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 earlyonset thrombocytopenia include trisomy 21, trisomy 18, trisomy 13, Turner's syndrome, Noonan's syndrome, and Jacobsen's syndrome. Cases of Noonan's syndrome presenting with mild dysmorphic features and very severe neonatal thrombocytopenia (mimicking congenital amegakaryocytic thrombocytopenia) have been recently 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).

The size of the platelets may give a clue to the etiology of thrombocytopenia, e.g., small platelets (mean platelet volume [MPV] <7) are seen in Wiskott–Aldrich syndrome. MYH-9srelated disorders and Bernard–Soulier syndrome are generally associated with large-sized platelets.

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 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 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, and 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).

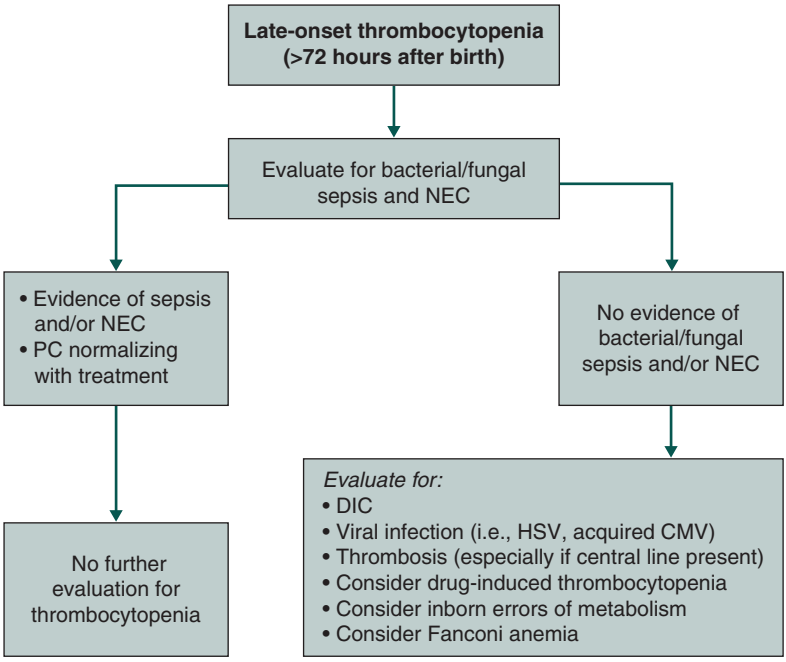

Figure 47.2. Guidelines for the evaluation of neonates with late-onset thrombocytopenia (>72 hours of life). CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; HSV, herpes simplex virus; NEC, necrotizing enterocolitis; PC, platelet count.

Novel tools to evaluate platelet production that aid in the evaluation of thrombocytopenia have been recently developed and are likely to become 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 thrombocytopenia associated with decreased platelet production from that with increased platelet destruction, in a manner similar to the use of reticulocyte counts to evaluate anemia. Raised IPF (>7%) indicates increased destruction. Recent studies 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. MPV is also an indirect indicator of IPF. Another novel tool is reticulated platelets (RP) which are newly produced platelets with increased ribonucleic acid content. Low RP% (<2%) indicates reduced platelet production and high RP% (≥10%) indicates accelerated destruction. RP is done by flow cytometry.

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 (IgG) 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 an antigen on the mother's own platelets (autoantibody) as well as on the baby's platelets. The maternal autoantibody crosses 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 examination. In a study of more than 200 neonates with thrombocytopenia, using a *platelet count <50 × 10^3/μL on 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.

1. **Laboratory investigation.** When NAIT is suspected, blood should be collected from the mother and the father and submitted for confirmatory testing (if accessible). The basis of testing is to document incompatibility between the mother and the neonate's platelet genotype or showing antibodies to paternal antigen in the neonate's serum. The initial antigen screening should include HPA 1, 3, and 5. This evaluation should identify approximately 90% of cases of NAIT in white population. 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. It is still uncertain whether there is any correlation between the affinity of the antibodies and the severity of the disease. 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.

2. **Management.** The management of NAIT differs depending on the specific clinical scenario:

   a. ***Management of a neonate with suspected NAIT, not known antenatally***. 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 $<30 \times 10^3$/mL, although this is arbitrary. In the case of a preterm infant, or a clinically unstable infant (i.e., respiratory distress, infection), a platelet transfusion is usually given when the platelet count falls below 50×10^3/mL during the first week of life (Table 47.1). 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 30 and 50×10^3/mL to try to prevent a further drop.

      ii. If the patient has evidence of an ICH, the goal is to maintain a platelet count $>100 \times 10^3$/mL, 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

Table 47.1. Guidelines for Platelet Transfusion

Platelet Count ($\times 10^3/\mu L$)	Guidelines
<30	*Transfuse all*
30–49	*Transfuse if:* ■ BW <1,500 g and ≤7 days old ■ Clinically unstable ■ Recent diagnosis of NEC ■ Concurrent coagulopathy ■ Previous major hemorrhage (i.e., grade 3 or 4 IVH) ■ Prior to surgical procedure ■ Postoperative period (72 hours)
50–100	*Transfuse if:* ■ Active bleeding ■ NAIT with intracranial bleed ■ Before or after neurosurgical procedures

BW, birth weight; IVH, intraventricular hemorrhage; NAIT, neonatal alloimmune thrombocytopenia; NEC, necrotizing enterocolitis.

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 BID for 3 to 5 days) has also been used in individual case reports and small series but can be considered in circumstances when the infant does not respond to random platelets and IVIG, and antigen-matched platelets are not readily available. We do not routinely use or recommend the use of steroids.

b. Management of a 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 a pregnant women with previous neonate with NAIT. Mothers who delivered an infant with NAIT should be followed in high-risk obstetric clinics during all future pregnancies as up to 20% of children born with NAIT can develop ICH, with 50% of them occurring *in utero*. 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), weekly**

starting at 12 or at 20 to 26 weeks' 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 mode of delivery, an elective cesarean section is recommended in most countries, regardless of the 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 the 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, the platelet count should be repeated in 2 to 3 days as it usually reaches the nadir between 2 and 5 days after birth.

If the platelet count is $<30 \times 10^3/\mu L$, 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 $<30 \times 10^3/\mu L$ and provide IVIG alone for platelet counts between 30 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 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. Regarding the mode of delivery, there is no evidence that a cesarean section is safer for the fetus with thrombocytopenia than an 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. There is great variability in neonatal transfusion practices in the United States and worldwide. To a large extent, this is attributable to the paucity of scientific evidence in the field. Only one randomized trial has compared different platelet transfusion thresholds in neonates, and it was limited to very low-birth-weight (VLBW) infants in the first week of life, excluding patients with severe thrombocytopenia (platelet count $<50 \times 10^3/\mu L$). This study found no differences in the incidence or severity of intraventricular hemorrhages (IVHs) between a group of neonates transfused for any platelet count $<150 \times 10^3/\mu L$ and a group transfused only for counts below $60 \times 10^3/\mu L$. Based on these findings, the investigators concluded that transfusing VLBW infants with platelet counts 60 to $150 \times 10^3/\mu L$ does not reduce the risk of IVH. In a prospective multicenter observational study, Platelets for Neonatal Transfusion—Study 1 (PlaNeT-1) platelet transfusions were administered at a median platelet count of $27 \times 10^3/\mu L$. In a secondary analysis, the temporal association between platelet transfusions and minor bleeding was assessed. This analysis showed that neonates had 21% fewer bleeding events during the 12 hours following a platelet transfusion, compared with the 12 hours prior to transfusion. However, these findings should be interpreted with caution, partly because of the study design (observational study being prone to confounders and lacking a control group), and because these results were part of a secondary analysis. A more recent analysis by von Lindern et al. compared bleeding outcomes in NICUs that used liberal transfusion thresholds with those in NICUs that used restrictive transfusion thresholds. The study found no significant differences in bleeding outcomes between units.

The relationship between the degree of thrombocytopenia and the bleeding risk has been assessed in a number of neonatal studies. The PlaNeT-1 found that 9% of thrombocytopenic neonates experienced clinically significant bleeding (most commonly intracranial). Eighty-seven percent of these hemorrhages occurred during the first 2 weeks of life, and 87% were in neonates <28 weeks' gestation. A secondary analysis found that a lower nadir platelet count was associated with only a slightly increased number of bleeding events. Importantly, the strongest predictors of hemorrhage were ***gestational age <28 weeks, postnatal age <10 days, and a diagnosis of NEC***, suggesting that factors other than the platelet count are the most important determinants of bleeding risk.

Based on this limited evidence, we currently propose administering platelet transfusions to neonates according to the criteria shown in Table 47.1.

There is more consensus regarding 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 m. 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. Two additional important considerations in neonatology are the prevention

of transfusion-transmitted CMV 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. 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 volume exchange transfusions), or receiving blood products from a first-degree relative. These are all absolute indications for irradiating blood products.*

When making platelet transfusion decisions, it is important for neonatologists to be aware of the risks associated with these transfusions. In the case of platelet suspensions, the risk of bacterial contamination is higher than the combined risk of all viral infections for which platelets are routinely tested. In addition, platelet transfusions can induce transfusion-associated lung injury (TRALI), a process characterized by the onset of hypoxemia and bilateral pulmonary infiltrates within 6 hours of a transfusion. Given that neonates have frequent episodes of respiratory decompensation due to different causes, TRALI is likely to be underrecognized in the NICU. Several recent publications have also shown a strong association between the number of platelet transfusions and the mortality rate among NICU patients. It is unclear from these studies whether this association simply reflects sicker patients receiving more platelets or whether platelet transfusions adversely affect outcomes. The data from well-designed randomized controlled study, the Platelets for Neonatal Transfusion—Study 2 (PlaNeT-2) trial, compared $25 \times 10^3/\mu L$ with $50 \times 10^3/\mu L$ as platelet transfusion thresholds in preterm neonates. The trial enrolled 660 neonates. The babies who were transfused at the threshold of $50 \times 10^3/\mu L$ received more transfusions (90% vs. 53% received at least one platelet transfusion) as would be expected and had higher mortality and ICH (26% vs. 19%) in the first 28 days. Bronchopulmonary dysplasia (BPD) was also more common at the threshold of $50 \times 10^3/\mu L$. The study clearly supports that platelet transfusion should be restricted to babies with platelet $<25 \times 10^3/\mu L$, unless actively bleeding.

Suggested Readings

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48 Viral Infections

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KEY POINTS

- COVID 19 pandemic started in December 2019 and is still raging at the time of publication. Pregnant women are mostly asymptomatic and not at greater risk of pneumonia. Vertical transmission is near to negligible. Transmission from care takers (including mothers) can be prevented by social distancing and hand hygiene.
- Breast feeding is safe and protective to baby (in other aspects) and should be continued. Cord clamping can be delayed.
- Mother to child transmission of HIV can be reduced to nearly nil by appropriate management of the infection in pregnancy, care at birth; breast feeding may continue. Infants should receive antivirals and prophylaxis against secondary infections.
- CMV infection in pregnancy can be associated with serious adverse outcomes in neonates. Treatment of babies is indicated only if nervous system is involved or in case of serious multiorgan involvement. Postnatal CMV infection through breast milk is cause of pneumonia/sepsis like illness in very low birth weight babies. Breast milk pasteurization (as a routine) is not recommended, as loss of valuable benefits of mother's own milk happens.
- Herpes infection should be suspected in all newborns presenting with sepsis like illness or encephalopathy after 1st week of life. Treatment with Acyclovir should be started while investigation reports (PCR) are awaited.
- Rubella infection in early pregnancy can be devastating to fetus; safe, effective, and very inexpensive vaccination is available. WHO has recommended that all countries include at least one dose between 9 to 12 months in national schedules, but it is important to immunize at least 80% of population, to prevent shift of susceptible population.
- Hepatitis B infection transmitted from mother to baby (intrapartum) is the commonest cause of chronic liver disease and malignancy in children. It can be completely eliminated by active and passive immunization at birth of babies to infected mothers.
- Zika virus is associated with microcephaly, arthrogryposis, and had almost 20 times increase in neurodisability in infected fetuses during the epidemic in Brazil.
- Parvo virus is associated with hydrops due to severe fetal anemia, timely treatment of anemia by intrauterine transfusion or delivery, and management of anemia is associated with good outcomes.
- Traditional practice of TORCH titers must be replaced by testing paired sera (2 weeks apart). Single values of IgG have no value, wrong interpretation is associated with disastrous decisions in pregnancy and infancy and must be completely stopped.

I. INTRODUCTION.

Vertically transmitted (mother to child) viral infections can generally be divided into three distinct categories by transmission modes. The first is **congenital infections**, which can be 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. 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 fetus and 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 as an anomaly, whereas perinatal infections (during delivery) 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 the 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).

Significant improvements have happened in the screening and treatment of perinatal CMV infection. Awareness of CMV infection as a health hazard in pregnancy in a study was found to be low among prospective parents. CMV is a highly species-specific virus that results in lifelong infection. It derives its name from the histopathologic appearance of infected cells, which have abundant cytoplasm and both intranuclear and cytoplasmic inclusions. The fact that CMV infection in pregnancy is common and may be associated with potentially damaging brain infection has made vaccine development a top priority.

A. Epidemiology.

CMV is present in the saliva, urine, genital secretions, breast milk, and blood/blood products of infected persons and can be transmitted by exposure to any of these. 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 women in the United States are infected before pregnancy, which is in contrast to over 90% seropositivity in underdeveloped nations (these mothers are at a lower risk of infecting their fetus). Primary CMV infection occurs in approximately 1% of pregnant women, likely

Table 48.1. Diagnostic Techniques for Diagnosis of Perinatal Infections

Pathogen	Test of Choice	Sensitivity	Expense	Turnaround Time
HSV	PCR of skin lesion, blood, or CSF	High	Moderate	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, oro-pharynx, stool	Moderate	High	Days
Rubella	Culture urine	Moderate	High	Many days
RSV	PCR of nasopharyn-geal secretions	Moderate	Moderate	Hours
COVID-19	RT-PCR of nasopha-ryngeal or oropha-ryngeal, rectum	Moderate	High	Hours

CMV, cytomegalovirus; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; IgM, immunoglobulin M; PCR, polymerase chain reaction; RIBA, recombinant immunoblot assay; RSV, respiratory syncytial virus; RT-PCR, reverse transcriptase PCR; VZV, varicella-zoster virus.
*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.

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 infant, with a fetal transmission rate of 30% to 40%. This high fetal transmission rate in primary infection contrasts with the low 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. Approximately half of congenital infections are due to primary maternal CMV infection during pregnancy. Although transmission in the setting of nonprimary maternal infection can result in hearing loss, congenital CMV infection in the setting of no preexisting immunity disproportionately contributes to the serious symptomatic infections. The risk of transmission to the fetus as a function of gestational age is uncertain, but infection during early gestation likely carries a higher risk of severe fetal disease.

Congenital CMV occurs in approximately 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 *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% 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, over 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, CMV is being recognized as a significant postnatal infection of very low-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 nearly eliminated by 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. The impact of this infection on long-term outcome and neurodevelopment is an area of ongoing investigation.

B. Clinical disease in congenital infection may present at birth or may manifest with symptoms later in infancy. Only very low-birth-weight preterm infants (<1,500 g) 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 (79%), hepatosplenomegaly (HSM) (74%), jaundice (63%), pneumonitis, 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 persist beyond the period of physiologic

jaundice. Approximately one-third of these infants are preterm, and one-third have fetal growth restriction (FGR) and microcephaly.

A second early presentation includes infants who are symptomatic, most commonly with SNHL but without life-threatening complications. These babies may also have FGR or disproportionate microcephaly (48%) 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 ventricular dilatation, cortical atrophy, and neuronal migration disorders such as lissencephaly, pachygyria, and demyelination as well as chorioretinitis in approximately 10% to 15% of infants. Babies with CNS manifestations almost always have developmental abnormalities and neurologic dysfunction. These range from mild learning and language disability or mild hearing loss to IQ scores below 50, motor abnormalities, deafness, and visual problems. Because SNHL is the most common sequela of CMV infection (60% in symptomatic and 5% in asymptomatic infants at birth), any infant failing the newborn hearing screen also should be screened for CMV infection. Conversely, infants with documented congenital CMV infection should be assessed for hearing loss as neonates and throughout the first 2 years of life.

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 disorders, and acquired microcephaly.

3. **Postnatally acquired CMV infection** may present as severe end-organ disease or sepsis-like syndrome in 5% of extreme preterm babies; most of the infection is transmitted via breast milk. Infection may be nosocomial; the source can be blood, urine or saliva. The time from infection to disease presentation varies from 4 to 12 weeks. Almost all term infants who are infected perinatally and postnatally remain asymptomatic, with the exception of severely immunocompromised infants. In extreme preterms, the infection may manifest late, at 1 to 2 months of life, as a sepsis like syndrome not responding to antibiotics. The infection may present as hepatitis and cholestasis, pneumonitis, neutropenia, and thrombocytopenia, and rarely as colitis. CNS involvement and long-term developmental and neurologic abnormalities are rarely seen. 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. Long-term sequelae 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 the saliva of infected infants.

5. **Transfusion-acquired CMV infection.** Significant morbidity and mortality could occur in newborn infants receiving CMV-infected blood or blood products. Cellular and humoral maternal immune systems are helpful in preventing infection or in ameliorating clinical disease; most severely affected are preterm, low-birth-weight infants born to CMV-seronegative women. Mortality is estimated to be 20% in very low-birth-weight infants. Symptoms typically develop 4 to 12 weeks after transfusion; last for 2 to 3 weeks; and consist of respiratory distress, pallor, and HSM. Hematologic abnormalities are 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). Most neonatal units in India and Asia do not have access to CMV-negative (leukoreduced/irradiated) blood.

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 the 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 the blood of a newborn; however, not all congenitally infected infants are viremic at birth. Thus, ***detection of CMV shedding in the 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 or more does rule out infection. 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 infants due to ease of collection. But urine PCR is the gold standard. 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 utilize 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, and 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 used only to follow the efficacy of the therapy and may be replaced by quantitative blood PCR tests.

4. **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 of the brain, 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 (LFT), 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. Treatment is considered in all infants with CNS or systemic disease. In case of asymptomatic infants or with only SNHL and CMV positivity, most centers offer the treatment but the results of the ValEAR multicentric trial would decide the best strategy for such infants in the future. Asymptomatic CMV-positive infants with no SNHL should be observed without treatment. The earliest studies of infants with symptomatic CMV disease showed a strong trend toward efficacy in the 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 when compared

with 6 weeks of treatment. The toxicity of valganciclovir treatment is primarily mild neutropenia. The occurrence of neutropenia was equally common between 6-week and 6-month course of valganciclovir. Families should be informed 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. 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. Recent literature suggests treating postnatal CMV in extreme preterms in blocks of 2 weeks and reassessing viral load. It is rarely required to treat for more than 4 to 8 weeks.

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, yet a subsequent randomized controlled trial did not demonstrate benefit in preventing congenital infection.
2. **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.
3. **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. 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.

4. **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 the active virus. 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.
5. **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.
6. **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 by leukoreduction. It is particularly important to use blood from one of these sources in preterm, low-birth-weight infants (see Chapter 42).

III. HERPES SIMPLEX VIRUS (HSV; PERINATAL). HSV, a lifelong infection, has two virologically distinct types: types 1 and 2. HSV-2 was previously the primary cause of genital lesions, now 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 type 1 by the fifth decade of life, the cause of recurrent orolabial disease and an increasing cause of genital disease. During 2015 to 2016, according to the National Health and Nutrition Examination Survey, the overall seroprevalence of HSV-1 and -2 in the United States in 19- to 49-year-olds was 47.8% and 11.9%, respectively. Globally, the projected incidence is 1 in 10,000 live births with more than 5,000 cases happening in Africa because of high prevalence of HSV-2 in that area and high fertility rate. 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 -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 more than 1% of all women with a history of recurrent HSV infection asymptomatically shed HSV at delivery. Yet, it is critical to recognize that most mothers of infants with neonatal HSV do not have a history of HSV symptoms. Approximately 30% to 50% of infants will acquire HSV infection if maternal primary infection occurs near delivery, whereas <1% 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 -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 3,000 to 1 in 20,000 (or 200 to 1,333 infants per year) 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 determinates of peripartum transmission. Transmission risks are greatest with primary maternal infection during pregnancy, with nonprimary acute infection with HSV-1 or -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 a 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 exposed to 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 multiorgan disease and congenital malformations. Chorioretinitis, microcephaly, and hydranencephaly may be found in these small numbers of congenitally infected patients.
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 clinical manifestations usually occur in the first 2 weeks of life but can appear anytime till 6 weeks after birth. The morbidity and mortality of neonatal HSV best correlates with three categories of disease. These are (i) infections localized to the SEM, (ii) encephalitis 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 in the form of clustering of vesicles on the skin, eye pain, keratoconjunctivitis, and oropharyngeal ulceration. Vesicles typically appear on the sixth to ninth day of neonatal life. A cluster of vesicles often develops on the part of the body presenting to the birth canal, where extended direct contact with virus may occur. Vesicles occur in 90% of infants with localized mucocutaneous infection, and recurrent disease is common. Significant morbidity can occur in these infants despite the absence of signs of disseminated disease at the time of diagnosis. Up to 10% of infants later show neurologic impairment, and infants with keratoconjunctivitis can develop chorioretinitis, cataracts, and retinopathy. Thus, ophthalmologic and neurologic follow-up is important in all infants with mucocutaneous HSV. 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 encephalitis in the absence of disseminated disease, and as many as 60% of these infants do not have mucocutaneous vesicles. These infants usually become symptomatic at 10 to 14 days of life with lethargy, seizures, temperature instability, and hypotonia. 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 and is approximately

15% with treatment. 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 22% of all infants with neonatal HSV infection and can result in mortality for over half. Pneumonitis and fulminant hepatitis are associated with greater mortality. Symptoms usually begin within the first week of neonatal life. The liver, adrenals, and other visceral organs are usually involved. Approximately two-thirds of infants also have encephalitis. 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.

D. Diagnosis. HSV infection should be considered in the differential diagnosis of ill neonates with a variety of clinical presentations. These include CNS abnormalities, fever, shock, DIC, and/or hepatitis. HSV also should be considered in infants with respiratory distress without an obvious bacterial cause or 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 the infant with mucocutaneous lesions, tissue should be scraped from vesicles, placed in the appropriate viral transport medium, and promptly processed for culture and/or PCR by a diagnostic virology laboratory. Virus also can be isolated or detected from the oropharynx and nasopharynx, conjunctivae, stool, urine, and CSF. In the absence of a vesicular rash, viral isolation or detection from these sites may aid in the diagnosis of disseminated HSV or HSV encephalitis. With encephalitis, 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 encephalitis. Viral isolation from CSF is reported to be successful in as many as 40% of cases, and rates of detection in CSF by PCR may reach close to 100%. Combined HSV-1 and -2 serology is of little value (one must test type-specific serology) 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 -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. Infant HSV-specific IgM detection is not useful. 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.

E. Treatment. Antiviral therapy (acyclovir, a nucleoside analog that selectively inhibits HSV replication) is highly efficacious in this setting, but the timing of

therapy is critical. Treatment is indicated for all forms of neonatal HSV disease. Initial antiviral studies were carried out with vidarabine, which reduced morbidity and mortality of HSV-infected neonates. Mortality with encephalitis 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. Recommendations include treating infants with disease limited to the SEM disease with 20 mg acyclovir per kilogram every 8 hours for 14 days, and those with CNS or disseminated disease for at least 21 days, or longer if the CSF PCR remains positive. 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. Yet, oral acyclovir suppressive therapy following initial acute treatment at a dose of 300 mg/m^2/dose three times a day for 6 months of life was beneficial in improving the developmental outcome for infants with neonatal HSV infection. 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 -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). 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.** Cesarean section is recommended for women with active genital lesions or prodromal symptoms at the time of delivery. 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 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 maternal serology should be obtained to determine whether a new acquisition of a nonprimary infection with HSV-1 or -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 the 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. 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. 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 a recurrent 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

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 -2 IgG negative)
■ Consider offering an elective cesarean section, regardless of lesion status at delivery, or if membranes ruptured <4 hours
■ Swab infant's conjunctivae, nasopharynx, and anus for PCR and culture to determine exposure to HSV □ Collect blood for HSV PCR and serum ALT □ Collect CSF for HSV PCR, cell count, and chemistries □ Initiation of acyclovir while pending laboratory results or if signs of neonatal HSV
■ 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)
■ Swab infant's conjunctivae, nasopharynx, and anus for PCR and culture to determine exposure to HSV □ Collect blood for HSV PCR
■ Treat with acyclovir if PCR or culture positive or signs of HSV infection

ALT, alanine aminotransferase; CNS, central nervous system; CSF, cerebrospinal fluid; IgG, immunoglobulin G; PCR, polymerase chain reaction; SEM, skin, eye, or mouth.

found to have either recent primary or nonprimary, first-episode infection and a genital lesion, 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 in 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).

Humans are the only known host to parvoviruses. 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 or 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, such that 90% of elderly persons are seropositive. 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 schoolteachers, or childcare workers may be at the greatest 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 would lower the risk of 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. 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. **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 1 to 4 days before the facial rash appears. Associated symptoms include myalgias, upper respiratory or gastrointestinal symptoms, and malaise, but these symptoms generally resolve with the appearance of the rash. The rash is usually macular, progresses to the extremities and trunk, and may involve the palms and soles. It may be pruritic and may recur. These children are likely most infectious before the onset of fever or 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.
2. **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.
3. **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.** 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 has been implicated in approximately 10% of cases of fetal nonimmune hydrops. 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. 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. Approximately 5% of cases of fetal hydrops can resolve on their own with near-normal delivery outcomes. 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, and serum levels begin to fall by the second to third month after infection. Serum IgG appears a few days after IgM and may persist for years. Serum or plasma can also be assessed for viral DNA by PCR and defines 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 involvement. However, no controlled studies have been performed to establish the efficacy of IVIG prophylaxis or therapy for B19 infections. There are no recommendations for the use of IVIG in pregnancy. In the carefully followed pregnancy in which hydrops fetalis is worsening, intrauterine blood transfusions may be considered between 18 and 35 weeks, 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 obviously 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) schoolteachers, 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 an 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.
3. Serial determinations of maternal serum alpha-fetoprotein (AFP) (AFP may rise up to 4 weeks before ultrasonography evidence of fetal hydrops), although it's use is of uncertain value.
4. Determination of fetal IgM or DNA PCR by percutaneous umbilical blood sampling (PUBS). The utility of this is questionable given the relatively high risk–benefit ratio at present, especially because it is unclear that obstetric management will be altered by results. It may be useful to confirm B19 etiology when hydrops fetalis is present.

   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 schoolteachers 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 crisis 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 and the causative agent of a 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 below 200/μL is highly susceptible to opportunistic infections and malignancies which define the 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.

1. 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 is still high at approximately 39,000 with 9% decrease between 2010 and 2017. Of these new infections, certain groups have disproportionately high infection rates, including men who have sex with men (MSM) and African Americans. Remarkably, one in seven HIV-infected individuals is unaware of his or her 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 adults and adolescents with AIDS.

In 2018, women accounted for 19% of the new diagnoses of HIV with 65% of them being in the childbearing age. The rates are highest in African American women. This incidence has declined by 24% since 2010. 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 2018, only 66% of HIV-infected women were engaged in care and only 53% had achieved viral remission. Whereas enormous successes in reduction of mother-to-child transmission have been realized with the introduction of antiretroviral prophylaxis and treatment—zidovudine in 1994 and potent antiretrovirals in 1996—it is estimated that approximately 70 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, in the United States, >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. AIDS-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

67% of HIV-infected women receive antiretroviral regimens 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 antiretrovirals 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 antiretroviral treatment (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 often not covered 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 AIDS is heterosexual contact.

2. **Parenteral inoculation.** Parenteral transmission of HIV results from the direct inoculation of infected blood or blood products. The groups affected have been intravenous 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 in the United States have been estimated to be 1 in 1.5 to 2 million units.

3. **Congenital and perinatal transmission.** More than 92% 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. Prior to ART availability in scenarios where breastfeeding was not practiced, 33% of the infections happened in the antenatal period with 67% occurring around the peripartum period. In scenarios where breastfeeding was practiced, 25% to 40% of the infections happened in the antenatal period, 50% in the peripartum period, and 10% to 15% via breastfeeding. With effective ART during pregnancy and avoidance of breastfeeding, the transmission rates have reduced to approximately 1%. A meta-analysis of transmission studies suggests that intrapartum infection occurs as a correlate of the 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 ensure that the infant or child receives every dose of medication is a critical component of success.

2. **HIV in pregnancy.** HIV-infected pregnant women should be closely monitored 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; and nevirapine, which has resulted in fulminant hepatitis in women with higher $CD4^+$ lymphocyte counts. 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.

There are four goals that are integral to the Prevention of Parent-to-Child Transmission (PPTCT). They include the following:

- Primary prevention of HIV
- Prevention of unwanted pregnancy
- Prevention of transmission from the mother to the child
- Provision of care to mothers and children and their families with HIV/AIDS

3. **HIV infection in children.** Most pediatric AIDS cases occur in infants and young children, reflecting the preponderance of congenital and perinatally acquired infections. Where HIV infection is undiagnosed, 50% of pediatric AIDS cases are reported in the first year of life, and approximately 80% are reported by the age of 3. Of these patients, HIV-related symptoms occur in >80% in the first year of life (median age at onset of symptoms is 9 months). It is estimated that 20% of untreated infants with congenital/perinatal HIV infection will die within the first year of life, and 60% will have severe symptomatic disease by the age of 18 months. These patients are defined as "rapid progressors." These statistics reflect only pediatric AIDS cases reported to the CDC and may reflect only the part of the spectrum of disease that is identified. Statistics are also heavily influenced by the natural disease progression in untreated children. It is possible that many infected children are undiagnosed and remain asymptomatic for years.

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 in adults. The HIV-infected newborn is usually asymptomatic but may present with lymphadenopathy and/or HSM. Generally, the infant infected peripartum does not develop signs or symptoms until after the first 2 weeks of life. These include lymphadenopathy and HSM (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 intravenous trimethoprim–sulfamethoxazole and steroids. Prophylaxis to prevent such life-threatening possibilities 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.

4. **Diagnosis.** The diagnosis of HIV infection in adults is made by the detection of specific antibody by an ELISA with confirmation by Western blot analysis.
   a. **Testing in pregnant women**. It is imperative that every testing needs to follow a pretest and post-test counseling. In pregnant woman, as an initial

screening, a whole blood finger prick is done. In case the test is reactive, confirmatory test by ELISA is done. In case this test is positive, CD4 count, tuberculosis testing, and clinical staging are done. The mothers who are negative do not require any more testing. All antenatal mothers need testing for syphilis as well. 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). Testing should be offered to anyone engaging in risk behaviors for HIV transmission and for all pregnant women.

b. Testing infants. 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. Cord blood should not be used for testing. 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.

Serology is of limited value in diagnosing vertically transmitted HIV infection in infants <15 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 <15 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:

- PCR to detect viral DNA in peripheral blood cells
- PCR for viral RNA in plasma, or viral load

In developing countries, the infants are first tested at 6 weeks of age. If negative, the infant is retested at 6 and 12 months of age with DNA PCR and rapid test. At 18 months age, rapid testing is done three times. The baby is then considered negative. In case any of the tests is positive, ART is initiated after a confirmatory test with whole blood sample.

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 test should be repeated at 3 to 6 months to increase sensitivity and pick up missed cases at birth. The blood samples for these tests should be collected in an anticoagulant, but not heparin, to avoid interference with PCR. Older tests of viral culture and p24 antigen detection are generally no longer done. Culture is sensitive and specific but is expensive and 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.

D. 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/azidothymidine [AZT]). These agents prevent viral RNA from being reverse-transcribed to DNA; therefore, infection of cells can be aborted.
2. Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) (e.g., nevirapine). These agents also act to prevent reverse transcription 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 agents excellent 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 CART 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), zidovudine (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 their 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.

E. Prevention. In this chapter, we will focus only on prevention strategies to reduce mother-to-child transmission both in the United States and globally.

1. **Antenatal interventions.** Efforts to prevent mother-to-child transmission of HIV have been highly successful in the United States. 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 intravenously 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 is continued to be recommended for all HIV-exposed infants. In developing countries, it is suggested to start a three-drug regimen of tenofovir + lamivudine + efavirenz as soon as the mother is diagnosed as HIV positive.

   Co-trimoxazole is recommended if maternal T cell count less than 250. In case the pregnant woman has been exposed to single-dose nevirapine, the above-mentioned regimen may not be effective and the mother needs to be treated with tenofovir + lamivudine + lopinavir or ritonavir.

2. **Intrapartum management.** The treatment should be started 3 hours prior to the elective cesarean section or as soon as possible if the mother arrives in labor. Elective cesarean section (before the onset of labor) can further reduce transmission if the HIV viral load remains >1,000 copies/mL. There is no added benefit to elective cesarean if the HIV viral load is suppressed below this value. In developing countries, routine cesarean is not recommended.

   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.

3. **Infant management**

   a. **Antiretroviral therapy.** For infants with maternal viral load of more than 1,000 copies/mL, instead of oral zidovudine alone (based on NICHD-HPTN 040/PACTG 1043 regimen), a two-drug (zidovudine plus three doses of nevirapine in the first week of life) or a three-drug (zidovudine, lamivudine, and nevirapine or raltegravir) combination therapy is recommended. The two-drug regimen has less neutropenia than the three-drug regimen. 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 the 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. In developing countries, nevirapine at a dose of 2 mg/kg is recommended for a period of 6 weeks. The nevirapine may be extended to 12 weeks if maternal ART is initiated after 24 weeks of pregnancy.

Globally also, there has 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 is above the level needed to reduce the 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.

b. Breastfeeding. In developing countries, early skin-to-skin contact and exclusive breastfeeding is recommended because of the reduction in mortality due to communicable diseases. The feeding counseling needs to follow AFASS (affordable, feasible, acceptable, sustainable, and safe) criteria.

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 2015 guidelines suggest that triple ART should be started in all pregnant and breastfeeding women with HIV and continued lifelong irrespective of the clinical stage and the $CD4^+$ count. For high-risk infants (high maternal viral load, short duration of ART in the mother), a combination therapy of daily nevirapine and zidovudine is recommended for 6 weeks. If the breastfeeding is continued, additional 6 weeks of either dual therapy or nevirapine alone is recommended. If the mother refuses or cannot tolerate ART and is breastfeeding, nevirapine prophylaxis should be carried on for 1 week after the cessation of breastfeeding. 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.

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.

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 those exposed to the 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.

c. Immunization and prophylaxis against pneumocystis. All vaccines can be administered. Prophylaxis with co-trimoxazole needs to be initiated at 6 weeks of age.

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 the maternal viral load to nondetectable levels during pregnancy (and after pregnancy to optimize maternal health) using combinations of the approved agents 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.

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 post-transfusion non-A, non-B hepatitis virus [NANB]), and hepatitis E virus (HEV) (enteric, epidemic NANB hepatitis virus). Very few suspected cases of perinatal transmission of HAV have been reported and it is generally not considered to be vertically transmitted, 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 DNA virus 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 in 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.** Approximately 1 to 1.4 million people in the United States and 240 million people globally are living with hepatitis B. In endemic populations, the carrier state is high, and perinatal transmission is a common event. In the United States, the prevalence of chronic hepatitis B among pregnant females is approximately 0.8% with approximately 25,000 infants at risk of acquiring the infection annually. Since 50% of the chronic infections are vertical, prevention of the same is an important strategy for global control of the disease. The risk of chronic HBV infection is inversely proportional to age, with a carriage rate of 90% following infection in neonates and only 20% to 30% if the infection is acquired during childhood. The overall incidence of HBV infections in the United States is relatively low. The incubation period for HBV infection is approximately 120 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, intravenous 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 is thought to result ***primarily from exposure to maternal blood at the time of delivery. Transplacental transfer accounts for <4% of all cases.*** (It has been reported from Taiwan, but this has not been reported in other parts of the world, including the United States. There is a high chronic carrier rate in Taiwan that may be related to the transplacental transfer observed in that country. When acute maternal HBV infection occurs during the first and second trimesters of pregnancy, there is generally little risk to the newborns (10%) 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.
3. **Diagnosis.** The diagnosis is made by specific serology and by the detection of viral antigens. The specific tests are as follows:
   - HBsAg determination. Usually found 1 to 2 months after exposure and lasts a variable period of time
   - Anti-hepatitis B surface antigen (anti-HBs). Appears after resolution of infection or immunization and provides long-term immunity
   - Anti-hepatitis B core antigen (anti-HBc). Present with all HBV infections and lasts for an indefinite period of time
   - 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

- HBeAg. Present in both acute and chronic infections and correlates with viral replication and high infectivity
- Anti-hepatitis B e antigen (anti-HBe). 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.

4. **Treatment.** 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. However, ***there is no specific therapy for infants with acute HBV infection***.
5. **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 a high risk for infection, as well as routine active neonatal immunization to protect against postnatal exposure (Table 48.3). High-risk infants born to HBsAg-positive mothers should receive HBV hyperimmune globulin (hepatitis B immune globulin [HBIG]) and active HBV vaccination within 12 hours of life. Combined active–passive immunization can reduce the transmission rates by 95%. Universal immunization severely reduced the chronic carrier state in Taiwan and is now routinely recommended for all U.S. infants born to all HBsAg-positive and HBsAg-negative mothers, with three doses administered before the age of 18 months. Certain high-risk populations, such as Alaskan natives, Pacific Islanders, and infants of immigrant mothers from areas where HBV is endemic, should receive the three-dose series by the age of 6 to 9 months. The recommended schedule is begun during the newborn period; 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. In India, 0–1–2 or 0–1–6 months is recommended. The third

Table 48.3. Doses of Hepatitis B Vaccines in Neonates*

	Active Immunization: Either		Passive Immunization HBIG
	Recombivax HB (Merck)	Engerix-B (SmithKline Beecham)	
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

HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.
*Both vaccine regimens use a three-dose schedule.

dose should preferably be given at 6 months of age or more and 4 months after the second dose. The preterm infant born to an HBsAg-positive mother should be started on the immunization series and given treatment with HBIG immediately (see Table 48.3). The *Red Book: Report of the Committee on Infectious Diseases* by the American Academy of Pediatrics is the best source for dosing based on gestational age and birth weight. Other methods of disease control have been considered; elective cesarean section is not recommended as a measure to reduce the vertical transmission.

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. If the mother is positive, then she would need to be tested for LFT and viral load around 28 to 30 week's gestation. If the viral load is high (>200,000 IU/mL or 10^6 copies/mL), consideration should be given for treatment of the mother with antiviral drugs to reduce the risk of transmission to the infant by decreasing the viral load. If the mother has emigrated from an endemic area, HBIG also should be considered unless the mother is known to be HBsAg negative. Postnatal transmission of HBV by the fecal–oral route probably occurs, but the risk appears to be small. 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** from HBsAg-positive infants in the nursery is minimized if nursery personnel wear gloves and gowns when caring for infected infants. Of course, with current precautions, the risk of exposure to blood and body secretions already should be minimized. 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 the agent responsible for most non-A, non-B 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.

1. **Epidemiology.** Six HCV subtypes have been characterized based on sequence heterogeneity of the viral genome. HCV is found worldwide, and different subtypes have been identified from the same area. Subtype 1 is the most common in the United States and has a poorer prognosis than other subtypes. Globally 71 million people have hepatitis C infection and this is a major cause of liver cancer and currently there is no vaccine against this virus. Genotype 3 is the predominant one in India, followed by genotype 1.

a. **Horizontal transmission.** Injection drug use is the most common risk factor; transfusion recipients, dialysis patients, and sexual partners of HCV-infected persons may also be infected. But 50% of infected persons are unable to identify a risk factor.

b. **Vertical transmission.** Overall rate of transmission is approximately 5% from known hepatitis C–infected women to their infants. The transmission rate may well be much higher and may approach 70% when the pregnant mother has a high viral load. HCV is transmitted at a higher frequency if the mother is also HIV infected (10%), 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. Detection of HCV by RNA PCR in the 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. PCR-negative infants at birth may develop PCR positivity later in infancy, suggesting perinatal infection. One study found that 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. (The mother may consider withholding breastfeeding till cracked and bleeding nipples heal.) 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 40 to 90 days 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 result in as many as 60% of community-acquired HCV infections. Cirrhosis may result in as many as 20% of chronic disease cases but may be less likely in pediatric patients. Infants are generally asymptomatic with some showing a transient increase in alanine aminotransferase (ALT) levels usually improving by 2 years.

3. **Diagnosis.** ELISA detects antibodies to three proteins (c100-3, c22-3, and c33c) that are components of HCV. This test may be able to detect infection as early as 2 weeks after exposure. Another serologic assay with even greater sensitivity is the radioimmunoblot assay, which detects antibodies to the three antigens detected by the ELISA and a fourth antigen, 5-5-1. Infants born to HCV-infected mothers will show evidence of passively acquired maternal antibody; therefore, to determine infection in the infant, RNA PCR, which detects the viral genome itself, must be performed. This assay can detect viremia within 1 week of infection in adults. 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; even if the PCR is negative, infants should be tested for anti-HCV antibodies at 18 months to confirm the absence of infection. Siblings must be tested for possible vertical transmission.

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 symptomatic 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.** All mothers should be screened for HCV infection during each pregnancy. Invasive obstetric procedures such as fetal scalp monitoring and chorionic villous sampling should be avoided. Blood products are routinely screened for antibody to HCV. Presence of the antibody likely also indicates presence of the virus, and the unit is discarded if antibody is positive. **Thus, there is *no* benefit expected by giving IVIG 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. Breastfeeding should be continued but a little period of abstinence is sometimes recommended if there are cracked or bleeding nipples. Mode of delivery should be based on obstetric reasons or concomitant HIV infection but not on the presence of HCV infection.

C. HEV. Enterically transmitted NANB viral hepatitis (HEV) is primarily spread by fecal-contaminated water supplies, yet there are several case reports of vertical transmission of HEV. 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 of the Southeast Asian countries (20% if they acquire the infection during the third trimester). There are limited data on the vertical transmission of hepatitis E in pregnancy but it is estimated to be around 40% to 50%. A small case series has suggested association with premature births and neonatal mortality due to hepatic necrosis. Among the survivors, there is no known long-term impact. Treatment is supportive, in the absence of any specific therapy.

D. Hepatitis G virus (HGV). HGV shares 27% homology with HCV. It 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. 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 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 the 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. Varicella is not included in the Indian or most Asian national immunization schedules.

The WHO (2014) estimated that approximately 4.2 million severe complications and 4,200 deaths happen every year globally following varicella infection. 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 the widespread use of varicella vaccine. The problem is estimated to be significant in countries where quality of life and health care are improving. According to one report, approximately 36% of women in the childbearing age are susceptible to varicella in Sri Lanka. There are recommendations to immunize nonimmune adults at risk for infection unless they are pregnant. The overall estimated risk of the congenital varicella syndrome following maternal infection is low, with only 0.4% in the first 12 weeks of pregnancy, and 2% from 13 to 20 weeks' gestation. It is primarily seen with gestational varicella but may rarely occur with maternal zoster.

The primary mode of transmission of VZV is through 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 and 5 days after the onset of rash.* Conventionally, a patient is no longer considered contagious when all vesicular lesions have dried and crusted over. The incubation period for primary disease extends from 10 to 21 days, with most infections occurring between 13 and 17 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, approximately 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 scars in dermatomal pattern, ocular defects, limb hypoplasia, gastrointestinal abnormalities such as atretic bowel, CNS abnormalities, FGR, 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. **Postnatal varicella.** Varicella acquired in the newborn period as a result of postnatal exposure is generally a mild disease likely due to the presence of

maternal antibodies against the virus. Rarely, severe disseminated disease with pneumonia, meningoencephalitis, and hepatitis occurs in newborn babies exposed shortly after birth, following an acute maternal infection. In these instances, treatment with acyclovir may be beneficial. Varicella has been detected in breast milk by PCR occasionally but the incidence is very remote and hence breastfeeding should be continued because the antibody being passed in the breast milk may be protective.

C. Diagnosis. Infants with congenital varicella resulting from *in utero* infection occurring before the peripartum period do not shed virus, and the determination of VZV-specific antibodies is often confounded by the presence of maternal antibodies. Therefore, the diagnosis is made on the basis of clinical findings and maternal history. With neonatal disease, the presence of a typical vesicular rash and a maternal history of peripartum varicella or postpartum exposure are all that is required to make the diagnosis. Laboratory confirmation can be made by (i) culture of the vesicular fluid, 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) detection from cells at the base of a vesicle 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. Antiviral therapy with acyclovir should be started in symptomatic infants as soon as possible; this may reduce the risk of disseminated disease. Data are not available on the most efficacious and safe dose of acyclovir for the treatment of neonatal varicella, but minimal toxicity has been shown with the administration of 60 mg/kg/day divided every 8 hours for the treatment of neonatal HSV infection. VariZIG should be given to infants delivered to mothers with varicella rash, within 5 days before and within 2 days of delivery. Some experts recommend extending prophylaxis to even when the mother develops rash beyond this period. 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. In women who are not vaccinated against varicella or did not have varicella disease earlier, it is recommended to given VariZIG or IVIG in case of nonavailability of specific immunoglobulin, within 10 days of exposure. Women who acquire primary varicella during pregnancy should be treated with acyclovir for their own health as well as to prevent fetal infection.
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 infant should be isolated in a separate room, and visitors and caregivers should be limited to individuals with a history of varicella. A gown should be worn on entering the room, and good hand-washing technique should be used. Bedding and other materials should be bagged and sterilized. VariZIG can be given to all other exposed neonates, but this can be withheld from full-term infants whose mothers have a history of varicella.

Neonates at <28 weeks' gestation should be given VariZIG or IVIG post-exposure 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. 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 proved. 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 day 8 to 21 after the 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 the 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. They are classified into four major groups: coxsackieviruses

group A, coxsackieviruses group B, echoviruses, and polioviruses. All four groups cause disease in the neonate. Infections occur throughout the year, with a peak incidence between July and November. 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. 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. Symptoms in the newborn often appear within the first week postpartum. Clinical presentations vary from a mild nonspecific febrile illness to severe life-threatening disease. There are three major clinical presentations in neonates with enterovirus infections. Approximately 50% have meningoencephalitis, 25% have myocarditis, and 25% have a sepsis-like illness, which can result in fulminant hepatic failure. The mortality (approximately 10%) is lowest for the group with meningoencephalitis. 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 and coxsackievirus 2 to 5. The symptoms generally present in the first week of life.

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 (half have a history of fever in the last week of pregnancy), as well as that of other family members, particularly young siblings, and especially during the summer and fall months, may be helpful. Nosocomial outbreaks could also be a source sometimes. 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 the 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.

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 and hence shorter the interval between maternal infection and delivery, worse the outcome. 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/g/ose 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). Rubella vaccination is safe, effective, and inexpensive; despite this, as a result of incomplete vaccine coverage, more than 100,000 cases per year of congenital rubella syndrome (CRS) were reported recently. This human-specific virus 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: 85% 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 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 abnormalities were found when fetal infection occurred beyond the 20th week of gestation. There are also case reports of vertical transmission with maternal reinfection. 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 the 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. By the end of 2016, 152 (78%) countries have included rubella vaccine in their immunization program. In 2020, WHO has advised all countries of the world to include Rubella containing vaccines (RCV) in their schedule. All countries must target 80% coverage, if coverage is <80% frame shift of susceptible population to older age places them at risk. The first vaccine should be given at 9 to 12 months and single dose confers reasonable protection.

B. Clinical manifestations. Classically, CRS is characterized by the constellation of cataracts, SNHL, and congenital heart disease. The most common cardiac defects are patent ductus arteriosus and pulmonary artery stenosis. Common early features of CRS are FGR, salt and pepper retinopathy, microphthalmia, cataract, meningoencephalitis, electroencephalographic abnormalities, hypotonia, dermatoglyphic abnormalities, HSM, thrombocytopenic purpura, radiographic bone lucencies, and diabetes mellitus. 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. It 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 the 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 more than 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. IgM rubella may be high in reinfection, vaccination, and false-positive cases, and low in subclinical cases.

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 the fetal blood obtained by percutaneous umbilical cord blood sampling. Direct detection of rubella antigen and RNA by reverse transcriptase PCR (RT-PCR) 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.

      Careful ocular and cardiac evaluation on antenatal ultrasound is recommended in suspected cases.

   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 of rubella virus (oropharynx, urine). Notify the laboratory in advance because special culture medium needs to be prepared.

      ii. Detection of rubella-specific IgM in the cord or neonatal blood

      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 9 to 12 months or older. In India, rubella initiative was launched in 2018 with two vaccinations at 9 to 12 and 16 to 24 months as MR vaccine. 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. Although hyperimmune globulin has not been shown to diminish the risk of maternal rubella following exposure or the rate of fetal transmission, it should be given in large doses to any woman who is exposed to rubella and who does not wish to terminate her 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 theoretic 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. RESPIRATORY SYNCYTIAL VIRUS (NEONATAL). RSV is a leading cause of bronchiolitis and severe or even fatal lower respiratory tract disease, especially in preterm infants. It was observed in a recent meta-analysis that hospital admission rates of infants who were preterm at birth are 16 times other children. Need for mechanical ventilation is several times more and case fatality seven times more in preterm infants.

Conditions that increase the risk of severe disease include cyanotic or complicated congenital heart disease, pulmonary hypertension, chronic lung disease (CLD), and immunocompromised states.

A. Epidemiology. RSV accounts for 31% of cases of severe pneumonia in Africa and Asia. Global yearly rate of RSV hospital admissions in children younger than 5 years is 4.4/1,000. Humans are the only source of infection, 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. Clinical features. In young infants, RSV infection presents with features of lower respiratory tract infection and bronchiolitis. Some infants may present with significant apnea. RSV infection has been linked to recurrent wheezing during childhood.

C. Diagnosis. Clinical features such as wheezing may be suggestive, but do not have high predictive ability. Rapid diagnosis can be made by PCR or immunofluorescent antigen testing of respiratory secretions. Point-of-care tests available currently have not demonstrated clear benefits in prognostication or antimicrobial use.

D. Treatment. Treatment is largely supportive, with hydration, supplemental oxygen, and mechanical ventilation as needed. Controversy exists as to whether nebulized bronchodilator therapy is beneficial. Ribavirin has been marketed for the treatment of infants with RSV infection because it does have *in vitro* activity; however, efficacy has never been 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 (mAb) against RSV fusion protein, 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. In immunocompromised individuals, immunoglobulins may be used, but a systematic review (Cochrane) has shown no benefits in the treatment of hospitalized children.

E. Prevention. Apart from general hygiene measures such as cough hygiene, hand hygiene, and prevention of exposure to tobacco smoke, palivizumab (Synagis), a humanized mouse mAb given intramuscularly, has been approved by the FDA for prevention of RSV disease in children younger than 2 years with CLD 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). Protection depends hugely on adherence to the recommended schedule. Because the drug is costly and its protection incomplete, the American Academy of Pediatrics has made the following recommendations regarding which high-risk infants should receive palivizumab, last updated in 2014:

1. Infants who have required therapy for CLD 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 CLD 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 CLD 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 require only one dose. Palivizumab does not interfere with the routine immunization schedule.

F. Antibody preparations are not recommended for the following:

- Healthy preterm babies >29 weeks' gestation without other risk factors
- Patients with hemodynamically insignificant heart disease
- Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure

Future anti-RSV mAbs 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 mAb 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. PARECHOVIRUS. Human parechovirus, initially classified as enterovirus, belongs to Picornaviridae family. Type 3 is associated with severe disease in neonates and young infants.

A. Epidemiology. This virus is prevalent across the globe with no strong seasonality. Transmission happens via the feco-oral and respiratory routes. Presentation during the first 2 days has been documented, suggesting a vertical transmission as well. This virus also has been implicated as a cause of nosocomial outbreaks in premature nurseries. It is the second most common cause of meningoencephalitis in children younger than 2 months in the United States (diagnosis based on multiplex panel PCR study).

B. Clinical features. It may result in prolonged fever, respiratory tract infections, gastrointestinal infections, exanthematous rash with erythema in the palms and soles, myocarditis, and a neonatal encephalitis with significant white matter injury mimicking hypoxic ischemic encephalopathy.

C. Diagnosis. RT-PCR is a rapid and sensitive method of diagnosis from both blood and CSF. Serology is not useful. Viral isolation is labor intensive and is utilized for typing the virus. CSF examination shows lack of cellular or biochemical response in most cases.

D. Treatment. Most cases resolve spontaneously, although myocarditis and encephalitis can be fatal. No specific therapy is available but in severe cases, IVIG therapy can be tried.

XII. ZIKA VIRUS. Zika virus infection in pregnancy is associated with risk of fetal loss, typical CN anomalies, contractures (arthrogryposis), chorioretinal atrophy.

Epidemiology - The infection was recognized as an health problem in Brazil in 2015, when there was a 20 times increase in microcephaly with a typical pattern. The infection spread to USA over the year, currently there is decrease in cases.

Clinical picture in mothers is typical of a viral syndrome that may or may not be apparent. The disease is spread by mosquitoes and rarely by sexual route. There are many features in common with dengue infection.

There are no definite medications although antivirals and chloroquine have been tried. Investigations have limited accuracy in confirming or excluding disease.

XIII. CHIKUNGUNYA INFECTION. Viral infections in pregnant women happens by bite from mosquito. it is not uncommon in some regions in India. Mother to child transmission risk is 15%. Risk of spread in intrapartum period is high (50%), spread is near zero in antenatal infection remote from birth, and low risk if mother is infected after birth of the baby.

Maternal symptoms include fever, joint pains and rash, many may not be noticed. Fetal wastage (loss) is desribed in 2.7%. Neonates may have fever, irritability, rash, joint swelling,\;/. and skin problems. Babies have typical pigmentation of nose (CHIK sign) when the baby is recovering. There can be joint pain and swellings or skin thickening and other changes.

There are no definitive bedside tests. No definite treatment is identified.

XIV. DENGUE FEVER. This infection is endemic in many areas of India. The fetus is susceptible in any febrile illness in a pregnant women. Risk of still birth, miscarriage, preterm birth, and low birth weight is higher. Severe thrombocytopenia can complicate decision making of operative delivery. Mothers can develop complications of dengue, which in turn can influence the fetus and newborn.

XV. CORONA VIRUS. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called the COVID-19 virus, associated with the pandemic started in Wuhan city in China in 2019 and then spread to the rest of the world by person-to-person contact. At the time of writing the text, the pandemic is still raging and knowledge evolving and much of the information is based on early published reports.

A. Epidemiology. Vertical transmission (from the mother to the child) seems to be uncommon; most case series have reported COVID-negative babies born to infected mothers. Studies found almost complete absence of the virus in the cord, amniotic fluid, and placenta. Horizontal transmission from caregivers after birth is likely and this includes the mother. A lack of mother -neonate separation from birth is associated with risk of COVID infection (OR 4.94), while breastfeeding is not (OR 0.35).

Pregnant women are mostly asymptomatic, and are detected to have infection as part of screening, at admission to hospital for delivery. Unpublished observations describe missed opportunities in pregnant women as fear of contracting COVID from hospitals has resulted in poor health seeking. Mothers missed their routine check ups

B. Clinical features. Fever, tachypnea, cyanosis, and feed intolerance are the commonest features of neonatal COVID. X-ray may reveal features of pneumonia.

C. Diagnosis. Rapid diagnosis is made by RT-PCR of nasopharyngeal, oropharyngeal, and rectal swabs. The test has a moderate sensitivity (60% to 70%) but the specificity is quite high. Antibody tests for IgM COVID-19 are not useful. Blood investigations might show leukocytosis, lymphopenia, and occasionally thrombocytopenia in some cases.

D. Treatment. Extra care is necessary, wearing full personnel protection equipment, while attending delivery of confirmed or suspected COVID-19 mothers, to

protect health care workers. Resuscitation should be done either in a separate room or in the same room as the mother with 6 feet (2 m) distance between the baby and the mother. Ideally the delivery room must have negative pressure, to prevent spread of virus out of the room. Resuscitation should be done by the most experienced person to limit the number of personnel required. Treatment of an affected neonate is largely supportive, experimental therapies such as hydroxychloroquine, remdesivir, and plasma therapy tried in adults are not evaluated in neonates.

E. Prevention. The neonate can get infected from mother or the caretaker. Delayed cord clamping is recommended as there are no data suggesting transmission through the placental blood. Skin-to-skin care and direct breastfeeding should be discussed with the family and the benefits be balanced against the uninfected baby's protection from the infected mother. The mother and the baby may be placed in the same room with at least 6 feet (2 m) distance between the two and the baby being brought to the mother only for feeding purposes. The mothers should wear a face mask and wash the hands before feeding.

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, chorioamnionitis, and prolonged rupture of membranes.
- Risk of neonatal late-onset sepsis (LOS) increases with lower gestational age and birth weight; also with longer duration of central venous access, mechanical ventilation, and use of parenteral nutrition.
- The most common organisms causing EONS (and LONS as well) in Asian region are E. Coli, Klebsiella, Acinetobacter, Pseudomonas, Staphylococcus Aureus, and Coagulase Negative Staphylococcus. Unlike high-income countries, the organisms causing LOS in low and middle-income countries are largely like those causing EOS.
- Group B Streptococcus is not a common cause of EONS, unlike in high-income countries.
- *Candida* is an important cause of sepsis among out born neonates referred to tertiary care centers.
- Dangerously high incidence of antibiotic resistance is being reported from hospital-based studies from Asia, this has led to the vicious spiral of overuse of broad spectrum antibiotics and associated antibiotic resistance.

I. BACTERIAL SEPSIS AND MENINGITIS

A. Introduction. Bacterial sepsis and meningitis continue to be major causes of morbidity and mortality in newborns. In a 2016 study from Delhi, India, the incidence of culture-positive sepsis was 9.5 per 1,000 live births. 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 (health care–associated) sepsis. Neonatal survivors of sepsis can have severe neurologic sequelae due to central nervous system (CNS) infection as well as from secondary hypoxemia resulting from septic shock, persistent pulmonary hypertension, and severe parenchymal lung disease.

B. Risk factors of sepsis. A recent meta-analysis on risk factors of neonatal sepsis in India included 15 studies, of which 9 were prospective. It was found that male sex (odds ratio [OR] 1.3), outborn neonates (OR 5.5), need for artificial ventilation (OR 5.61), gestational age <37 weeks (OR 2.05), and **premature rupture of membranes** (ROM; OR 11.14) were risk factors of neonatal sepsis.

C. Organisms that cause neonatal sepsis. In many low and middle-income countries (LMICs), especially those in South Asia, there is no difference in the profile of organisms causing EOS and late-onset sepsis (LOS). Overall, the main bacterial etiologic organisms reported from a large Indian study were *Acinetobacter* spp. (22%), *Klebsiella* spp. (17%), coagulase-negative staphylococci (CONS) (15%), *Escherichia coli* (14%), *Staphylococcus aureus* (12%), *Pseudomonas* spp. (7%), *Enterococcus* spp. (6%), and *Enterobacter* spp. (4%). Group B *Streptococcus* (GBS) accounted for only 1% of organisms grown. *Listeria* is another organism hardly ever reported from LMICs.

The profile of etiologic organisms is slightly different among outborn neonates admitted to level III units with sepsis. Data from 2,588 outborn neonates in India showed that sepsis accounted for two-thirds of neonatal deaths. About one-quarter of infections were caused by *Candida* spp. *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the two most common bacterial pathogens.

This contrasts with high-income countries, where nearly half of cases of LOS are caused by CONS and most cases of EOS are caused by GBS. In a National Institute of Child Health and Human Development (NICHD) study, after CONS, 22% of cases of LOS were caused by other Gram-positive organisms (*S. aureus*, *Enterococcus*, GBS), 18% by Gram-negative organisms (*E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, and *Serratia*), and 12% by fungal species (*Candida albicans* and *Candida parapsilosis*). In high-income countries, the second most common organism causing EOS is *E. coli.*

1. Gram-negative organisms. Neonatal sepsis caused by Gram-negative organisms is generally more severe than that caused by Gram-positive organisms. LOS caused by Gram-negative organisms is complicated by a 40% mortality rate in the NICHD cohort.

a. *Acinetobacter* spp.

i. Microbiology. *Acinetobacter* species are Gram-negative, nonfermenting, coccobacilli of the family Moraxellaceae. *A. baumannii* is most frequently implicated in human infections. It is associated with high multidrug resistance. The World Health Organization (WHO) has declared *A. baumannii* as one of the most serious ESKAPE organisms (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) that efficiently evade the effects of antibiotics.

ii. Clinical presentation. *A. baumannii* can cause septicemia, pneumonia, meningitis, wound and soft-tissue infections, and urinary tract infections (UTIs). The symptoms of *Acinetobacter* sepsis are nonspecific and are similar to those seen with any other Gram-negative septicemia.

iii. Treatment. Serious, invasive *Acinetobacter* sepsis usually requires treatment with a carbapenem, such as imipenem or meropenem. Unfortunately, the rate of carbapenem-resistant *A. baumannii* isolates is increasing globally, particularly so in LMICs in South Asia. Carbapenem-resistant *Acinetobacter* requires treatment with a polymyxin antibiotic—colistin or polymyxin B. It is also susceptible to tigecycline and minocycline, but safety data and experience of use of these antibiotics in the neonatal age group are lacking. Alternative approaches include combining carbapenems with ampicillin–sulbactam, minocycline, colistin, tigecycline, and rifampicin.

iv. **Antibiotic resistance.** *Acinetobacter* species have a wide range of intrinsic resistance mechanisms that are upregulated under antibiotic pressure. The mechanisms include enzymatic degradation of antibiotics, target modification, the flux pumps, and permeability defects. *Acinetobacter* species are also highly adapted to acquire resistance genes from other bacteria through mobile genetic elements.

b. *E. coli* and other enteric Gram-negative bacilli. In LMICs, *E. coli* and other enteric Gram-negative bacilli have always been important causes of early and late-onset neonatal sepsis. In high-income countries, with the implementation of intrapartum antibiotic prophylaxis (IAP) against GBS, an increasing proportion of EOS cases are caused by Gram-negative organisms. **Increases in non-GBS EOS and ampicillin-resistant EOS are reported among VLBW infants.** In a report from the NICHD from 2006 to 2009, 78% of cases of *E. coli* EOS infections among VLBW infants were resistant to ampicillin.

i. **Microbiology.** *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 a 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.

ii. **Clinical presentation.** *E. coli* sepsis can present with neonatal septicemia, meningitis, UTI, gastroenteritis, and less commonly bone, joint, and soft-tissue infections. The clinical signs are nonspecific and similar to other causes of neonatal infections.

iii. **Treatment.** When there is a strong clinical suspicion of sepsis in a critically ill infant, the possibility of ampicillin-resistant *E. coli* must be considered. The addition of a third-generation cephalosporin such as cefotaxime or ceftazidime 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 cefotaxime as indicated by sensitivities.

c. *P. aeruginosa*

i. **Microbiology.** Mortality associated with *P. aeruginosa* sepsis in low-birth-weight (low-BW) infants is high (76% in the NICHD cohort). A number of bacterial factors, including LPS, mucoid capsule, adhesins,

invasins, and toxins (notably exotoxin A), contribute to its extreme virulence in premature infants. 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, disseminated intravascular coagulation [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 the 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.

ii. **Treatment.** 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 emerging in pseudomonal species (see subsequent text), and treatment must be guided by isolate antibiotic sensitivity testing. 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.

iii. **Antibiotic resistance.** Selection of the bacteria, likely due to the resistance of *Pseudomonas* to most common antibiotics, also plays a role in colonization; prolonged exposure to intravenous (IV) antibiotics is an identified 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.

d. *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. Although *Enterobacter* spp. account for <5% of total infections in the NICHD and our local data, there are multiple reports of epidemic outbreaks of cephalosporin-resistant *Enterobacter* in neonatal intensive care units (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 are usually recommended for the treatment of infections caused by *Enterobacter* spp. Infection control measures and restriction of cephalosporin use can be effective in controlling outbreaks of resistant organisms.

2. Gram-positive bacteria

a. GBS. Data regarding GBS have almost exclusively come from high-income countries. 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 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.

i. Microbiology. GBS are facultative diplococci that are easily cultivated in selective laboratory media. They 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 the analysis of capsular polysaccharide composition. Most neonatal diseases in the United States are currently caused by type Ia, Ib, II, III, and V GBS. Type III GBS are associated with the development of meningitis and are commonly a cause of late-onset GBS disease.

ii. 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 the risk for any individual infant (see subsequent text).

iii. Clinical risk factors for GBS EOS (Table 49.1). 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 an independent risk factor for GBS EOS.

iv. 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

Table 49.1. 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)

BW, birth weight; CI, confidence interval; 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.

pregnant women for GBS colonization. The most recent Centers for Disease Control and Prevention (CDC) guidelines published in 2010 (http://www.cdc.gov/groupbstrep/guidelines/guidelines.html) recommend universal screening of pregnant women for GBS by rectovaginal culture at 35 to 37 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 ≥100.5°F occurs, or if the duration of ROM is ≥18 hours prior to delivery. The 2010 guidelines for the first time, endorsed intrapartum nucleic acid amplification testing (NAAT) as an alternative to culture-based detection of maternal GBS colonization. Penicillin and ampicillin are the recommended antibiotics for GBS IAP. The document addresses the challenges to providing adequate IAP to the roughly 10% of women who report penicillin allergy. There are no data directly supporting the efficacy of any antibiotic other than penicillin, ampicillin, or cefazolin for GBS IAP. Because a significant proportion of GBS isolates (15% to 40%) are resistant to macrolide antibiotics, it is recommended that any GBS isolate 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 2010 guideline does not consider the administration of clindamycin or vancomycin to constitute fully adequate IAP.

v. **Evaluation of infants after maternal GBS IAP.** The 2010 CDC guidelines recommends a full diagnostic evaluation (complete blood count [CBC] with white cell differential, lumbar puncture (LP), cerebrospinal fluid [CSF], blood cultures, and chest radiograph) and empiric antibiotic therapy for any infant with clinical signs of infection. For asymptomatic infants, a limited evaluation including CBC with differential and blood culture and empiric antibiotic therapy is recommended if there were intrapartum signs of maternal chorioamnionitis. The CBC with differential may be delayed until 6 to 12 hours after birth for optimal predictive value. Only the administration of penicillin, ampicillin, or cefazolin ≥**4 hours prior to delivery** constitutes adequate IAP. If GBS IAP was indicated but not adequately administered, the revised guideline recommends limited diagnostic evaluation **only if other risk factors for EOS are present (gestational age <37 weeks and/or ROM ≥18 hours).**

vi. **Treatment of infants with invasive GBS disease.** When GBS is identified as the sole causative organism in EOS, empiric antibiotic treatment should be narrowed to ampicillin (200 to 300 mg/kg/day) or penicillin G (250,000 to 450,000 units/kg/day) alone, with the higher dosing reserved for cases complicated by meningitis. The total duration of the 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.

vii. **Recurrent GBS infection.** Recurrent GBS infections are 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 meningococcal disease, does not reliably eradicate mucous membrane 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).

b. CONS

i. **Microbiology.** CONS are a heterogeneous group of Gram-positive organisms with a structure similar to that of *S. aureus*, but these organisms lack protein A and have different cell wall components. *Staphylococcus epidermidis* is the most prevalent species, of all coagulase-negative *Staphylococci* on the skin. 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, has been implicated in adherence to and colonization of the catheter surface; subsequent biofilm and slime production inhibits the ability of the host to eliminate the organism.

ii. **Treatment.** Most CONS are resistant to penicillin, semisynthetic penicillins, and gentamicin, and empiric treatment 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 ventilatory support and is associated with prolonged hospitalization and poorer neurodevelopmental outcome.

c. *S. aureus*

i. **Microbiology.** *S. aureus* is an encapsulated Gram-positive organism that elaborates multiple adhesins, virulence-associated enzymes, and toxins to cause a wide range of serious diseases, including bacteremia, meningitis, cellulitis, omphalitis, osteomyelitis, and arthritis. It 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.

ii. **Clinical presentation.** 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.

iii. **Treatment.** The treatment of methicillin-sensitive *S. aureus* (MSSA) requires the use of semisynthetic penicillins such as nafcillin or oxacillin. **Methicillin-resistant *S. aureus* (MRSA)** is an increasingly recognized pathogen in NICUs. An NICHD Neonatal Research Network (NRN) study of infants born with BW 400 to 1,500 g between 2006 and 2008 reveals that 3.7% had a late-onset infection due to *S. aureus*; roughly one-third of these infections were due to MRSA. Mortality was high in this study, occurring in approximately 25% of infants infected with either MSSA or MRSA.

iv. **Antibiotic resistance.** 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 the community. MRSA isolates can be grouped as hospital associated (HA-MRSA) or community

associated (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 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 the spread and persistence of the organism. 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.

d. Enterococci

i. **Microbiology.** Formerly categorized as members of group D streptococci, both *Enterococcus faecalis* and *E. 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.

ii. **Clinical presentation.** Although disease can be complicated by meningitis and is sometimes associated with necrotizing enterocolitis (NEC), enterococcal LOS is associated with low overall mortality.

iii. **Treatment.** Enterococci are resistant to cephalosporins and may be resistant to penicillin G and ampicillin; treatment requires the synergistic effect of an aminoglycoside with ampicillin or vancomycin.

iv. **Antibiotic resistance.** 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 disease 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 the spread and persistence of the organism.

D. Early onset sepsis

1. **Epidemiology of EOS.** EOS is commonly defined as the onset of neonatal sepsis before 72 hours of life. In a large multicentric study from India, 68% of sepsis episodes had an early onset.

2. **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. The incidence of GBS EOS in LMICs is very low, particularly so in South Asia. This contrasts with the experience from high-income countries. Maternal risk factors of EOS include intrapartum fever (>38°C) and other signs of chorioamnionitis, prolonged ROM (>18 hours), preterm prelabor ROM, foul-smelling liquor, and frequent or unclean per vaginal examinations. Neonatal risk factors include prematurity (<37 weeks' gestation) and low BW (<2,500 g). These factors are modified by the administration of intrapartum antibiotics. In a prospective cohort study from India, on multivariable logistic regression modeling, vaginal examinations more than or equal to 3 (adjusted OR [aOR] 9.5), clinical chorioamnionitis (aOR 8.8), BW <1,500 g (aOR 2.8), male sex (aOR 2.7), gestation <30 weeks (aOR 2) and no intrapartum antibody prophylaxis (aOR 2) were independent predictors of culture-proven EOS.

3. **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 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. 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 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 more 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, NEC, and inborn errors of metabolism.

4. **Evaluation of the symptomatic infant for EOS.** Laboratory evaluation of the symptomatic infant suspected of EOS includes at minimum a CBC with differential and blood culture. Other laboratory abnormalities can include hyperglycemia and metabolic acidosis. Thrombocytopenia as well as evidence

of DIC (elevated prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]; 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 is clinically stable. 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.

5. **Treatment of EOS. Empiric antibiotic therapy** includes broad coverage for organisms known to cause EOS, usually a β-lactam antibiotic and an aminoglycoside. Community-acquired EOS can be treated with ampicillin and gentamicin. The emergence of multidrug-resistant (MDR) organisms (MDROs) in the newborn units of many LMICs poses a major challenge for devising empiric antibiotic policies. It is highly recommended that each unit audit its own culture sensitivity data every 6 months and revise its empiric antibiotic policy accordingly. Common choices of β-lactam antibiotics include piperacillin–tazobactam and cefotaxime (see Table 49.2 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 whether 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.

6. **Adjunctive immunotherapies.** A variety of adjunctive immunotherapies for sepsis have been trialed since the 1980s to address deficits in immunoglobulin and neutrophil number and function. Double-volume exchange transfusions, granulocyte infusions, the administration of intravenous immunoglobulin (IVIG), and treatment with granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have all been investigated with variable results.

   a. **Double-volume exchange transfusion and granulocyte infusion.** Both of these approaches to replete neutrophils in neutropenic septic infants have been studied in small numbers of infants. Most trials on exchange transfusion are from India. Exchange transfusions have primarily been tried in severely sick neonates with sclerema, DIC, and metabolic acidosis. There

Table 49.2. Suggested Antibiotic Regimens for Sepsis and Meningitis*

Organism	Antibiotic	Bacteremia (days)	Meningitis (days)
GBS	Ampicillin or penicillin G	10	14–21
Escherichia coli	Cefotaxime or ampicillin and gentamicin	10–14	21
CONS	Vancomycin	7	14
Klebsiella, Serratia†	Cefotaxime or meropenem and gentamicin	10–14	21
Enterobacter, Citrobacter‡	Cefepime or meropenem and gentamicin	10–14	21
Enterococcus§	Ampicillin or vancomycin and gentamicin	10	21
Listeria	Ampicillin and gentamicin	10–14	14–21
Pseudomonas	Ceftazidime or piperacillin/tazobactam and gentamicin or tobramycin	14	21
Staphylococcus aureus¶	Nafcillin	10–14	21
MRSA	Vancomycin	10–14	21

CONS, coagulase-negative staphylococci; GBS, group B Streptococcus; MRSA, methicillin-resistant *Staphylococcus aureus*.

*All treatment courses are counted from the first documented negative blood culture and assumed that antibiotic sensitivity data are available for the organisms. In late-onset infections, all treatment courses assume that 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. Many infectious disease specialists recommend repeat lumbar punctures at the completion of therapy for meningitis to ensure eradication of the infection.

†The spread of plasmid-borne extended-spectrum β-lactamases (ESBL) among enteric pathogens such as *E. coli*, *Klebsiella*, and *Serratia* is an increasing clinical problem. ESBL-containing organisms can be effectively treated with cefepime or meropenem. Reports of carbapenemase-producing organisms are of concern and infection with these requires consultation with an infectious disease specialist.

‡*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 such as cefotaxime. 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 (VRE) 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 Staphylococcus aureus* (VISA) and *vancomycin-resistant Staphylococcus aureus* (VRSA) strains requires consultation with an infectious disease specialist.

is not enough evidence to recommend the use of exchange transfusions. Both exchange transfusions and granulocyte infusions have significant risks, including graft-versus-host disease; blood-group sensitization; and transmission of infections such as cytomegalovirus (CMV), HIV, and viral hepatitis.

b. IVIG. The use of IVIG in the acute treatment of neonatal sepsis has been studied in several small trials, with mixed results. A definitive trial including 3,493 infants was conducted in nine countries from 2001 to 2007. This was a randomized, placebo-controlled trial of IVIG administration to infants with suspected or proven sepsis. The administration of IVIG resulted in 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 the treatment of neonatal sepsis.

c. Cytokines. Recombinant G-CSF and GM-CSF have been shown to restore neutrophil levels in small studies of neutropenic growth-restricted infants, ventilator-dependent neutropenic infants born to mothers with preeclampsia, and neutropenic infants with sepsis. A rise in the absolute neutrophil count (ANC) above 1,500/mm^3 occurred in 24 to 48 hours. To date, nine randomized, controlled trials of recombinant colony-stimulating factors have been reported all enrolling small numbers of infants. Assessment of these trials is complicated by the use of different preparations, dosages, and durations of therapy as well as variable enrollment criteria. None of the trials included neurodevelopmental follow-up. These studies suggest that G-CSF may result in lower mortality among neutropenic, septic VLBW infants, but overall, there is currently insufficient evidence to support the routine use of these preparations in the acute treatment of neonatal sepsis.

d. Activated protein C (APC) and pentoxifylline. Both of these immunomodulatory preparations have been studied in adults with severe sepsis. Both are active in preventing the microvascular complications of sepsis, by promoting fibrinolysis (APC) and improving endothelial cell function (pentoxifylline), and both decrease the production of tumor necrosis factor (TNF). APC has not been studied in neonates in randomized trials and has been withdrawn from clinical production due to safety concerns in adult patients. Pentoxifylline has been studied in a small number of preterm infants with LOS with potential improvement in mortality. Neither medication can be recommended for use in neonates without further study.

7. 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 who may have colonization or bacteremia that places them at risk for the development of symptomatic EOS. These infants include those born to mothers who have received inadequate IAP and those born to mothers with suspected chorioamnionitis. 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-proven sepsis, but no single test has adequate sensitivity and specificity.

a. Blood culture. With advances in the development of computer-assisted, continuous-read culture systems, such as BACTEC and BacT/Alert, most

blood cultures will be positive within 24 to 36 hours of incubation if organisms are present. Although such automated systems have become the standard in high-income countries, they are still too expensive and not sufficiently sturdy for implementation in most centers in LMICs. Manual conventional blood culture systems have a lower yield and longer time to growth compared to automated systems. Manual blood cultures are usually incubated for at least 5 days, by which time 89% of isolates recover.* Most institutions empirically treat infants for sepsis for a minimum of 48 to 72 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 most pediatric blood culture bottles. 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 grow only under anaerobic conditions; 5% to 10% 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.

b. 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 ANC and immature to total neutrophil (I/T) ratio curves (values vary widely with every hour of life) 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 are 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 1 to 4 hours after birth, with low values (<0.15) reassuring, while elevated values (>0.3) are weakly associated with EOS. The combination of low ANC and elevated I/T ratio is the most predictive combination of WBC indices for EOS.

*Murray PR. Determination of the optimum incubation period of blood culture broths for the detection of clinically significant septicemia. *J Clin Microbiol* 1985;21:481–485.

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.

c. **C-reactive protein (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 and 48 hours later, have been used to manage infants at risk for LOS. Some centers use serial CRP measurements to determine the length of antibiotic treatment for infants with culture-negative clinical sepsis, despite the absence of data to support the efficacy of this practice.

d. **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, TNF-α, and procalcitonin (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.

e. **LP.** The use of routine LP in the evaluation of asymptomatic neonates at risk for EOS remains controversial. A retrospective review of 13,495 infants born at all gestational ages from 150 NICUs on whom an LP was performed found 46 cases of culture-proven GBS meningitis. In 9 out of 46 cases, the accompanying blood culture was sterile. Another retrospective study of CSF taken from a population of 169,849 infants identified 8 infants with culture-positive CSF but with negative blood cultures and no CNS symptoms. In both studies, the authors concluded that the selective use of LP in the evaluation of EOS might lead to missed diagnoses of meningitis. However, in both studies, all infants were not evaluated for sepsis in the absence of symptoms, and the subjects were drawn from large numbers of hospitals with likely disparate culture systems. Another study reviewed the results of sepsis evaluations in a population of 24,452 infants from a single institution. This study found 11 cases of meningitis, all in symptomatic infants; 10 of 11 corresponding blood cultures were positive for the same organism. No cases of meningitis were found in 3,423 asymptomatic infants evaluated with LP.

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, (ii) symptomatic infants with a high risk for EOS whose condition is stable enough to tolerate LP, and (iii) 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, and 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 neonates 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 cells/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 due 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.

8. **Algorithm for the evaluation of the infant at risk for EOS.** Assessing risk of EOS among term and late preterm infants is a common clinical task in birth centers. Risk factors used to identify newborns at risk for EOS include maternal intrapartum fever ≥38°C, foul-smelling liquor, multiple per vaginal examinations, gestational age <37 weeks, VLBW, inadequate indicated IAP, and premature and/or prolonged duration of ROM. The use of an algorithm to guide assessment can ensure consistency among caregivers. An example of such an algorithm is shown in Figure 49.1. There are consensus guidelines for risk stratification of neonates in settings where GBS is common; however, such guidelines are lacking in situations where GBS is not common.

   Sepsis risk calculators. EOS algorithms based on risk factor threshold values are limited by an inability to account for interactions between risk factors and do not utilize the full value of information that falls just below or well above threshold values. A recent study used a cohort of >600,000 infants born ≥34 weeks' gestation to develop a multivariate predictive model of sepsis risk using established risk factors. This model provides estimates of individual infant EOS risk using only objective clinical data available at the time of birth, combined with the infant's clinical condition in the first 6 hours of

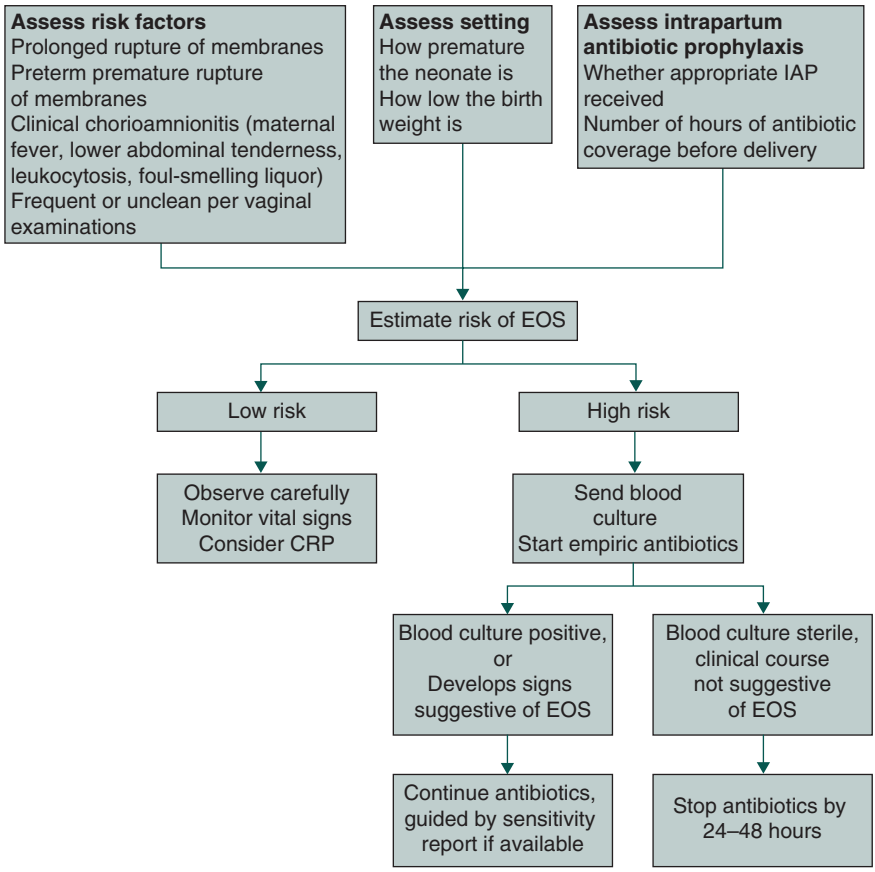

Figure 49.1. Suggested algorithm for sepsis evaluations in at-risk ***asymptomatic*** infants.

life. The model provides a Sepsis Risk Score and is available as a web-based calculator at https://www.dor.kaiser.org/external/DORExternal/research/infectionprobabilitycalculator.aspx and http://newbornsepsiscalculator.org. The care recommendations provided are those used in a large integrated health care system in the United States and may not be universally appropriate. A recent meta-analysis on 13 studies showed that the proportion of missed cases of EOS was comparable between management guided by the EOS calculator (28%) and that guided by conventional management strategies (29%). This sepsis calculator includes items for GBS colonization and antibiotics for GBS prophylaxis, which makes it difficult to use in many LMIC settings, where GBS is not common.

E. Late-onset sepsis

1. **Epidemiology.** Late-onset neonatal sepsis is defined as occurring from 72 hours to 90 days of life. As mentioned earlier, in LMICs, the profile of organisms causing LOS and EOS is almost identical.

In high-income countries, there appear to be two distinct subsets of neonates who develop LOS. The majority are premature infants with risk factors related to ICU care (e.g., central lines) who are infected by CONS. Another subset of LOS comprises otherwise healthy term and near-term infants infected by GBS and Gram-negative species such as *E. coli* and *Klebsiella* spp.

a. Causes of bacteremia in older infants (such as *Streptococcus pneumoniae* and *Neisseria meningitidis*) occur less frequently. **Gram-negative bacteremia** is often associated with UTI. Different series report that 20% to 30% of UTIs in infants <1 month of age are complicated by bacteremia. Mortality is low if promptly treated, and sequelae are few unless meningitis occurs.

In high-income countries, 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 in most centers includes at minimum a CBC; urinalysis; CSF cell count; glucose and protein; and cultures of blood, urine, and CSF. Infants younger than 1 month are generally hospitalized for empiric IV therapy that includes coverage for GBS, *Listeria*, and Gram-negative organisms (commonly ampicillin and cefotaxime); over 1 month, management varies in different centers.

b. Epidemiology of LOS in premature infants. Most LOS occurs in the NICU among low-BW infants. The NICHD NRN data from 2008 to 2012 revealed that 24% of their VLBW cohort (BW <1,500 g and gestational age 22 to 28 weeks) had at least one episode of blood culture–proven sepsis beyond 3 days of life. There was considerable variability with gestational age in the incidence of LOS, ranging from 46% at 23 weeks' to 12% at 28 weeks' birth gestation among the 20 NICHD network centers. NICHD network LOS data from 1998 to 2000 demonstrated that overall mortality from LOS was 18% of infected infants versus 7% of uninfected infants. The mortality among infants was about 40% with Gram-negative infections and about 30% with fungal infections.

c. Risk factors for LOS. A number of clinical factors are associated with an increased risk of LOS (Table 49.3). The incidence of LOS is inversely related to BW. The risk of developing LOS associated with central catheters, parenteral nutrition, and mechanical ventilation is increased with longer duration of these therapies.

2. 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 ventilatory 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 draw a CBC with differential, ±CRP, and a blood culture and wait for the results of the tests (while monitoring the infant's symptoms closely) before beginning empiric antibiotic therapy. Head-to-head comparisons of PCT and CRP show that PCT is somewhat superior to CRP. If laboratory tests are abnormal or the infant's status worsens, empiric antibiotic therapy should be started. If the suspicion for sepsis is still

Table 49.3. Risk Factors for Late-Onset Sepsis in Infants with Birth Weight <1,500 g

Birth weight <750 g
Presence of central venous catheters (umbilical, percutaneous, and tunneled)
Delayed enteral feeding
Prolonged hyperalimentation
Mechanical ventilation
Complications of prematurity
Patent ductus arteriosus
Bronchopulmonary dysplasia
Necrotizing enterocolitis

Source: Data from Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;110(2, Pt 1):285–291; Makhoul IR, Sujov P, Smolkin T, et al. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. *Pediatrics* 2002;109(1):34–39.

low, and/or the clinical impression is that a CONS infection is likely, it is not unreasonable to obtain a blood culture only. Ideally, urine culture should also be obtained before antibiotic therapy, both to guide empiric therapy and to ensure proper follow-up (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 over 9,000 infants had 1 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. In an Indian study on 300 LPs performed as part of septic workup for LOS or symptomatic EOS, no subgroup could be identified that was at such a low risk of meningitis that LP could be safely avoided in it. 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 aspiration (SPA) in VLBW infants; cultures of urine obtained by other means are likely to contain contaminant species.

If a previously well, convalescing premature infant presents primarily with increased apnea with or without upper respiratory infection (URI) symptoms, consideration should be given to a viral source of infection as well. Tracheal or nasal aspirate should be sent for rapid analysis and culture to rule out respiratory syncytial virus (RSV), parainfluenza, and influenza A and B if seasonally appropriate.

3. **Treatment of LOS.** Table 49.2 lists suggested antibiotic regimens for selected organisms. Note that for many antibiotics, dosing is dependent on the gestational and postnatal age. 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 on identification of a positive culture. This was 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. They 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.

4. **MDR organisms.** The emergence of MDRO in NICUs is a major problem in LMICs. In a large multicentric study, multidrug resistance among Gram-negative bacteria was defined as resistance to any three of five antibiotic classes (extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and piperacillin-tazobactam). High rates of multidrug resistance were seen with *Acinetobacter* spp. (82%), *Klebsiella* spp. (54%), and *E. coli* (38%) isolates. Methicillin resistance was observed in 61% of CONS and 38% of *S. aureus* isolates.

   Multiple international reports document an increasing impact of ESBL-producing organisms in NICUs. The magnitude of the problem in American NICUs is limited to case reports of outbreaks, primarily with ESBL-containing *Klebsiella* spp. 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 MDROs have been recently recognized 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 *K. pneumoniae* carbapenemase (KPC), but other enzymes such as the New Delhi metallo-β-lactamase (NDM) and the Verona integron-encoded metallo-β-lactamase (VIM) are common outside the United States. Early recognition of these organisms is critical, both for proper individual treatment and to prevent nosocomial spread. Laboratory standards for the identification of carbapenem-resistant Enterobacteriaceae (CRE) organisms include reduced susceptibility to meropenem, imipenem, or doripenem using breakpoints defined in 2012 clinical laboratory standards and resistance to all third-generation cephalosporins. Current treatment of infections with most carbapenemase-producing organisms requires the use of polymyxin B, an antibiotic with significant toxicity. Recent reports of hospital-acquired infections by extensively drug-resistant *A. 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.

5. **Prevention of LOS.** In addition to significant mortality, LOS is associated with prolonged hospitalization and overall poorer outcome in VLBW infants compared to those who remain uninfected. A number of strategies to lower the 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).

   a. **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 IVIG is generally not recommended.

   b. **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.

   c. **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.

   d. **Probiotics.** Several clinical trials have evaluated the administration of probiotic formulations in the prevention of both LOS and NEC. A large, randomized, double-blind, placebo-controlled trial of an oral synbiotic preparation (*Lactobacillus plantarum* plus fructo-oligosaccharide) was conducted in rural India on a sample size of 4,556 neonates weighing 2,000 g or more at birth and delivered at 35 weeks' gestation or more. There was a significant reduction in sepsis or death in the treatment arm, along with significant reductions in both culture-positive and culture-negative sepsis.

      A recent meta-analysis of 10 randomized, placebo-controlled trials (most published since 2010) concluded that probiotic administration significantly reduced the risk of death or NEC among VLBW infants but found no significant effect on the incidence of LOS. The bacterial formulations and doses used varied among the studies; all included some form of *Lactobacillus* or *Bifidobacterium* spp. Some experts feel that this evidence is strong enough to offer probiotic formulations to all VLBW infants without further placebo-controlled trials. Others argue that the lack of standardized, regulated probiotic products and the relative lack of data among infants with BW <1,000 g suggest that further study is required.

e. **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. Lactoferrin supplementation to enteral feeds with or without probiotics decreases late-onset sepsis and NEC stage II or III in preterm infants without adverse effects (evidence of low quality, Cochrane 2020).

f. **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 [IgA], lactoferrin, lysozyme) and by aiding in the establishment of enteral feeds. Systematic reviews 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. Human milk feeding may impact the risk of LOS by decreasing the time to full enteral feeding and thus decreasing the duration of central venous access and use of parenteral nutrition (PN).

6. **Antibiotic restriction.** Limitation of the use of broad-spectrum antibiotics in neonatal, pediatric, and adult ICUs has been inconsistently associated with decreased 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 MDR 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 organism and may decrease the acquisition and spread of VRE and other antibiotic-resistant organisms.

7. **Surveillance practices.** A concern over emergence of MRSA, VRE, and MDR Gram-negative organisms has led to an 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 the ongoing use of a weekly MRSA surveillance program in our NICU did help prevent patient-to-patient spread of MRSA but did not completely eliminate introduction of MRSA into the NICU, likely due to the prevalence of this pathogen in the general population. 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.

8. **Implementation of recommended best practices to prevent CLABSI.** Most bloodstream infections that occur in VLBW infants are associated with the presence of central venous catheters. CLABSI are defined as culture-proven 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 49.4. 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 http://www.cpqcc.org.

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*

Table 49.4. 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

CLASI, 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; 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.

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 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 strains 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 ampicillin, gentamicin, and clindamycin (or metronidazole) to provide coverage for the spectrum of organisms that can complicate these illnesses.

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 developing countries. The Mother and Neonatal Tetanus Elimination initiative of the WHO aims to reduce maternal and neonatal tetanus cases to a level where they are no longer a major public health problem. By July 2019, there were 12 countries that had still not been able to eliminate maternal and neonatal tetanus (defined as less than 1 case per 1,000 live births in every district). The WHO estimates that in 2018, a total of 25,000 newborns had died of neonatal tetanus globally. It has set multiple target dates for neonatal tetanus worldwide elimination since 1989. Elimination has been achieved in many developing countries, but neonatal tetanus persists in remote and poverty-ridden regions, associated with lack of adequate maternal tetanus toxoid immunization and unsanitary delivery settings. This disease is virtually nonexistent in the United States due to maternal immunization and good infection control practices; only one case was reported to the CDC from 2001 to 2008. Infected infants develop hypertonia and muscle spasms including trismus and consequent inability to feed. Treatment consists of the administration of tetanus immunoglobulin (TIG) (500 units intramuscular [IM]) and penicillin G (100,000 units/kg/day divided every 4 to 6 hours for 7 to 10 days) 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 units/mL) is the 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 the 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 the 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 VLBW infants. Candidemia is a major problem among outborn neonates referred to tertiary care centers in LMICs. In an observational study on 2,588 outborn neonates in Delhi, India, fungi constituted one-quarter of the 401 pathogens isolated. The fungal species were predominantly *Candida tropicalis*, *C. albicans*, and *C. parapsilosis*. In this study, the mean (SD) BW and gestation were 1,551 (698) g and 33.8 (4) weeks, respectively. Ninety percent of cases were diagnosed within 12 hours of hospital admission, with three-quarters having been previously hospitalized and received broad-spectrum antibiotics.

Data on late-onset candidal sepsis from the NICHD NRN showed that 9% of a cohort of 1,515 infants with BW <1,000 g developed candidal sepsis or meningitis, primarily caused by *C. albicans* and *C. parapsilosis*. One-third of these infants died. Invasive candidiasis is associated with overall poorer neurodevelopmental outcomes and higher rates of threshold retinopathy of prematurity, compared to matched VLBW 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 candidal LOS in the NICHD cohort studies were BW <1,000 g, 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 in the BW <1,000 g population 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 has also been identified as an independent risk factor for the development of invasive fungal infection.

1. **Microbiology.** Disseminated candidiasis is primarily caused by *C. albicans* and *C. parapsilosis* in preterm infants, but infections with *C. 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.
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 VLBW infants, most often after the second or third week of life. The initial clinical features of late-onset invasive candidiasis are often nonspecific and can include lethargy, increased apnea or need for increased ventilatory 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 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.

4. **Treatment.** Systemic candidiasis is treated with **amphotericin B**, 0.5 to 1.0 mg/kg/day for durations of 7 to 14 days after a documented negative blood culture if the infection is considered to be catheter associated and the catheter has been promptly removed. Otherwise, the recommended length of treatment for neonatal candidemia is 3 weeks and for longer periods if specific end-organ infection is present. 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 the treatment. The medication is given over 2 hours to minimize the risk of seizures and arrhythmias during the infusion. There is increased experience in VLBW babies with **liposomal preparations of amphotericin B** and this formulation can be used for invasive candidiasis if urinary tract and CNS involvement is excluded. Doses of 5 mg/kg/day can be used without toxicity, and the medication can be given over 2 hours with less irritation at the site of infusion. There is some concern that liposomal preparations are less effective in neonates. CNS disease can be treated with nonliposomal amphotericin alone; an additional second agent, commonly 5-fluorocytosine (flucytosine [5-FC]) (50 to 150 mg/kg/day) or fluconazole (6 mg/kg/day), should be added only if initial therapy with amphotericin is not effective. Flucytosine achieves good CNS penetration, and appears to be safe in infants, but is available only for enteral administration, limiting its utility in sick VLBW infants. Bone marrow and liver toxicity has occurred in adults and correlates with elevated serum levels of the medication. Serum levels can be monitored (40 to 60 μg/mL is desirable.) Fluconazole is safe for use in infants and can be successfully used for primary treatment of candidemia. It should not be used until candidal speciation is completed because *C. krusei* and *C. glabrata* are frequently resistant to fluconazole.

   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 renal and brain 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 the use of broad-spectrum antibiotics (particularly cephalosporins and carbapenems) 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 borne 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 the overall mortality or neurodevelopmental outcome. A recent randomized 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 the neurodevelopmental outcome. In light of these findings, individual NICUs should balance the potentially severe consequences of invasive fungal infection (in the NICHD cohort, 73% of infants 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 BW alone.

IV. FOCAL BACTERIAL INFECTIONS

A. Skin infections. The newborn may develop a variety of rashes associated with both systemic and focal bacterial diseases. 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 the 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 an 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 in a particular setting, 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 the accompanying osteomyelitis or septic arthritis. Therapy is guided by the organism identified (see Tables 49.1 and 49.2).

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 a sterile fashion with Betadine 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 the disease stops and skin lesions are healing.

   Pediatricians who diagnose infectious pustulosis in an infant younger than 2 weeks 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. 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.

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, the incidence is 20% to 25% and remains a major cause of blindness.

1. **Prophylaxis against infectious conjunctivitis.** One percent silver nitrate solution (one to two drops to each eye), 0.5% erythromycin ophthalmic ointment or 1% tetracycline ointment (1-cm strip to each eye), or 2.5% povidone-iodine solution (one 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). 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 common 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 culture 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. However, use of NAATs for nongenital specimens may be done with local verification of clinical laboratory standards because they are not currently Food and Drug Administration (FDA) approved for detecting chlamydia in conjunctival specimens. Chlamydial conjunctivitis is treated with oral erythromycin base or ethylsuccinate 40 mg/kg/day divided into four doses for 14 days. Topical treatment alone is not adequate and is unnecessary when systemic therapy is given. An association of oral erythromycin therapy and 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 endotracheal aspirates (ETA) 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. There is evidence that ETA culture has a high risk of contamination, but the other methods of bronchoalveolar lavage or lung biopsy are too invasive for sick neonates. 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 5 days. Polymerase chain reaction (PCR)–based diagnostics have been developed but are not widely available. It will not be identified on routine bacterial culture. It is sensitive to erythromycin, but is difficult to eradicate, and few data are available on the dosing, treatment duration, and efficacy of treatment when this organism is found in tracheal secretions. There is no current evidence to support the use of *Ureaplasma* treatment to prevent bronchopulmonary dysplasia (BPD).

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 <3 months of age. 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. Evaluation for infection in this population often excludes urine culture, focusing on central line, pulmonary, and gastrointestinal sources of infection.

The most common causative organisms are Gram negative, such as *E. coli* and *Klebsiella*, 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. 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. Catheter collection sample has a higher risk of contamination than SPA; yet success rate in sample collection and parent acceptance to catheter insertion is more common.

We have seen a very large number of babies *treated wrongly as UTI* with multiple courses of antibiotics based on *"few pus cells"* in urine (>10 pus cells/mm^3 is considered abnormal) and equally wrong culture report obtained from *incorrect culture* of bag or "clean catch" urine sample. False-positive cultures are to the tune of 50%. Another error is that of delay between collection of urine (at home) and transfer of the sample to the lab (could be several hours!). Urinary nitrites and leukocyte esterase are unreliable in neonates. Empiric treatment in term and

preterm infants is as for LOS; 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. (Traditionally babies were treated with IV antibiotics for 10 to 14 days. A short course of IV [3 days] followed by oral antibiotics was found to be equally effective as a longer duration of IV antibiotics.)

The American Academy of Pediatrics recommends that infants with UTI undergo renal ultrasound after a first episode of UTI. Ultrasound abnormalities include duplex collecting systems, posterior urethral valve, and pelviureter junction abnormalities. Ultrasound may show evidence of scarring, but radionuclide imaging will detect more cases than ultrasound. Twenty percent of neonates with UTI have VUR. 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. It must be done 2 to 4 weeks after the infection is treated and the neonate is better. 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. The risk of infection recurrence is highest in the first 6 months after infection.

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*. Very often the blood culture is sterile and tissue (aspirated pus) cultures are obtained after antibiotics have been administered for several days; this makes microbe identification difficult. Symptoms include localized erythema, swelling, and apparent pain or lack of spontaneous movement of the involved extremity. We have seen babies presenting with mere swelling or restricted movement; there were no systemic signs of infection and no typical risk factors for infection. When septic arthritis is suspected, arthrotomy must be done without wasting time (attempts to confirm joint involvement by ultrasound, MRI, or even joint aspiration are not mostly inconclusive). 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. Classical teaching of 3 to 4 weeks' parenteral therapy has been challenged; in uncomplicated cases (except MRSA and Panton-Valentine Leukocidin [PVL]-producing *S. aureus*), 3 to 4 days of IV antibiotics followed by 3 weeks of oral antibiotics was associated with similar outcomes as long IV

treatment. Significant disability can result from joint or growth plate damage, despite immediate treatment.

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50 Congenital Toxoplasmosis

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KEY POINTS

- Toxoplasmosis can be acquired *without exposure to cats* via ingestion of oocysts in *contaminated food or water* or tissue cysts in *undercooked/raw meat*.
- In the United States, 500 to 5,000 infants are born with congenital toxoplasmosis annually. In India, between 56,737 and 176,882 children born every year are at a risk for congenital toxoplasmosis.
- The risk of intrauterine infection increases with gestational age, but the effects on the fetus are more severe with fetal infection occurring earlier in gestation.
- Congenital toxoplasmosis can occur secondary to acute maternal infection during pregnancy and also due to reactivation of prior infection in an immunocompromised mother.
- Treatment of congenital toxoplasmosis for 1-year duration has been associated with reduction of sequela and improved outcomes.

I. EPIDEMIOLOGY. *Toxoplasma gondii*, an obligate, intracellular protozoan parasite, is an important human pathogen, especially for the fetus, newborn, and immunocompromised patient.

A. Transmission. *T. gondii* exists in three infectious forms: tachyzoites, tissue cysts containing bradyzoites, and oocysts containing sporozoites. The tachyzoite is the form responsible for symptoms during acute infection, whereas the tissue cyst is responsible for latent infection. The only definitive host of *T. gondii* is the cat. When infected, cats are usually asymptomatic. Intermediate hosts include all warm-blooded animals and humans. Tissue cysts form in the intermediate host, particularly in the brain, eye, and muscle. The cysts are infectious. Cats are infected by ingesting cysts from an infected intermediate host, ultimately shedding oocysts from their intestinal lumen into the environment. They can shed up to 10 million oocysts a day for 20 to 24 days following initial infection. Sporulated oocysts remain infective in the soil for up to 18 months. Other animals become infected by ingesting the oocysts, resulting in tissue cysts containing viable organisms predominately in the muscle and brain.

T. gondii infection can be acquired via ingestion of infected oocysts from the environment (contaminated food or water), viaingestion of tissue cysts from raw or undercooked meat (most common in developed world), or via transplacental transmission (congenital infection). Risk factors associated with acute infection in the United States include eating raw ground beef and lamb; eating locally

produced, cured, dried, or smoked meat; working with meat; drinking unpasteurized goat's milk; and having three or more kittens. 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. In developing countries, lower socioeconomic status, residing in mud-plastered houses, consumption of raw salad, drinking untreated water, owning pets, and advanced age are all considered as risk factors for infection in women. The prevalence of *T. gondii* varies broadly among different countries and geographic areas. The presence of serum antibodies to *T. gondii* increases with age. 22.5% of people ≥12 years of age in the United States have been infected with *T. gondii*. In India, the overall seroprevalence rate is 22.4%, with an estimated incidence rate of around 1.43.

The reported prevalence of *T. gondii* antibodies in women of childbearing age ranges from 10% to 80% worldwide. Women without antibodies are at risk for acute toxoplasmosis during pregnancy.

Seroconversion during pregnancy also varies by geographic location. Rates range from 1.5% in France, a high-prevalence country, to 0.17% in Norway, a low-prevalence country. Incidence of maternal seroconversion during pregnancy in the United States is estimated at 0.2% to 1%. The rate of mother-to-child transmission in the United States is 50% to 60% for mothers not treated during pregnancy and 25% to 30% for those treated.

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. From a conservative estimate in India, between 56,737 and 176,882 children born every year are at a risk for congenital toxoplasmosis.

II. PATHOPHYSIOLOGY

A. Postnatal infection. Normal children and adults are susceptible to acute infection if they lack specific antibody to the organism. Both humoral and cell-mediated immunity are important in the control of infection. The majority of *T. gondii* infections in immunocompetent hosts are asymptomatic. Possible mild symptoms include lymphadenopathy, malaise, fever, and headache. More severe symptoms such as encephalitis, myocarditis, pneumonia, and hepatitis are less common. Chorioretinitis has also been reported in postnatally acquired cases. In immunocompetent hosts, infection with *T. gondii* imparts lifelong immunity.

B. Congenital infection. Congenital infection is most commonly secondary to acute maternal infection during pregnancy and less commonly due to reactivation of previous infection in an immunocompromised mother. Vertical transmission is also possible in women infected within 3 months prior to conception. Parasitemia in the mother leads to placental invasion by the parasite and subsequent passage into the fetal circulation and tissues resulting in fetal infection.

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. However, the effects on the fetus are more severe with maternal infection occurring earlier in pregnancy.

Sixty-one percent of infants will have clinical manifestations when seroconversion occurs at 13 weeks' gestation in contrast to about 9% at 36 weeks. 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 antenatally infected infants.

Immunocompetent women with prior *Toxoplasma* infection are protected from transmitting infection to the fetus. Immunocompromised pregnant patients previously infected with *T. gondii* may transmit infection to the fetus if their immune system is unable to suppress the parasite (i.e., HIV infection, lymphoma, immunosuppressive therapy).

III. MATERNAL/FETAL INFECTION

A. Clinical manifestations

1. Maternal infection is asymptomatic in more than 90% of women. However, symptoms can include fatigue, painless lymphadenopathy, and chorioretinitis.
2. Fetal findings on ultrasound (US) include hydrocephalus, brain, splenic and hepatic calcifications, hepatosplenomegaly, and ascites.

B. Diagnosis

1. Recommended maternal tests

a. Screening: Serum immunoglobulin M (IgM) and immunoglobulin G (IgG)

i. Detection and quantification of antibodies in pregnant women can determine whether and potentially when infection has occurred. Serology performed earlier in pregnancy (i.e., first trimester) is more helpful in determining whether *infection was acquired during pregnancy than serology drawn after 18 weeks' gestation*.

ii. *Toxoplasma* IgG and IgM. Initial testing can be done at a nonreference commercial lab. Negative results or positive IgG and negative IgM (old infection) should be reliable to rule out infection during current pregnancy if done before the third trimester. A positive or equivocal IgM should be confirmed at the local reference laboratory (e.g., Palo Alto Medical Foundation Toxoplasma Serology Laboratory, www.pamf.org/serology).

iii. IgM can be positive 2 weeks after infection and peaks in 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 whether 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, they would indicate that infection occurred prior to

conception. AC/HS compares IgG titers in sera against formalin (HS)–fixed with those against acetone (AC)–fixed tachyzoites. AC antigens detect acute IgG antibodies formed only during the acute stage of infection. Even with low or intermediate avidity, the rates of infection to fetus were low in mothers treated with spiramycin.

ii. IgA and IgE antibodies become undetectable earlier than IgM antibodies.

2. **Fetal testing.** Fetal infection must be confirmed by polymerase chain reaction (PCR) in amniotic fluid and US; when the pregnancy is >14 weeks, empiric treatment with pyrimethamine and sulfa must be started, till the results of PCR and USG are available.

   a. US is recommended monthly in women suspected of having acute infection acquired during or just before gestation. Fetal abnormalities detected include hydrocephalus; brain, splenic, and hepatic calcifications; splenomegaly; and ascites.

   b. Amniotic fluid PCR is recommended to diagnose fetal infection in cases when there is serologic evidence of acute infection or infection acquired during pregnancy cannot be ruled out, there is evidence of fetal abnormality on US, or a pregnant woman is significantly immunocompromised with a risk of reactivation. *The optimal time for the performance of an amniotic fluid PCR is at 18 weeks' gestation or later.* Gestational age at the time of maternal infection significantly influences the sensitivity and negative predictive value of the PCR testing. Sensitivity (NPV) of PCR testing is greatest when maternal infection occurs between 17 and 21 weeks (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. *A negative amniotic fluid PCR does not rule out fetal infection* (with exception if maternal infection occurred at <7 weeks, 100% NPV) because the accuracy range is wide and *parasite transmission from the mother to the fetus may be delayed.* The performance of amniotic fluid PCR is high when *tested 5 weeks after maternal infection*.

C. Treatment. For maternal infection confirmed or suspected to have occurred at <18 weeks' gestation, treatment with spiramycin is recommended in an effort to prevent placental transmission of toxoplasmosis. For mothers with confirmed or acquired infection at ≥18 weeks' gestation or those with positive amniotic fluid PCR or abnormal US findings of congenital toxoplasmosis, treatment with pyrimethamine, sulfadiazine, and folinic acid is recommended in an effort to prevent and treat fetal infection. Treatment should be instituted for mothers with acute infections and immunocompromised mothers with evidence of distant infection.

1. **Spiramycin** can potentially prevent placental transmission of *Toxoplasma* but does not cross the placenta so will not treat the fetus. There is some controversy to its efficacy because no clearly designed prospective trials have been performed. Incidence of congenital infection was decreased by up to 60% in some retrospective studies. This macrolide antibiotic reduces or delays 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 from maternal infection acquired earlier in gestation. Spiramycin

is available in the United States as an Investigational New Drug through the U.S. Food and Drug Administration. In a case series from Columbia, if mothers were treated with spiramycin, the infants were less likely to get ocular lesions. Similar observations were reported from Turkey. In a study from Italy, spiramycin combination with cotrimoxazole was more effective in preventing perinatal transmission when compared to spiramycin alone or pyrimethamine and sulfa combination. A large series from Brazil also demonstrated that this combination has teratogenic potential and should not be used prior to 18 weeks' gestation. It can cause bone marrow suppression, so patients should have complete blood count (CBC) monitoring during therapy. Antenatal treatment with pyrimethamine and sulfadiazine when compared with spiramycin resulted in lower transmission rates to the fetus; fewer babies had cerebral lesions.

2. For women with infection acquired ≥6 months before gestation, no treatment is recommended with exception of women who are immunosuppressed.

IV. NEONATAL INFECTION. A detailed technical report on the diagnosis, treatment, and prevention was published in 2017 by the AAP. A detailed experience on the management of toxoplasmosis was published from France in 2019.

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%) do not have overt signs of infection at birth. If untreated, a large proportion will demonstrate visual and central nervous system (CNS) deficits, including hearing impairment, learning disabilities, or mental retardation, several months to years later.

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 may manifest in the first 3 months of age.

4. **Sequelae or relapse in infancy through adolescence of a previously untreated infection.** Chorioretinitis develops in up to 85% of adolescents/young adults with previously untreated congenital infection.

B. Differential diagnosis. The clinical and laboratory findings are common to congenital infections caused by rubella, cytomegalovirus, syphilis, neonatal herpes simplex virus, HIV, 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. All neonates suspected of having congenital toxoplasmosis based on symptoms, maternal acute *T. gondii* infection during pregnancy, or maternal HIV with a history of chronic *T. gondii* infection should be evaluated. Diagnosis

may be made by serology, PCR, and less commonly pathology. *Combination of immunosorbent agglutination assay (ISAGA) IgM and IgA increased sensitivity and specificity to near 100%.* Currently, the vast majority of states in the United States do not screen or report congenital toxoplasmosis.

1. **IgG, IgM, and IgA.** Testing should be performed in a reference laboratory with special expertise in *Toxoplasma* serologic assays (i.e., Palo Alto Medical Foundation Toxoplasma Serology Laboratory or local reference laboratories in the respective countries). Sabin–Feldman dye test (IgG), ISAGA, and IgA enzyme-linked immunosorbent assay (ELISA) should be obtained from the infant. In addition, serologic testing should also be performed in the mother after birth in an effort to determine whether she could have been infected during gestation.
   - **a.** IgG appears within 1 to 2 weeks, 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 and IgA 77.4% of the time, and when either *IgM and IgA were taken into consideration, 93.3% were positive.*
   - **c.** In congenital toxoplasmosis, antibody production varies significantly and is changed by treatment.
   - **d.** Low avidity in newborns was associated with a high likelihood of vertical infection.
2. **PCR.** Blood, CSF, and urine should be tested in infants with suspected infection. A positive PCR is diagnostic of infection. When CSF PCR results were combined with IgM and IgA antibody results for the diagnosis of congenital toxoplasmosis, sensitivity for diagnosis was increased. Ideally, samples should be obtained prior to starting therapy.
3. **Other tests.** CSF cell count, CSF eosinophilia, and/or elevated protein can be seen.
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** is recommended at birth and every 3 months until 18 months of age followed by 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 is done 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.** Randomly distributed brain calcification and ventriculomegaly are noted on fetal US, in comparison to periventricular calcification in cytomegalovirus and Zika virus. 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 scan may detect calcifications not seen by ultrasonography. They may be single or multiple.

b. Hydrocephalus is usually due to periaqueductal obstruction. Massive hydrocephalus may develop in as quickly as 1 week.

9. Multidisciplinary consultation is usually helpful for patient management. Specialty consultation is typically required from the following:

a. Infectious diseases

b. Ophthalmology

c. Neurosurgery

d. Neurodevelopmental pediatrics

D. Treatment

1. Symptomatic infants

a. Combination therapy for 1-year duration has been associated with a decreased incidence of neurologic, cognitive, auditory, and retinal sequelae; resolution of acute symptoms; and improved outcomes. Patients should be weighed periodically and dosing adjusted accordingly. Monitoring for toxicity should occur weekly as well. Improved outcomes occur if infants are treated in the first year of life. *Infected newborns who are not treated or who receive short courses of treatment have poor outcomes including a high risk of developing new chorioretinal lesions later in life along with other long-term sequelae.*

i. Pyrimethamine at a dose of 1 mg/kg, is administered twice daily for 2 days, then once daily for 6 months, and then three times per week to complete a 12-month total course of the therapy (maximum 25 mg/dose) PLUS

ii. Sulfadiazine 50 mg/kg every 12 hours for 1 year PLUS

iii. Folinic acid 10 mg three times a week, administered until 1 week after completing pyrimethamine

iv. **Prednisolone** (0.5 mg/kg every 12 hours) may be added if CSF protein exceeds 1 g/dL or active chorioretinitis is present with lesions very close to the macula, until CFS protein <1 g/dL or resolution of severe chorioretinitis occurs. If steroids are to be used, they should be initiated after 72 hours of anti-*Toxoplasma* therapy.

2. Asymptomatic infection. The same regimen as used for symptomatic infants, but the treatment duration is shorter, for 3 months.

Adverse events

a. Most common adverse effect of pyrimethamine (a dihydrofolate reductase inhibitor) is neutropenia. Other adverse effects are are thrombocytopenia and anemia. CBC should be monitored weekly. Check levels at start, on day 15 of treatment, and monthly thereafter. Temporary cessation of pyrimethamine may be necessary if absolute neutrophil count (ANC) falls

below 800. Continue folinic acid. Treatment can be restarted after ANC is >800.

b. Adverse effects of sulfadiazine include hemolysis in infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency, bone marrow suppression, renal failure, and hypersensitivity. Alternative therapy for infants who develop allergy to sulfadiazine includes clindamycin.

c. The same treatment regimen is recommended for infants born to mothers infected with both HIV and *T. gondii*. However, combining these agents with antiretrovirals such as zidovudine may increase bone marrow toxicity.

Ventricular shunting for hydrocephalus is recommended when necessary. Early shunt placement (before 25 days of life) was associated with better cognitive outcomes and tended to better motor outcomes.

V. OUTCOMES. The National Collaborative Congenital Toxoplasmosis (NCCT) study has reported outcomes in a series of children with congenital infection. Treatment for 1-year duration significantly 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. Sixty-four percent of children with moderate or severe neurologic disease at birth 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. Long-term follow-up is recommended.

B. Hearing problems. Incidence of hearing loss (sensorineural) is as high as 28% in untreated infants; this can be reduced to near 0 with early and effective treatment.

C. 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.

These outcomes are significantly improved as compared to in previous studies of untreated patients or patients treated for a short duration.

D. Prevention. There are no recommendations on routine screening of all pregnancies, although there are suggestions that the French model of screening may reduce the burden of congenital toxoplasmosis. Belgium, Austria, France, Germany, Iran, and Tunisia suggest screening; Canada does not recommend screening.

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51 Syphilis

Gloria Heresi

KEY POINTS

- Syphilis transmitted from mother to baby in pregnancy can cause fetal/neonatal death, prematurity, and fetal growth restriction (FGR).
- Congenital syphilis may be asymptomatic for a few months, active untreated syphilis can affect nervous system, skeletal system, and have mucocutaneous manifestations.
- Prevention of congenital syphilis depends on the identification and adequate treatment of pregnant women with syphilis.
- No newborn should be discharged without determination of maternal serologic status for syphilis at least once during pregnancy and also at delivery.
- The most important risk factors for congenital syphilis are lack of prenatal health care (no serologic test in pregnancy) and maternal illicit drug use.
- Women with syphilis should be tested for human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs).
- Nontreponemal tests should be used to screen for syphilis and treponemal tests be used to confirm syphilis.
- Adequate treatment for pregnant women is defined as "completion of a penicillin-based regimen," *initiated 30 or more days before delivery*.
- The recommended treatment for congenital syphilis is aqueous crystalline penicillin G for 10 days.
- Treated neonates must have a nontreponemal test at 3 months.
- Patients with untreated syphilis are highly infectious until 24 hours of penicillin therapy is completed: Isolation must be ensured; people exposed in this period must have clinical follow-up for 3 weeks and lab tests at 3 months.

I. INTRODUCTION. 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/or long-term sequelae such as deafness and neurologic impairment. Prevention of congenital syphilis depends on the identification and adequate treatment of pregnant women with syphilis. Syphilis is a sexually transmitted infection caused by the spirochete Treponema pallidum, women can acquire the infection before or during any period of pregnancy.

II. CLINICAL CLASSIFICATION

A. Congenital syphilis results from transplacental passage of *T. pallidum* or contact with infectious lesions during birth. The risk of transmission to the fetus correlates largely with the duration of maternal infection—the more recent the maternal infection, the more likely the transmission to the fetus. During the primary and secondary stages of 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. Transplacental transmission of *T. pallidum* can occur throughout pregnancy.

1. **Clinical presentation.** Congenital infection may result in stillbirth, hydrops fetalis, prematurity, or a wide spectrum of symptoms and signs. Most affected infants will be asymptomatic at birth, but clinical signs usually develop within the first 3 months of life. The most common signs of early congenital syphilis (<2 years old) include hepatosplenomegaly, rash, condylomata lata, watery nasal discharge (snuffles), jaundice, anemia or edema, and skeletal abnormalities (osteochondritis, periostitis, epiphysitis, pseudoparalysis). Late congenital syphilis in an untreated older child (>2 years old) may have stigmata with bony changes (frontal bossing, short maxilla, high palatal arch, Hutchinson teeth, saddle nose), interstitial keratitis, and sensorineural deafness, among others.
2. **Lab criteria for diagnosis of congenital syphilis**
   Demonstration of T. pallidum in nasal secretions, body fluids, lesions, placenta, and umbilical cord or autopsy specimen by
   - **a.** Dark field microscopy
   - **b.** Polymerase chain reaction (PCR) or other direct molecular methods
   - **c.** Immunohistochemistry (IHC) or special stains (e.g., silver staining)
3. **Case classification**
   - **a. Confirmed**
     Case that is laboratory confirmed
   - **b. Probable**
     Infant whose mother had untreated or inadequately treated syphilis at delivery, or an infant who has a reactive nontreponemal test for syphilis and any one of the following:
     - **i.** Any evidence of congenital syphilis on physical examination
     - **ii.** Any evidence of congenital syphilis on radiographs of long bones
     - **iii.** A reactive cerebrospinal fluid (CSF) VDRL test
     - **iv.** An elevated CSF cell count or protein (without other cause)
       Abnormal CSF during the first 30 days of life: CSF WBC count >15 WBC/mm^3 or a CSF protein >120 mg/dL. After 30 days of life, more than 5 WBC and a protein greater than 40 are considered abnormal
4. **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 the mother, physical findings, and laboratory tests can help to make the diagnosis.

B. Maternal infection can be divided into three stages.

1. First stage or primary syphilis is manifested by one or more chancres (painless indurated ulcers) at the site of inoculation, typically the genitalia, anus, or mouth. It is often accompanied by regional lymphadenopathy. Lesions appear around 3 weeks after exposure and heal spontaneously in a few weeks.
2. Second stage or secondary syphilis is a disseminated process that occurs in around 25% of untreated patients, 3 to 6 weeks after the appearance of the chancre. The secondary stage is characterized by a polymorphic rash, most commonly maculopapular, generalized, and involving the palms and soles, sparing the face. Sore throat, fever, headache, diffuse lymphadenopathy, myalgias, arthralgias, alopecia, condylomata lata, and mucous membrane plaques may also be present. The symptoms resolve without treatment in 3 to 12 weeks, leaving the person completely asymptomatic. A latent period follows. Most women present at this stage.
   a. Latent syphilis is defined as "the period after infection" when patients are seroreactive but demonstrate no clinical manifestations of the disease.
   b. Early latent syphilis refers to infection <1 year.
   c. Late latent syphilis if initial infection is >1 year or indeterminate
3. Tertiary stage or tertiary syphilis usually occurs 4 to 12 years after the secondary stage in about one-third of untreated patients and is characterized by gummata, cardiovascular syphilis, especially inflammation of the great vessels, or neurosyphilis. These lesions are thought to be due to a pronounced immunologic reaction.

   Neurosyphilis may occur at any stage of the disease especially in human immunodeficiency virus (HIV) patients and in neonates with congenital syphilis. Early manifestations include syphilitic meningitis, uveitis, and neurovascular disease. Late manifestations include dementia, posterior column disease (tabes dorsalis), and seizures, among others.

III. EPIDEMIOLOGY.

Trends in congenital syphilis usually follow trends in primary and secondary syphilis among women, with a lag of 1 to 2 years.

The CDC reported that the rate of primary and secondary syphilis among women declined by 95.4% (from 17.3 to 0.8 cases per 100,000 females) during 1990 to 2004. And the rate of congenital syphilis declined by 92.4% (from a peak of 107.6 to 8.2 cases per 100,000 live births) during 1991 to 2005. Rates of both female primary and secondary and congenital syphilis increased during 2005 to 2008. During 2008 to 2012, rates of both female primary and secondary and congenital syphilis declined (from 1.5 to 0.9 cases per 100,000 population and from 10.5 to 8.4 cases per 100,000 live births, respectively). However, during 2012 to 2018, the rate of primary and secondary syphilis in women and congenital syphilis had increased each year.The year 2018 had the highest rate (33 cases per 100,000 live births) of congenital syphilis in the USA since 1991.

The most important risk factors for congenital syphilis are lack of prenatal health care and maternal illicit drug use, particularly cocaine. 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 test 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 failure of treatment in an infected pregnant woman.

IV. DIAGNOSIS OF SYPHILIS. Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. The CDC recommends additional testing at 28 weeks' gestation and again at delivery for women who are at an increased risk or live in communities with increased prevalence for syphilis infection. Routine screening of newborn sera or umbilical cord blood is not recommended because it does not prevent symptomatic congenital syphilis. No mother or newborn infant should leave the hospital without maternal serologic status having been documented at least once during pregnancy, and preferably again at delivery.

A. Serologic tests for syphilis

1. **Nontreponemal tests** include the RPR card test, the VDRL slide test, the unheated serum reagin (USR), and the toluidine red unheated serum test (TRUST). These tests measure antibody directed against a lipoidal antigen from *T. pallidum* and/or its interaction with host tissues. These antibodies give quantitative results, allowing establishment of a baseline titer, which ***allows evaluation of recent 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 with treatment demonstrates adequate therapy; a similar increase after treatment suggests reinfection.***

   Nontreponemal tests will be 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, 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. A cause of false-negative nontreponemal tests is the prozone phenomenon, a negative or weakly positive reaction that occurs with very high antibody concentrations. In this case, dilution of the serum will result in a positive test.

   In 1% of cases, a positive RPR or VDRL result is not caused by syphilis. This has been called a biologic false-positive (BFP) reaction and is probably related to tissue damage from various causes. Rarely, BFPs are seen as a result of pregnancy alone. Patients with BFPs usually have low titers (1:8 or less) and nonreactive treponemal tests. Patients with systemic lupus erythematosus may have a positive RPR or VDRL test result. The titer is usually 1:8 or less. Nontreponemal test results may be falsely negative in early primary syphilis, latent acquired syphilis of long duration, and late congenital syphilis.

   A reactive nontreponemal test positive in patients with classical symptoms indicates a presumptive diagnosis; however, *any positive nontreponemal test*

should be confirmed by one of the specific 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, and enzyme immunoassay (EIA). Although these tests are more specific than nontreponemal tests, they are also more expensive and labor-intensive and are therefore not used for screening. Rather, they are used to confirm positive nontreponemal tests. ***The treponemal tests correlate poorly with disease activity and usually remain positive for life, even after successful therapy, and therefore should not be used to assess treatment response.***

   In populations of low disease prevalence, treponemal tests can be used for screening, utilizing a rapid test or EIA format. Then, all positive patients would either be treated presumptively because the serious consequences of untreated infection far outweigh the effect of overtreatment or have a follow-up RPR or VDRL to determine whether they have active infection before treatment. This "reverse sequence screening" approach is associated with high rates of false-positive results (14% to 40%), and in 2011, the CDC reaffirmed that nontreponemal tests be used to screen for syphilis and that treponemal testing be used to confirm syphilis as the cause of nontreponemal reactivity. False-positive treponemal tests occur occasionally, particularly in other spirochetal diseases such as Lyme's disease, yaws, pinta, leptospirosis, and rat-bite fever; nontreponemal tests should be negative in these situations. Also, in some cases where antibodies to DNA are present, such as in systemic lupus erythematosus, rheumatoid arthritis, polyarteritis, and other autoimmune diseases, a false-positive FTA-ABS test result may occur.

B. CSF examination. CSF abnormalities in patients with neurosyphilis include increased protein concentration, increased WBC count, and/or a reactive CSF VDRL test. The CSF VDRL is highly specific but is insensitive. Therefore, a positive CSF VDRL test result is diagnostic of neurosyphilis, but a negative CSF VDRL test result does not exclude neurosyphilis. 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.***

V. EVALUATION AND TREATMENT OF INFANTS FOR CONGENITAL SYPHILIS.

No newborn should be discharged from the hospital until the mother's serologic syphilis status has been determined at least once during pregnancy and also at delivery. 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 confirmed by a treponemal test should be evaluated with the following:

1. Complete physical examination looking for evidence of congenital syphilis
2. Quantitative nontreponemal test (RPR or VDRL). This test should be performed on infant serum. 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. Pathologic examination of the placenta or umbilical cord using specific fluorescent antitreponemal antibody staining, if available
4. Darkfield microscopic examination or direct fluorescent antibody staining of any suspicious lesions or body fluids (e.g., nasal discharge)

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. The CDC recommends classifying infants evaluated for congenital syphilis into one of the following four scenarios:

1. **Scenario one**
   - **a. Proven or highly probable disease**
     - **i.** Abnormal physical examination consistent with congenital syphilis
     - **ii.** Nontreponemal titer that is fourfold higher than the mother's titer, i.e., 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.)
     - **iii.** A positive darkfield test or PCR of lesions or body fluids
   - **b. Recommended evaluation** (section V.A)
     - **i.** CSF analysis for VDRL, cell count, and protein concentration
     - **ii.** Complete blood count (CBC) with differential and platelet count
     - **iii.** Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brainstem response
   - **c. Recommended treatment regimens**
     - **i.** Aqueous crystalline penicillin G, administered as 50,000 units/kg/dose every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
     - **ii.** Penicillin G procaine 50,000 units/kg/dose intramuscular (IM) in a single dose daily for 10 days
2. **Scenario two (mother's treatment not complete)**
   - **a. Possible congenital syphilis.** Any neonate who has a normal physical examination AND a quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer AND one of the following:
     - **i.** Maternal treatment not given, inadequately treated, or has no documentation of having received treatment
     - **ii.** The mother was treated with erythromycin or any other nonpenicillin G regimen.
     - **iii.** Maternal treatment administered <4 weeks before delivery

b. Recommended evaluation (as in B.1. b)

c. Recommended regimens

i. Aqueous crystalline penicillin G 100,000 to 150,000 units/kg/day intravenous (IV), administered as 50,000 units/kg/dose every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

ii. Penicillin G procaine 50,000 units/kg/dose IM in a single dose daily for 10 days

iii. Penicillin G benzathine 50,000 units/kg/dose IM in a single dose

The penicillin benzathine can be given if the complete evaluation is 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 penicillin G should be given.

3. Scenario three

a. Congenital syphilis less likely. Neonates who have a normal physical examination and a serum quantitative nontreponemal titer the same as or less than fourfold the maternal titer and both of the following are true:

i. The mother was treated ***during pregnancy*** with a penicillin regimen appropriate for the stage of infection and >4 weeks before delivery.

ii. No evidence of maternal reinfection or relapse

b. Recommended evaluation

i. Such infants require no further evaluation.

c. Recommended regimen

i. Penicillin G benzathine 50,000 units/kg/dose IM in a single dose

ii. Another approach involves not treating the infant but providing a close follow-up every 2 to 3 months for 6 months for infants whose mother's nontreponemal titers decrease at least fourfold after proper therapy for early syphilis or remained stable for low-titer, latent syphilis (VDRL <1:2; RPR <1:4).

4. Scenario four

a. Congenital syphilis unlikely. Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer and both of the following:

i. Adequate maternal treatment ***before pregnancy***

ii. Maternal nontreponemal titer remained low and stable (serofast) before and during pregnancy and at delivery (VDRL <1:2 or RPR <1:4).

b. Recommended evaluation

i. No evaluation is recommended.

c. Recommended regimen

i. 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 whether the child has congenital or acquired syphilis. Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

1. Recommended evaluation (as in B.1. b)

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. If the infant or child has no clinical manifestations of congenital syphilis and the evaluation (including the CSF examination) is normal, treatment with 3-weekly doses of penicillin G benzathine 50,000 units/kg IM can be considered. 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.

D. Special considerations

1. Penicillin allergy. If an infant develops an allergic reaction, presumed secondary to penicillin, he or she should be desensitized and then treated with penicillin. Skin testing is not established for infants.

2. Penicillin shortage. If IV aqueous penicillin G availability is limited, substitute with procaine penicillin IM as a single daily dose for the same duration. If both aqueous and procaine penicillin are not available, then a 10-day course of IV ceftriaxone can be considered with clinical and serologic follow-up; evidence is insufficient to support the use. CSF examination may be repeated at 6 months if the initial evaluation was abnormal. Ceftriaxone must be used with caution if there is jaundice as it can displace bilirubin.

3. For premature infants (in either scenario two or three) who might not tolerate IM injections because of decreased muscle mass, ceftriaxone can be considered IV.

VI. SCREENING AND TREATMENT OF PREGNANT WOMEN FOR SYPHILIS

A. All pregnant women should be screened early in pregnancy for syphilis with a nontreponemal STS. Testing should be performed at the first prenatal visit and, in high-risk populations, the test should be repeated at the beginning of the third trimester (28 to 32 weeks' gestation) and at delivery. 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 from the hospital until the test 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.

B. Pregnant women with a reactive nontreponemal STS confirmed by a reactive treponemal STS should be treated regardless of the stage of pregnancy unless

previous adequate treatment is clearly documented and follow-up nontreponemal titers have declined at least fourfold. Treatment depends on the stage of infection:

1. Primary and secondary syphilis. Penicillin G benzathine 2.4 million units IM in a single dose. Some experts recommend a second dose of 2.4 million units IM 1 week after the first dose.
2. Early latent syphilis (without neurosyphilis). Treatment is the same as in primary and secondary syphilis.
3. Late latent syphilis (without neurosyphilis). Penicillin G benzathine 2.4 million units administered as three single doses at 1-week intervals
4. Tertiary syphilis (without neurosyphilis). Penicillin G benzathine 2.4 million units administered as three single doses at 1-week intervals
5. 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.
6. 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 the 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.
7. 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.
8. Adequate treatment for pregnant women is defined as "completion of a penicillin-based regimen," in accordance with CDC treatment guidelines, appropriate for the stage of infection***, initiated 30 or more days before delivery***.
9. The Jarisch–Herxheimer reaction—the occurrence of 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.
10. If a mother is treated for syphilis in pregnancy, monthly follow-up should be provided. A sustained fourfold decrease in nontreponemal titer should be seen with successful treatment.

    All patients with syphilis should be evaluated for other sexually transmitted diseases (STDs), such as chlamydia, gonorrhea, hepatitis B, and HIV.

VII. FOLLOW-UP OF INFANTS TREATED FOR CONGENITAL SYPHILIS. All neonates with reactive nontreponemal tests should receive careful follow-up examinations and nontreponemal titer every 2 to 3 months until the test becomes nonreactive. In the

neonate who was not treated because unlikely infected 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. Neonates with negative nontreponemal tests at birth born to mothers who were seroreactive at the time of delivery should be retested at 3 months to rule out incubating congenital syphilis. Treated neonates who exhibit persistent nontreponemal test titers by 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 require retreatment for possible neurosyphilis and should be managed in consultation with an expert.

VIII. INFECTION CONTROL

A. Isolation of hospitalized patient. *Red Book 2015* 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 ***until 24 hours of treatment has been completed*** because moist open lesions, secretions, and possible blood are contagious in all patients with syphilis.

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 first 24 hours of therapy*** should be examined clinically for the presence of lesions 2 to 3 weeks after contact. Serologic testing should be performed and repeated 3 months after contact or sooner if symptoms occur. Infants and their mothers at risk for syphilis or those who are infected with syphilis should be evaluated for other STDs such as hepatitis B, gonorrhea, chlamydia, and HIV.

Suggested Readings

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52 Tuberculosis

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KEY POINTS

- Congenital tuberculosis (in-utero transmission of infection) is very rare.
- Neonatal (congenital) tuberculosis is associated with very high mortality, delay in diagnosis and therapy is a major determinant.
- High index of suspicion in pregnancy is necessary in populations where TB infection is high –cough (any duration), fever (may not be present in pregnancy), poor weight gain are nonspecific; absence of these symptoms has high negative predictive value.
- In pregnancy, immuno-suppression results in very few symptoms; most mothers often manifest in immediate postpartum period with cough/fever. Some asymptomatic mothers are diagnosed after neonatal disease is identified.
- Signs and symptoms of neonatal TB include a sepsis-like episode that does not respond to empiric antibiotics or a presentation consistent with congenital infection.
- Diagnostic criteria for congenital TB are the following:
  - Proved tuberculous lesions such as positive smear or culture, AND one of the following:
    - Lesions in the first week of life
    - Primary hepatic complex or caseating hepatic granulomas
    - TB infection of the placenta or maternal genital tract
    - Exclusion of the possibility of postnatal transmission
    - Lab confirmation of neonatal tuberculosis is challenging. Tuberculosis skin test may be negative, ESR may not be raised; AFB from gastric aspirate/tracheal secretions may be positive, DNA test from bronchial secretions (ventilated babies) have high sensitivity. Chest x-rays are almost always abnormal but findings are nonspecific. CT abdomen to look for liver lesions is advised in suspected congenital tuberculosis.
- All neonates suspected of having congenital TB should be put in airborne isolation, and all visitors should be screened for TB disease.
- The health department should be notified of all suspected TB disease cases, so as to start a contact investigation.
- The neonate with possible congenital TB should be evaluated for disseminated disease and meningitis. The cerebrospinal fluid (CSF) must be examined.
- Treatment should always include the following:
  - Rifampin
  - Isoniazid
  - Pyrazinamide

- Ethambutol
- Breast-fed newborns being treated with isoniazid should be given pyridoxine supplementation at a dose of 1 mg/kg/day.
- In India, recent National Tuberculosis Elimination Program 2019 endorses daily treatment for TB.

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 at the outset (Table 52.1).

Over one-fourth of the world's population is infected with *M. tuberculosis*. According to the WHO Global TB Report 2020, at least 10 million people developed TB disease, and almost 1.4 million people died as a result. The World Health Organization (WHO) estimates that 1.2 million children developed TB disease in 2019.

The advent of effective anti-TB medications in the 1950s resulted in a declining TB prevalence. In the mid-1980s, the HIV epidemic caused a sudden upsurge in cases (20% increase overall and 40% increase among children).

II. TRANSMISSION AND PATHOGENESIS. Transmission of *M. tuberculosis* most commonly occurs when an individual expectorates infectious droplet nuclei, which may

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 gamma release assay result (defined in the text), a normal physical examination, and a chest radiograph that either is 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 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, through either 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.

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 less infectious than those who are AFB smear positive, but many can still transmit the organism. Fomites and other secretions rarely cause transmission.

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 "paucibacillary 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, newborns 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 by hematogenous route 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 the disease. The exception to this occurs in *infants, who are at a 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% risk 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, 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. Diagnosing tuberculosis infection. TB infection is defined as having evidence of an immune response to *M. tuberculosis*–related antigens. *It is determined through use of either the Mantoux tuberculin skin test (TST) or an interferon gamma release assay (IGRA).*

1. **The TST** is a delayed-type hypersensitivity test to determine whether 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 current recommendation uses 2TU PPD RT23, which is equivalent to 5TU PPD-S available in the United States. Using a 26-gauge needle, 0.1 mL is injected intradermally, typically on the middle third of the ventral 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 (see Table 52.2).

2. **IGRAs** are blood tests that detect the production of interferon gamma, a chemical routinely released by immune cells as they combat TB organisms. They 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 whether someone has been infected with *M. tuberculosis*, but they do not differentiate between infection and disease. Although PPD contains hundreds of mycobacterial antigens, the *IGRA tests utilize 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, except in children <2 years of age; the American Academy

Table 52.2. Definition of Positive Tuberculin Skin Test Results in Children

Induration ≥5 mm	Induration ≥10 mm	Induration ≥15 mm
Clinical evidence of TB disease	Recent immigration from a high-prevalence country	Age ≥4 years without any risk factors
Close contact with a person with known or suspected TB disease	Children exposed to individuals who are infected with HIV, injectable drug users, incarcerated individuals, or residents of nursing homes	
Radiographic changes consistent with active or previous TB Immunosuppression due to medications, immunosuppressive conditions, or HIV infection	Medical conditions such as lymphoma, diabetes, renal failure, and malnutrition Age <4 years	

TB, tuberculosis.

of Pediatrics currently *recommends against using IGRAs in children younger than 2 years* because there are limited data regarding the reliability of a negative test result, and a false-negative result has important implications because these children are more prone to rapidly advance to severe disease.

3. **Microscopy.** The tissue (sputum in mothers/gastric aspirate in neonates) is stained by Ziehl–Neelsen staining which helps in identifying acid-fast bacteria. Fluorescence staining is also an acceptable form of staining. In neonates, the middle ear fluid may also be tested.
4. **Culture**. The following culture media systems may be used:
   - Lowenstein–Jensen
   - Automated liquid culture systems—BACTEC MGIT 960
   - Drug sensitivity testing
5. **Rapid molecular diagnostic testing**
   - Line probe assay for mycobacterium tuberculosis (MTB) complex
   - Nucleic acid amplification test (NAAT) Xpert MTB

   In infants, gastric aspirate is taken for the isolation of tubercular bacilli.

III. MATERNAL TUBERCULOSIS. 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 the disease. The clinical suspicion of TB in pregnancy may be challenging as the symptoms of TB may be ascribed to or masked by the pregnancy. Women who are contacts to a current or previous TB case should be tested 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 affect the woman or the fetus. Similarly, the IGRA results do not appear to be affected by pregnancy. The obstetric complications include spontaneous abortion, small-for-date uterus, preterm labor, low birth weight, and increased neonatal mortality.

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 examination 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 is 300 mg of isoniazid (INH) taken daily. Pyridoxine supplementation is recommended for all pregnant women taking INH because deficiency is more likely than in general population, pyridoxine deficiency can cause a peripheral neuropathy. INH preventive therapy (IPT) in HIV-positive mothers during pregnancy (immediate) was associated with adverse outcomes to

the mother and fetus when compared to IPT postpartum (deferred). Composite outcomes of preterm birth, low birth weight, and neonatal mortality were higher.

When the pregnant woman has TB infection, it is recommended that the contacts of the household and extended family be investigated for TB infection and disease. The purpose is to find, diagnose, and treat potentially infectious individuals that the child could be exposed to, thereby minimizing the 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 in the family, her infant does not need to be treated for TB infection or disease.*

B. Management of maternal 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 the 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. 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 apexes 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 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 drug susceptibility testing takes 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.

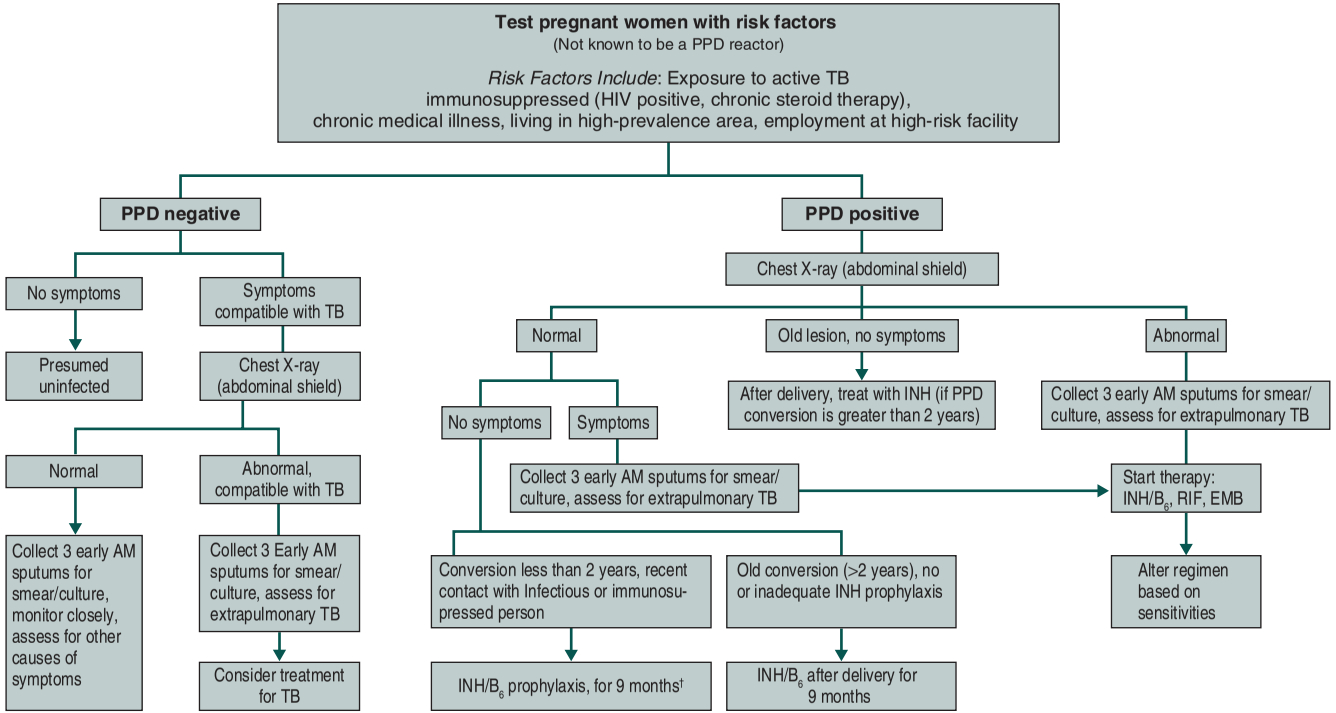

Figure 52.1. Diagnosis and treatment of tuberculosis in the pregnant woman. EMB, ethambutol; INH, isoniazid; PPD, purified protein derivative; RIF, rifampin; TB, tuberculosis.

†Although there are no known teratogenic effects of isoniazid, some experts recommend waiting until the second trimester before initiating treatment for tuberculosis infection.

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. GeneXpert MTB/RIF (Cepheid, Sunnydale, CA) is a nested real-time polymerase chain reaction (PCR) that tests for *M. tuberculosis* DNA as well as the genetic material that confers resistance to the first-line drug rifampin (RIF). GeneXpert is less sensitive than culture but yields results within 2 to 3 hours. The sensitivity is higher in instances of AFB smear–positive disease. Presently, GeneXpert or cartridge-based nucleic acid amplification test (CBNAAT) is considered the first-line investigation in the pediatric population (paucibacillary forms of TB); early detection and diagnosis of multidrug resistance provide clinical benefits. Molecular line probe assays can detect low-level or high-level resistance to inhA gene and resistance to rifampicin. Multidrug resistance is defined as resistance to two categories of drugs (INH and RIF).

4. **Treatment**

   a. **Pregnant women.** Treatment in pregnant women differs in that the initial regimen often includes only INH, RIF, and ethambutol (EMB). Pyrazinamide (PZA) is often excluded because there is a smaller amount of data on its safety during pregnancy. Some experts do not recommend its routine use in pregnant women, although 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 three first-line drugs are considered relatively safe for the fetus, and the risks of poorly treated disease far outweigh the risks of treatment.* In pregnancy, drug compliance may be limited due to vomiting. Hence, supervision therapy is mandatory. Other anti-TB drugs that are contraindicated for pregnant women include kanamycin, amikacin, capreomycin (hearing loss), and the fluoroquinolones (inadequate safety data). If drug resistance is found that requires use of medications with unknown or adverse fetal effects, consultation with a TB expert is recommended.

   b. **Lactating women.** 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 taking INH or whose mother is taking the drug. Breastfeeding mothers may take their medication immediately after breastfeeding.

   c. **Preventing spread of infection.** 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 a contact investigation 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. CONGENITAL TUBERCULOSIS

A. 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. 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 secondary 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, gastrointestinal (GI) tract, spleen, kidneys, meninges, and skin.

If the placenta develops a caseous lesion that ruptures into the amniotic fluid, 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. Primary foci may be found in the lungs or in the GI tract. The disease can then 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 diagnostic criteria of congenital TB were established by Cantwell et al. in 1994 and the neonate must have proven tuberculous lesions and at least one of the following:

- Lesions in the first week of life
- Primary hepatic complex or a caseating hepatic granuloma
- Tuberculous infections of the placenta or maternal genital tract
- Exclusion or postnatal transmission by thorough investigation of contacts

B. Symptoms. The clinical signs and symptoms of congenital TB vary in relation to the intensity of transmission as well as the site of the 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 is similar to that of 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.

C. 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.

D. Investigate mother. Investigation of congenital TB should include examination of placenta or uterine tissue. 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 consider to perform a uterine dilation and curettage because endometrial specimens often yield positive culture results.

E. Microbiology studies in infant. 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.* Yield of acid-fast smear and culture is higher, mostly in congenital TB. Molecular diagnosis techniques enable early diagnosis and detection of drug resistance mutations. TST is usually negative, and IGRAs have low sensitivity.

V. POSTNATAL TRANSMISSION OF *M. 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 4 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 TUBERCULOSIS DISEASE.

A. DRUG THERAPY. Once the diagnosis of congenital or postnatal TB is *suspected*, treatment should be initiated promptly. Due to the rarity of the disease, definitive recommendations of anti-TB drugs in neonates are limited. *Neonates and infants have a high risk of developing disseminated disease or meningitis*; if the organism is susceptible to first-line medications, the initial four-drug regimen (INH, RIF, PYZ, and EMB or streptomycin) should be continued for the first 2 months of therapy, followed by treatment with INH, RIF, and EMB for an additional 7 to 10 months, *a total duration of treatment of 9 to 12 months.* If TB meningitis is suspected, 2 mg/kg/day of prednisone (or equivalent corticosteroid) should be administered for the first 4 weeks, followed by a tapering dose over 4 weeks to prevent the development of hydrocephalus or infarcts caused by vasculitis. Neonatal TB always should be managed with the help of an expert in TB.

The recommended drug doses are as follows:

- Rifampicin: 10 to 20 mg/kg/day
- INH: 10 to 15 mg/kg/day
- Pyrazinamide: 15 to 30 mg/kg/day
- EMB: 15 to 25 mg/kg/day
- Streptomycin: 20 to 30 mg/kg/day

For infants weighing more than 4 kg, fixed drug combinations are recommended; for babies less than 4 kg, follow the above-mentioned daily dose regimen for the treatment of congenital TB.

The current Indian guidelines (2019), as well as the WHO, recommend the usage of a fixed- drug combination (FDC) based on weight category for children.

According to the guidelines, anti-TB drug formulations are available as FDC:

- 3 FDC: H50, R75, Z150
- 2 FDC: H50, R75 +

For infants weighing 4 to 7 kg, the schedule is a single tab "3 FDC" + single tab E100 in the intensive phase and single tab "2 FDC" + single tab E100 in the continuation phase.

B. Respiratory isolation

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.

C. 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 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. 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

If the mother or a 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. The mother can breastfeed her child.

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 may 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.* If the mother is suspected of having MDR-TB disease, an expert in TB disease treatment should be consulted. When the mother and the 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*.

Mothers with active-phase TB can breastfeed once they have become smear negative after having received appropriate treatment.

Women with drug-susceptible TB disease taking anti-TB drugs can breastfeed, keeping in mind the cough hygiene. Breast-fed newborns being treated with INH should be given pyridoxine supplementation at a dose of 1 mg/kg/day.

Once congenital TB is excluded in the baby, INH (10 mg/kg/day) and pyridoxine (10 mg/day) are given for 6 months.

VIII. INDIAN GUIDELINES ON MANAGEMENT OF TB IN PREGNANCY. TB affects as many as 2 lakhs pregnant women globally, 20% of these are in India. WHO recommends screening of pregnant women in populations where TB prevalence is high (> 100/100, 000). Recently (in 2020), Government of India published a "Collaborative framework for management of TB in pregnancy". This is an important component of the national campaign to eliminate TB from India by 2025. The problem of high prevalence of disease in India is complicated by malnutrition. Poor nutrition is associated with severe disease, toxicity of drugs, and relapse of infections. There is specific focus on improving nutrition. Effective treatment of TB in pregnant women is critical for newborn survival.

IX. BACILLE CALMETTE-GUÉRIN VACCINATION. BCG vaccines are among the oldest vaccines worldwide. They are attenuated strains of *M. bovis*, a close relative of *M. tuberculosis*. 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 very limited. The Centers for Disease Control and Prevention 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 children; patients with congenital immunodeficiency or malignancy; or patients on immune-modulating drugs such as corticosteroids, chemotherapy, or radiation. BCG vaccination can be given safely to stable infants who are preterm and/or have LBW. Early BCG vaccination has a similar safety profile, reactogenicity, and TST conversion rate as delayed vaccination.

It should be noted that after BCG immunization, the child may develop a positive reaction to a TST. 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.

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53 Antimicrobials in NICU

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KEY POINTS

- A dangerously high incidence of antimicrobial resistance is being reported from hospital-based studies from Asia.
- Antimicrobial stewardship is the way one organizes oneself for selection and usage of antimicrobials.
- Ampicillin and gentamicin may not cover most infections in the Asian setting.
- Adherence to protocols on starting, stopping, and choosing antimicrobials is critical to decrease antimicrobial resistance.
- Faith of clinicians on the antibiotic protocols will depend on periodic audits of regional data on common microbes and their sensitivity to antimicrobials.
- Examples of decision support systems on when to start antibiotics are the following:
  - NICE* neonatal early onset sepsis guidance
  - Neonatal early onset Sepsis Risk Calculator (SRC)
  - European Medicine Agency (EMA) sepsis criteria
- Neonates with persistent/severe signs of infection must be treated with antibiotics; others may be observed closely, and antibiotics may be withheld.
- The choice of antibiotic depends on host, bug, and drug factors.
- Blood culture (1 mL) must be drawn before the start of antibiotics.
- A clinician must document the reason to continue antibiotics despite negative cultures.
- Sepsis screen must be performed only if it alters the antibiotic decision.
- Antiviral and antifungal agents are underutilized.
- Treatment of congenital cytomegalovirus (CMV) involving the nervous system is associated with improved hearing outcomes.
- Serious postnatal CMV infections (pneumonia) may require treatment.
- Acyclovir is safe and must be started early when herpes simplex virus (HSV) is suspected (culture-negative sick neonates presenting with sepsis-like illness after 1 week of life).
- Varicella infection prophylaxis with varicella zoster immunoglobulin (VZIG)/intravenous immunoglobulin (IVIG) may be indicated in immunocompromised babies.
- Amphotericin is the preferred empiric antifungal in neonates; it is well tolerated.
- Fluconazole prophylaxis may be indicated in extremely low-birth-weight (ELBW) neonates in units with a high incidence of invasive candidiasis.

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Neonatal sepsis is a major health problem; the global incidence is reported to be as high as 2,202 per 100,000 live births (extrapolated to 3 million cases per year!) and case fatality rate is 11% to 19%. In a recent prospective study from India, the incidence of total sepsis was 14.3% (95% confidence interval [CI] 13.8 to 14.9) and of culture-positive sepsis was 6.2% (5.8 to 6.6). Case fatality in the same study was nearly 50% in culture-positive babies. The problem is even greater in the neonatal intensive care units (NICU). Data even from high-income countries show a high incidence (38%) of culture-positive sepsis among extremely low-birth-weight (ELBW) babies. In the low- and middle-income countries (LMIC), the risk of serious bacterial infections is 3 to 20 times higher. Gram-negative sepsis is more common (60%), and it is more fulminant and fatal. Added to the challenges is *the high incidence of resistance to most antibiotics*; this places the infected babies at near-total fatality. An estimated 215,000 babies die each year in India, China, Pakistan, Nigeria, and Democratic Republic of Congo put together, possibly due to infection with resistant microbes.

The problems of antimicrobial resistance in LMIC are partly due to *lack of uniform protocols for antimicrobial use*. The way forward is that clinicians have clear knowledge of right indications, dose, route, schedule, dispensing, and drug interactions peculiar to neonates (especially preterm).

The antimicrobial choice must be based on scientific knowledge of the drug (drug factor), the clinical scenario (host factor), and the common microbes in the setting and their reported sensitivity (bug factor).

Antimicrobial prescriptions are possibly the most frequent decisions made in any intensive care unit. NICU has a few added challenges:

- Neonates are immunocompromised; preterm babies are extremely vulnerable.
- Case fatality of neonatal sepsis is exponentially higher compared to that of adult or pediatric population.
- Hospital stay of NICU babies is exceptionally long, can be months!
- Symptoms and physical signs cannot reliably guide antimicrobial decisions in neonates.
- The metabolism of antimicrobials in the liver, handling of drug by the kidney, and the compartments in which antimicrobials are distributed are totally different from those in adults and children.
- In the Asian region, only a few antimicrobials are commercially prepared and packaged for neonates; this adds to risks of incorrect storage and dispensing.

The chapter describes antimicrobial science peculiar to neonates, in a ready-to-use capsule, and is not a comprehensive guide. The neonatologist must ***refer a standard drug formulary for complete information*** on dosing, preparation and dispensing, adverse effects (AE), and interactions of the antimicrobials.

The chapter will be organized as follows:

- When is starting the antimicrobial justified (when one may consider waiting)?
- What minimum lab work must be done before starting?
- How to choose the empiric antimicrobial?
- When to stop?

We will discuss under the following three sections:

I. Antibiotics in NICU

II. Antifungals in NICU

III. Antivirals in NICU

I. ANTIBIOTICS IN NICU

A. How can I be reasonably sure that starting an antibiotic is justified?

"Antibiotics kill bacteria, not your anxiety. Stop the 'just-in-case' indications."

As some of the asymptomatic neonates delivered to mothers with risk factors for early onset neonatal sepsis (EONS) may become seriously ill hours after looking well, antibiotics are started by most neonatologists in the setting of EONS risk factors. This results in 200 times overuse of antibiotics. Neonatologists also start antibiotics for the safety of a baby, when symptomatic, and promise to stop when the infection is excluded. But the reality is that there is a paucity of universally accepted, evidence-based decision support systems to guide starting or stopping antibiotics in neonates; and none of them are developed or validated for the Asian region.

Survival of infected neonates is directly associated with *the time of administration of the first antibiotic dose*. Hence, any delay in the start of antibiotics, when an infection is likely, may be detrimental. Although the decision to "not start" an antibiotic may never be foolproof, there are guidelines to suggest when one must preferably start. A simplified approach is outlined in the Figure 53.1. Three decision support systems that have been extensively used are described.

NICE neonatal early onset sepsis guidance, neonatal early onset Sepsis Risk Calculator (SRC), and European Medicine Agency (EMA) sepsis criteria are some of the well-evaluated decision support systems; they take into account perinatal

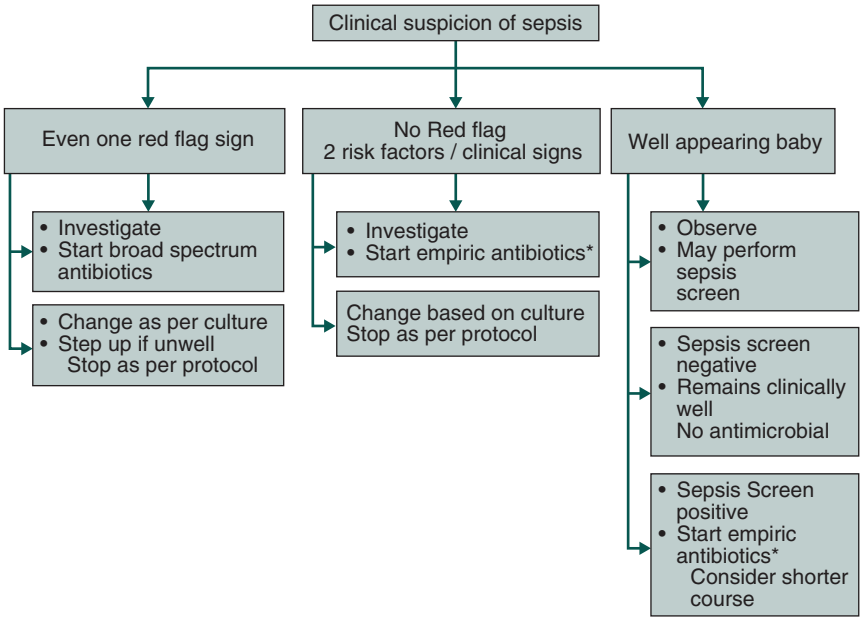

Figure 53. 1. Approach to antibiotics prescription. *Empiric antibiotics - narrow spectrum based on regional antibiogram

risk factors, clinical condition of the neonate, and lab tests to select a group of babies, in whom the risk of infection is high and withholding antibiotic may not be justified. Although these decision support systems have been evolved and validated in entirely different settings (high-income countries, with group B *Streptococcus* [GBS] and coagulase negative Staphylococcus [CONS] as the commonest cause), the principles are highly scientific and may be adapted in the Asian region. The decision support systems are far from perfect, but surely will make the process of decision making objective and available to audit.

1. NICE neonatal early onset sepsis guidance

- EONS has been discussed in detail in Chapter 49.
- In the setting of EONS, in babies with *any red flags, or with two or more "non–red flag" risk factors or clinical indicators* (Table 53.1), perform investigations and start antibiotic treatment. Do not delay starting antibiotics pending the test results.

Table 53.1. Clinical Indicators of Possible EONS, Including "Red Flags"

Red flag (any one)
Signs of shock
Seizures
Need for mechanical ventilation in a term baby
Respiratory distress, **starting** more than 4 hours after birth
Suspected or confirmed infection in another baby in the case of a multiple pregnancy
Clinical indicators or risk factors (any two)
■ *Risk factors*
□ Prelabor rupture of membranes
□ Preterm birth following spontaneous labor (before 37 weeks' gestation)
□ Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth
□ Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis
■ *Clinical indicators*
□ Altered behavior or responsiveness
□ Altered muscle tone (e.g., floppiness)
□ Feeding difficulties (e.g., feed refusal)
□ Feed intolerance, including vomiting, excessive gastric aspirates, and abdominal distension
□ Abnormal heart rate (bradycardia or tachycardia)
□ Signs of respiratory distress
□ Hypoxia (e.g., central cyanosis or reduced oxygen saturation level)

Table 53.1. Clinical Indicators of Possible EONS, Including "Red Flags" *(Continued)*

▫ Jaundice within 24 hours of birth
▫ Apnea
▫ Signs of neonatal encephalopathy
▫ Need for cardiopulmonary resuscitation
▫ Need for mechanical ventilation in a preterm baby
▫ Persistent fetal circulation (persistent pulmonary hypertension)
▫ Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors
▫ Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulation (international normalized ratio greater than 2.0)
▫ Oliguria persisting beyond 24 hours after birth
▫ Altered glucose homeostasis (hypoglycemia or hyperglycemia)
▫ Metabolic acidosis (base deficit of 10 mmol/L or greater)
▫ Local signs of infection (e.g., affecting the skin or eye)
The questions on GBS have been omitted from the table. Adapted from the NICE guidance on EONS.

- In babies without red flags and only one risk factor or one clinical indicator, using clinical judgment
  - Consider whether it is safe to withhold antibiotics.
  - Continue ***monitoring for at least 12 hours***.

2. **Neonatal Sepsis Risk Calculator.** Using this tool, the risk of EONS can be calculated in neonates born ≥34 weeks' gestation. It takes into consideration maternal risk factors and the neonate's clinical presentation.
   The variables to be entered into the calculator include the following:
   - Incidence of EONS in the institution (per 1,000 live births)
   - Gestation at birth
   - Highest maternal temperature (antepartum)
   - Duration of rupture of membranes
   - Type of intrapartum antibiotics (broad spectrum or GBS specific) and timing of administration in hours prior to birth
   - Maternal GBS status (relevance to Asia not known)

   The above-mentioned details provide the risk of EONS at birth. EONS risk is further calculated based on clinical examination. Babies are classified as "appearing well", '"equivocal" or "clinical illness" (Table 53.2). The calculator guides the clinician to one of the following decisions:
   - Strongly consider starting empiric antibiotics.

Table 53.2. Details to Be Entered into Early Onset Neonatal Sepsis Calculator

EONS Risk after Clinical Examination	Infant's Clinical Presentation
Well appearing	No persistent physiologic abnormalities
Equivocal	***One sign persisting (≥4 hours)*** ***Two or more signs (≥2 hours)*** Physiologic instability ■ Tachycardia (HR ≥160 bpm) ■ Tachypnea (for ≥60 breaths per minute) ■ Temperature instability (>100.4/<97.5°F) ■ Respiratory distress not requiring oxygen
Clinical illness	■ Persistent need for HFNC/CPAP/ventilation ■ ***Need for oxygen*** for ≥2 hours to maintain saturation of 90% ■ Hemodynamic instability, ***need for vasoactive drugs*** ■ Neonatal encephalopathy (Apgar at 5 minutes <5, seizures)

HR, heart rate.

- Draw blood culture; ***observe vitals 4 hourly for 24 hours***.
- No culture, no antibiotics

3. **European Medicines Agency (EMA) sepsis criteria.** Experts agreed on the following operational definitions for sepsis: early onset sepsis (onset in the first 72 hours after birth inclusive) and late-onset sepsis (onset more than or equal to 72 hours after birth); up to 44 weeks of corrected age:
   - Presence of at **least two clinical symptoms and at least two laboratory signs** (Table 53.3) in the presence of or as a result of suspected or proven infection (positive culture, microscopy, or polymerase chain reaction [PCR])

   All the three decision support systems discussed use ***persistent clinical signs, two or more clinical signs, or red flag signs*** (presence of one serious

Table 53.3. Operation Definition of Sepsis (EMA Sepsis Criteria)

Clinical Signs	Lab Signs
Modified body temperature	WBC count
Cardiovascular instability	Immature to total neutrophil ratio
Skin and subcutaneous lesions	Platelet count
Respiratory instability	C-reactive protein or procalcitonin
Gastrointestinal	Metabolic acidosis
Nonspecific	

WBC, white blood cell.

sign) along with risk factors and lab parameters to select a group of babies in whom antibiotics are indicated. In babies not meeting these criteria, one may choose to observe (12 to 24 hours) and not start antibiotics, although the question when one need not start antibiotics may never be perfectly answered!

B. What should I do, before I start antibiotics?

1. **Blood culture.** The gold standard for the diagnosis of neonatal sepsis is blood culture. A bacterial growth on blood culture confirms infection (except an uncommon growth of a contaminant). If no bacteria are grown, but the neonate is sick, the treating team is unable to conclude "no infection" and withhold antibiotics. The nonavailability of reliable microbiology facilities is a limiting factor in LMIC. There is also a falsely held belief that there may not be enough bacteria to grow in the lab, but they are significant enough to causes sepsis. This is not true. The reasons for cultures to be falsely negative include the following:
   - Insufficient blood volume inoculated to culture bottle (1 mL is ideal; there is a 10% to 40% decrease in detection rated by taking only 0.5 mL)
   - Antibiotic administered prior to drawing blood culture (or mother on antibiotics prior to delivery)

   There is robust evidence that if the baby has bacterial load sufficient to cause a disease, the lab will be able to culture it. Thus, proper collection technique, enough blood culture volumes, and immediate entry of culture bottle into culture systems will improve detection rates.

   A pediatrician must document his or her clinical reason to continue antibiotics despite negative cultures.
2. **Rapid molecular diagnostics—polymerase chain reaction.** Detection of the microbe may be improved by rapid molecular diagnostics (PCR); although false positives are possible, a negative report should increase confidence in stopping antibiotics. Currently, availability of the test and costs limit its utility. Even PCR may be falsely negative in a few cases, thus not allowing 100% surety in withholding antibiotics. Fast I(n)dentification of Pathogens in Neonates (FINDPATH-N) is a prospective study that plans to use pathogen-targeted next-generation sequencing; this is expected to be faster and more sensitive.
3. **Sepsis screens.** Various biomarkers have been evaluated as surrogates for culture in the diagnosis of neonatal sepsis; they are adjuncts in classifying sick babies as "most likely infected" or "clear of infection" in the setting of negative cultures. Currently available biomarkers (C-reactive protein [CRP]) may become positive late in the course of infection and, hence, one cannot withhold antibiotics even if the biomarker is negative. The biomarkers may be falsely abnormal in babies with no infection and may reflect only inflammation. Biomarkers commonly used are the following:
   - **Complete blood count (CBC)** is neither sensitive nor specific. The normal range of total white blood cell (WBC) count values varies significantly in the early hours of life, making interpretation difficult.
   - CBC and **absolute neutrophil count (ANC)** are more predictive, when low.
   - **Immature to total neutrophil (I/T) ratio** ratio is a more sensitive indicator of sepsis, having a better negative predictive value.

- **Thrombocytopenia** alone has a modest positive predictive value especially in the setup of EONS.
- Single value of **CRP** has an unacceptable low sensitivity, especially in the early stage of infection. Serial determinations 24 to 48 hours after the onset of symptoms achieve sensitivity of 74% to 89% and specificity of 74% to 95%.

Sepsis biomarkers (screen) must be performed only if a decision on antibiotics can be made in the setting of culture-negative sepsis. The lab tests increase the cost of care, require blood sampling, and sometimes confuse decision making.

- *If the decision to stop antibiotics has been made* in a clinically well baby with negative blood cultures, do not perform a CBC, CRP or procalcitonin (PCT) "just to be sure." In the NICE guidance on EONS, the algorithm included a repeat CRP to guide discontinuation of antibiotics; this led to further investigations, increased lumbar punctures (LPs), and longer durations of treatment and stay in the hospital. This, in turn, increased workload and cost, and influenced parental experience in the first few days of life.
- *If the decision to continue antibiotics is obvious*, as the baby is sick enough to treat (e.g., any red flag sign), then one may draw only blood cultures and start antibiotics; skip the step of biomarkers (even normal reports do not allow to stop antibiotics).

C. How do I choose the empiric antibiotics? The choices of antibiotics must take into consideration the ***bug-drug-and-host factor***: virulence and anticipated resistance of the microbe (bug), the state (gestation, organ dysfunction) of the neonate (host), and the peculiar characteristics of the drug in neonates (drug).

Factors that help in choosing empiric antibiotics include the following:

1. **Seriousness of illness.** For example, ***in a baby with shock, give the first dose of a broad-spectrum antibiotic combination as soon as possible***. On the contrary, if CONS is suspected in a preterm baby with nonspecific lethargy or hyperglycemia and otherwise the baby is well, one may send cultures and wait or start cloxacillin. (CONS is often resistant to cloxacillin; as these babies have a smoldering and slow progression, it is possible to wait for sensitivity reports. Thus, empiric overuse of vancomycin may be avoided.)
2. **Vulnerability of the host and site of infection.** ELBW babies have a higher mortality and the ***timing of right antibiotics is a significant determinant of survival***. Babies with central catheters are predisposed to serious bacterial and fungal infections; empiric therapy may have to cover for both. The site of infection determines the choice (e.g., cephalosporins for meningitis), dose, and duration.
3. **Bug factors**

3.a. Virulence. Some bugs are highly virulent (e.g., *Pseudomonas*), whereas others may be less (e.g., CONS). ***If a virulent bug is suspected, de-escalation strategy is preferred*** (initially hit hard with one or two broad-spectrum antibiotics; later change to the narrow-spectrum antibiotic as suggested by the culture report).

3.b. Resistance patterns. In a neonatal sepsis expert meeting (2016) by the World Health Organization (WHO), reviewers observed that the empiric choice of aminopenicillin and gentamicin in LMIC would not cover a large proportion of infections. A recent systematic review evaluated three antibiotic plans (carbapenem OR aminopenicillin with gentamicin OR cefotaxime plan) for expected success as empiric antibiotic for neonatal sepsis in the Asian region. The review included studies from 2014 to 2019; data were collected from 10 Asian countries. Seven common microbes were included in the analysis for resistance to antibiotics. Over 8,000 culture reports were analyzed. ***Only carbapenem (Meropenem) plan had a reasonable coverage in the Asian setting of neonatal sepsis***; carbapenem had a significantly higher coverage than aminopenicillin (ampicillin/amoxycillin) and gentamicin or cefotaxime plans. Indian data showed only 65% sensitivity even to Meropenem, and sensitivity to other antibiotics was much lower. The data were obtained from tertiary care hospitals and may be skewed; if cultures had been evaluated from primary health care facility, the problem of selection bias could have been avoided. There may be possibly another reason for falsely high reporting of antibiotic resistance; bacteria that survive to grow in a lab are the ones that are resistant to antibiotics given to the mother or baby; the sensitive ones would be cleared by even a single shot and fail to grow in a lab. Thus, only resistant bugs are represented in antibiograms (one may have to analyze antibiograms obtained from babies not exposed to any antibiotics, before or after birth, a rare occurrence in Asia!). This selection bias was illustrated in a study that added PCR to diagnostics. Many of the microbes detected by PCR (culture negative) were sensitive (genetic studies) to most antibiotics. The use of Colistin in the same unit dropped significantly following the study, as the confidence in using carbapenem or piperacillin alone increased.

In response to this crisis of having no effective antibiotics, the Global Antibiotic Research and Development Partnership (GARDP) recently initiated new treatment strategy research and hope to find an answer by 2025; the key area of focus includes neonatal sepsis. The neonatal sepsis program aims to develop two treatments, one to replace the current WHO standard of care, ampicillin and gentamicin, for use in areas with high levels of resistance to extended-spectrum β-lactams (Target Product Profile [TPP] 1), and one to treat multidrug-resistant carbapenem-resistant infections (TPP 2).

4. **Expected adverse effects.** Certain antibiotics have a greater potential for side effects, for example, colistin is nephrotoxic; a safer antibiotic must be selected in babies at risk of renal injury.

5. **Pharmacodynamics.** Drugs that are cleared by renal mechanism may require modification in asphyxia, during cooling therapy and with concomitant use of indomethacin.

6. **Comparison of antibiotics.** In a randomized controlled trial in India, amikacin was found to be equally effective as piperacillin–tazobactam.

Table 53.4 discusses selected points to be considered in choosing individual antibiotics.

Table 53.4. Some Important Points on Commonly Used Antibiotics in Neonates

	Information
Amikacin	Effective first-choice empiric antibiotic in the Asian region (many Gram-negative and -positive bacteria are sensitive to amikacin) (systematic review, 2020) Peak to trough ratio is a determinant of success and safety ■ Extended interval dosing is preferred
Piperacillin	Considered as alternative (carbapenem sparing) to carbapenems
Ampicillin	Extremely high incidence of resistance
Gentamicin	Nephrotoxicity/ototoxicity (some genes predispose to hearing loss with a single dose) May cause increased neuromuscular blockade
Cefoperazone	Good blood–brain barrier penetration Effective against most Gram-negative and -positive microbes
Cefotaxime	Increases risk of *Candida* infections, should not be used as empiric antibiotic (reserved for suspected meningitis)
Ceftazidime	Effective only against Gram-negative infections, not a good choice for empiric antibiotic
Ceftriaxone	May displace bilirubin, caution in the first week of life Interaction between ceftriaxone and calcium-containing solutions or products may lead to fatal reactions with calcium–ceftriaxone precipitates in the lung and kidney
Cefepime	Stability to beta-lactamase hydrolysis Good choice for LONS when resistance is expected
Ciprofloxacin	Effective against many drug-resistant Gram-negative bacteria, good second-line antibiotic Safe in neonates, no joint toxicity noted Good CSF penetration Decreased clearance in shock and with use of inotropes
Meropenem	Slow clearance from CSF Can cause meningeal inflammation Prolonged infusion over 4 hours preferred ■ Higher rate of clinical and microbial improvement Stability after reconstitution is a concern Increased risk of secondary fungal infections
Colistin	Poor penetration across blood–brain barrier, intraventricular or intrathecal routes have been used Inhalational route may ensure more concentration of the drug in pulmonary parenchyma Safe in ELBW babies Nephrotoxic

Table 53.4. Some Important Points on Commonly Used Antibiotics in Neonates *(Continued)*

	Information
Vancomycin	Late-onset sepsis, catheter-related infection, shunt infections nephrotoxic/ototoxic Hypotension/neutropenia/phlebitis
Linezolid	Linezolid is essentially bacteriostatic It has excellent penetration into tissues (ventilator-associated pneumonia) Its availability after oral administration is almost equivalent to that after intravenous administration Effective in multidrug-resistant Gram-positive infections

CSF, cerebrospinal fluid; ELBW, extremely low birth weight.

D. When to upgrade antibiotics? In a baby who remains unwell, if the culture and sensitivity report show resistance to the antibiotics in use, it is a clear indication to upgrade. In this setting, the choice of second-line antibiotics may be guided by the lab report.

Escalation of antibiotics in a baby, ***who remains seriously ill or has worsened***, who has the initial culture sterile is a common clinical scenario. The neonatologist may be justified in starting one or two broad-spectrum antibiotics, ***as valuable time has already been lost with an antibiotic that has not worked***. There are limited scientifically robust methods of excluding infection as a cause in babies who are seriously ill; most biomarkers identify inflammation and are common to sick neonates with "infection" and "no infection." In the setting of EONS, the use of PCT was able to decrease the use of antibiotics (but the clinical difference was ridiculously small).

E. When to stop antibiotics?

1. **De-escalation of antibiotics.** As discussed earlier, in critically ill babies, the clinician is justified in starting one or two broad-spectrum antibiotics. If the culture report identifies a sensitive antibiotic, the others may be stopped; a broad-spectrum antibiotic may be replaced by the specific "narrow-spectrum" antibiotic. Clinicians often hesitate in stopping antibiotics that seem to be working in a sick baby; this lack of faith in blood culture reports has resulted in gross overuse of the last-resort antibiotics. In a prospective study from Malaysia, de-escalation of antibiotics in the setting of EONS was associated with a significant decrease in the duration of antibiotics with no increase in risks. A normal baseline CRP (<5 mg/L) was the strongest predictor of successful de-escalation in the study.
2. **Discontinuation of antibiotics.** Consider stopping the antibiotics at 36 to 48 hours if:
   - Blood culture is negative.
   - Initial clinical suspicion of infection was not strong.

- The baby's clinical condition is reassuring and there are no clinical indicators of infection.

Around 90% of positive blood cultures grow by 48 hours, and 97% by 72 hours. Stopping antibiotics after the blood culture is reported negative at 48 hours in clinically stable patients does not increase the risk of treatment failure.

As a quality initiative, units have tried using ***stop orders for antibiotics after 48 hours***; the doctor will have to prescribe the antibiotic again if he or she wishes to continue. This resulted in a significant decrease in the antibiotic use.

In addition to the clinical status, other serum biomarkers such as ***serial CRP and PCT (NeoPIns trial)*** have been evaluated in antibiotic stop decisions. Two CRP values of less than 10 mg/L obtained 24 hours apart made sepsis highly unlikely, and antibiotics were stopped safely.

3. **Shorter-course antibiotics.** A short course of antibiotics (48 to 96 hours) was equally effective as a 7-day course in babies (>30 weeks and 1 kg at birth) with probable sepsis (culture sterile, CRP positive).

In a randomized controlled trial from India, a 7-day course of antibiotics was as effective as a 14-day course in culture-positive sepsis; meningitis/bone infections and *Staphylococcus aureus* were excluded from the study.

F. Supportive care. Antimicrobials alone are insufficient to treat sepsis. Nutrition, hemodynamic stability for tissue perfusion, oxygenation at tissue levels, and normal gut flora helps to integrate immune system with antimicrobial therapy.

II. ANTIVIRALS.

The COVID-19 pandemic has revealed the might of a virus and we hope that search for antivirals and vaccines will leapfrog to the next level. In everyday practice, most neonatologists prefer to wait, rather than start an antiviral medication. The underutilization of antivirals is probably greater in proportion than the overuse of antibiotics. The reasons include lack of diagnostic facilities for viral illnesses (described in detail in Chapter 48) and the fear of AEs of medicines that are not commonly prescribed.

The vulnerability of the neonate to viral infections is the same as that to bacteria (previous section).

A. Valganciclovir for congenital CMV. Congenital cytomegalovirus (CMV)-associated *sensorineural hearing loss (SNHL)* accounts for 25% of all SNHL in children. Half of the symptomatic babies and 10% of the asymptomatic babies with congenital CMV develop SNHL and motor disability. *Treatment of congenital CMV is associated with an improvement in hearing outcomes.*

1. Challenges in diagnosis of congenital CMV

- Most children with congenital CMV *are asymptomatic at birth*.
- Most children with congenital CMV are born to mothers with nonprimary infection, and hence *maternal serology cannot always guide*.
- Even among symptomatic babies, *clinical signs evolve late*: Only 10% have eye findings in the early infancy (chorioretinitis or optic atrophy); only half of the babies have lab abnormalities in neonatal period—thrombocytopenia, raised liver enzymes, and conjugated hyperbilirubinemia. Absence of lab abnormalities does not exclude a silent active CMV infection (and future risk of hearing impairment).

Predictors of a poor outcome of ***congenital CMV are neurologic involvement*** (microcephaly, clinical neurologic abnormalities, abnormal neuroimaging [intracerebral calcification], and other nonspecific conditions such as ventriculomegaly) in the first month and ***multiple system manifestations of CMV*** *(fetal growth restriction [FGR], thrombocytopenia, cholestasis, hepatosplenomegaly, chorioretinitis, congenital heart disease, etc.)*. As mortality and disability are frequent and severe in these settings, antiviral therapy is justified.

2. **Postnatal CMV.** Postnatal CMV is increasingly being recognized in NICU, especially in extremely preterm babies. Presentations include pneumonia (bronchopulmonary dysplasia [BPD]-like), failure to thrive, thrombocytopenia, and other nonspecific findings such as neonatal cholestasis. Central nervous system (CNS) involvement is uncommon. *Treatment may be considered in severely ill babies, severe pneumonia being the commonest.*

3. **Indications for use of valganciclovir in neonates**
   - Congenital CMV involving CNS/severe multisystem disease
   - Postnatal CMV with severe organ dysfunction (pneumonia)
   - Currently *not advised* for milder illness (such as isolated neonatal cholestasis) or an asymptomatic neonate (with only lab evidence of infection)

4. **Valganciclovir.** Valganciclovir is the prodrug of ganciclovir. It has good oral bioavailability.

   a. **Adverse effects.** Neutropenia (uncommon as compared to ganciclovir), thrombocytopenia, anemia, renal dysfunction, and teratogenic potential (when used in pregnant women). Valganciclovir is more effective and safer than Ganciclovir, Ganciclovir is not used anymore due to the need for IV therapy and high incidence of toxicity (neutropenia in 50% of treated neonates).

   b. **Treatment schedule for congenital CMV.** Treatment schedules of 6-week versus 6-month therapy have been compared in a clinical trial; this trial had shown stabilization in hearing impairment in babies treated for 6 months. *Six-month treatment was associated with better hearing* by 25 to 30 dB.

   c. **Treatment schedule for postnatal CMV.** Postnatal CMV treatment schedules are planned in *2-weekly blocks*. CMV viral load is tested weekly after starting valganciclovir. If symptoms persist and viral load is not suppressed, treatment may continue for another block. Treatment for more than 8 weeks is unusual.

B. Acyclovir

1. **Acyclovir for neonatal herpes simplex virus (HSV)**

   Suspicion of HSV is a sufficient indication to start acyclovir.

   Clinical clues to HSV infection include skin vesicles, lethargy, irritability, seizures, marked elevation of transaminases, and sepsis-like picture including hypothermia (with cultures negative for bacteria). It must be considered as a possibility in any ***sick, febrile neonate presenting after 7 days of life*** (even if there are no vesicles or history of HSV in the mother).

Lab clues to HSV infection include marked elevation of liver transaminases or high cerebrospinal fluid (CSF) proteins; EEG and MRI changes may point to HSV.

Use of acyclovir in neonatal HSV *decreases mortality and improves neurodevelopmental outcomes*.

Acyclovir is a very safe and efficacious antiviral medication in mild-to-moderate HSV and varicella disease. It is the drug of choice for HSV and Varicella infection (it is 10 times more effective against HSV than against Varicella).
Dose. 20 mg/kg/dose 8 hourly for:

- Three weeks for disseminated/CNS HSV disease
  - Six-month suppressive therapy following acute care
- Two-week treatment is enough for SEM (skin, eye, mouth) HSV disease.

2. Acyclovir for varicella infection

a. Indications

- Neonate *symptomatic with varicella* (rash and systemic signs)-Acyclovir 30 mg/kg/day for 3 weeks
- Neonate exposed to *Varicella** and at high risk (mother's status—not immunized, mother symptomatic just before delivery [<5 days] to immediate postnatal [2 days] OR premature baby)

Start acyclovir 7 days after *exposure (contact)*: oral medication 80 mg/kg/day for 7 to 10 days.

b. Adverse effects. These are uncommon:

- Obstructive nephropathy and hematuria; caution in babies with pre-existing renal dysfunction or when combined with Amphotercin or another nephrotoxic drug
- Hypotension, neutropenia, and self-resolving neurologic symptoms.

c. Caution. Sixty percent of Acyclovir is eliminated by the kidney, dose modification is required if glomerular filtration rate (GFR) is exceptionally low (peritoneal dialysis does not eliminate the drug, hemodialysis does).

d. Treatment duration

- May be stopped if surface cultures/HSV PCR is negative
- Duration of therapy for SEM disease is 14 days.
- Duration of therapy for CNS or disseminated disease is 21 days.
- Pre-emptive treatment followed by suppressive therapy for 6 months in babies with CNS disease has shown to improve the neurologic outcome.

3. Varicella zoster immunoglobulin (VZIG)/intravenous immunoglobulin (IVIG). It is not typically an antiviral medication; we are discussing it here because of its role in prevention.

a. Indications

**Exposed to Varicella (contact)—person in close contact/same room for 1 hour (some state 5 minutes).*

- Infuse immediately after birth, if the mother had signs of varicella within 5 days before to 2 days after delivery.
- Postnatal exposure in the first 2 weeks after birth, if the mother is not immune (not vaccinated or no history of varicella infection in the past)
- Postexposure prophylaxis in preterm neonates <28 weeks (or <1 kg) at birth OR preterm >28 weeks at birth born to susceptible mothers

Families must be informed that the risk of infection is reduced, although infants may develop varicella infection even after VZIG therapy. The risk of severe infection is also reduced.

b. Adverse effects. These include tachycardia, hypotension, and reactive hypoglycemia following infusion.

- IVIG may be considered if VZIG is not available.

C. Oseltamivir

- **Indications.** It is Food and Drug Administration (FDA) approved for the treatment of influenza in infants 2 weeks to <12 months of age. It may be more effective if treatment is started within 48 hours of illness. A clinical trial on Oseltamivir for influenza in infants showed no difference in treated and untreated cases of influenza.

  In preterm neonates, it was well tolerated and may be helpful in influenza outbreaks.
- **Dose schedule.** It is given as 3 mg/kg/dose, twice a day for 5 days in older children (equivalent dose in preterm babies is 1 mg/kg dose twice a day).
- **Adverse events.** These include vomiting and transient rise in liver transaminases.

D. Palivizumab. Palivizumab is a human monoclonal antibody (passive immunoprophylaxis) against F protein of the respiratory syncytial virus (RSV). Palivizumab has to be repeated on a monthly basis for the period during which the infant is at risk.

RSV is a common cause of rehospitalization and intensive care unit (ICU) admission, apnea, and even reventilation of ex-preterm neonates, especially those with BPD. Infants with congenital heart disease and other chronic/congenital lung conditions are also at an increased risk. In this group, palivizumab is protective; hospital admissions and need for ICU care are significantly decreased. In fact, epidemiologic proof is available from the United States and Italy, where significant increases in serious RSV cases occurred after the policy to give palivizumab became more selective.

Current indications. Palivizumab prophylaxis is recommended in the first year of life in preterm neonates, neonates born before 29 weeks' gestation and <1 kg birth weight, or preterm babies born before 32 weeks' gestation and having BPD.

Previously it was recommended for use in all preterm neonates and babies with congenital heart disease.

- It is administered monthly by the intramuscular route (dose 15 mg/kg); begin a month before the RSV season and continue monthly through the season.

As the medication is expensive, newer studies have tried different dose schedules. A recent study found that most modified schedules resulted in the antibody levels in blood falling significantly below the protective levels.

E. HIV medications are discussed in detail in Chapter 48.

F. Ribavirin (not routinely used). Ribavirin is the only licensed drug against severe RSV. But routine use is not recommended due to necessity of long-term aerosol application and potential toxicity.

There are only case reports of use of the IV medication in severe cases.

III. ANTIFUNGALS.

In preterm neonates, *Candida* represents the third most common causative agent of ***late-onset sepsis*** in India and is associated with significant morbidity and mortality. Invasive *Candida* infection (ICI) occurs in 4% to 18% of ***critically ill neonates***, with higher incidence among ***ELBW*** infants (birth weight ≤1,000 g). Risk factors for *Candida* infections apart from prematurity include *fungal colonization of more than two body sites*; *parenteral nutrition*; H2 receptor antagonists; antenatal and postnatal *antibiotics*, particularly third-generation cephalosporins and carbapenems; corticosteroids; *presence of indwelling catheters*; mechanical ventilation; and *abdominal surgeries*.

Challenges in diagnosis of fungal infections

- The diagnosis of invasive candidiasis (IC) is challenging. Signs and symptoms may be nonspecific and are often subtle; therefore, a combination of clinical, radiologic, and mycologic assessments is required.
- Although fungi grow easily in a culture medium, their identification requires ***large volumes of blood***. On few occasions even when blood cultures were negative, the CSF has grown fungi, further increasing the complexity in diagnosis.

A. Amphotericin B deoxycholate

Amphotericin B (Amp B) as empiric antifungal in suspected neonatal sepsis

- Action is by interaction with ergosterol on the fungal cell wall.
- Fungicidal effects against *Candida* species, *Aspergillus* species, zygomycetes, and dimorphic fungi
- Poor absorption through the gastrointestinal tract (GIT) warrants intravenous administration.
- Mostly protein bound, poor penetration into extracellular spaces such as CSF
- CNS infections are common in neonatal IC (25%). Neonatal pharmacokinetic studies show CSF penetration to be as high as 90% for parenteral Amp B, and monotherapy with Amp B for fungal has been advocated for neurologic fungal infections.
- Recent studies show little added advantage and more toxicity potential of combining flucytosine (previously recommended for meningitis and deep-seated infections)
- In neonates, Amp B is the drug of choice for treating *systemic candidiasis including meningoencephalitis and urinary tract infection (UTI)*.
- Unlike children and adults, neonates tolerate Amp B well, with minimal toxicity.

- Most studies have used a dose of 1 mg/kg/dose, once a day IV. Survival rate in babies with IC was >75%, mortality rate was 0% to 10%, and time to eradicate was 6 to 10 days.
- In CNS infections, mortality decreased from 60% to 26% with the use of Amp B and it is the drug of choice
- Babies must be monitored for nephrotoxicity (rise in creatinine values [1 to 1.5 mg/dL] or hypokalemia); these AEs are transient and reversible. One may consider changing to liposomal amphotericin if signs of toxicity to Amp B are noted.
- Sodium loading has been shown to reduce the nephrotoxicity of Amp B in newborns (sodium more than 4 mEq/kg/day).
- Infusion-related adverse events include rigors, fever, hypotension/hypertension, hypoxia, and nausea.

B. Liposomal amphotericin B

- Amp B was combined with lipids to *reduce the adverse events (hypokalemia or nephrotoxicity)* associated with long-term use.
- Lipid formulations *are **not** the drug of choice in neonates with renal candidiasis/UTI* because of poor penetration into renal tubules.
- Liposomal preparation is associated with a high cost.
- Significant AEs with liposomal products are lesser, but most AE with Amp B are transient and resolve when it is discontinued, or the dose is reduced.
- Rise of creatinine and hepatotoxicity is less uncommon with the use of liposomal amphotericin (this resolved when babies with toxicities while on Amp B were switched to liposomal preparation).
- Hypokalemia is noted with liposomal preparation also.
- Benefits of liposomal preparation were best noted at higher doses of 5 to 7 mg/kg/day.
- Benefits with liposomal preparation are greater in sicker babies and in those with a low birth weight and long duration mechanical ventilation.
- In a retrospective study comparing Amp B with liposomal preparation, rates of fungal eradication and mortality were similar. Hypokalemia, oliguria, and thrombocytopenia were also similar. Liposomal amphotericin was associated with a significant decrease in nephrotoxicity and hepatotoxicity, and a shorter duration of therapy.
- Liposomal Amp B may be reserved as an alternative drug in babies without CNS/renal candidiasis in the setting of nephrotoxicity/hepatotoxicity or fluconazole resistance.

C. Fluconazole

- Antifungal activity is through the inhibition of sterol 14α-demethylase, key enzyme in the ergosterol biosynthetic pathway.
- Fluconazole is used *for antifungal prophylaxis*. The reported incidence of IC is much higher among ELBW babies (10% to 16% in babies <1,000 g birth weight) as compared to among very low-birth-weight (VLBW) babies (2% to 4% in babies <1,500 g birth weight). The Infectious Diseases Society of America (IDSA) suggests that prophylaxis for IC with fluconazole may be

considered for VLBW babies in NICU with rates of IC higher than 10%. The European Society of Clinical Microbiology Infectious Diseases considers prophylaxis based on risk stratification:

- In unit, with a high incidence of IC >5%, fluconazole prophylaxis at 3 mg/kg twice weekly for ELBW
- In unit, with a low incidence of IC <2%, fluconazole prophylaxis may be individualized to ELBW with risk factors (central catheter, on cefotaxime or carbapenem).

Prophylaxis is associated with a decrease in colonization, invasive fungal disease, and mortality. Prophylaxis with fluconazole for 42 days was found to be superior to that for 28-day duration (relative risk [RR] of invasive fungal infection 0.3 vs. 0.8, CIs have been omitted). No difference was found in IC in the daily versus twice-weekly fluconazole groups. No significant AEs or resistance to fluconazole was reported.

- Fluconazole is readily absorbed, with *good oral bioavailability* resulting in concentrations equal to ~90% of those achieved by intravenous administration.
- Half-life in preterm babies is 73 hours at birth, 53 hours at 6 days of age, and 46 hours at 12 days of age. These pharmacokinetic characteristics make it an excellent drug for prophylaxis, allowing for *infrequent administration*.
- The dose scheme is *3 to 6 mg/kg/dose* once a day:
  - Twice a week in the first 2 weeks of life
  - Alternate day from the third week of life
- Good penetration into the *CSF and vitreous*, achieving concentrations of >70% of those in serum.
- Hepatotoxicity appears to be transient and resolves with discontinuation of therapy.
- Fluconazole is *not the preferred empiric antifungal agent* because of its *poor activity against C. krusei and C. glabrata*, both of which are common causes of neonatal fungal disease.

D. Voriconazole

- Voriconazole is available in oral and intravenous formulations and is the primary therapy for *invasive aspergillosis*.
- It has an increased efficacy against non-*albicans* sp., including *C. krusei*, that have inherent resistance to fluconazole. Voriconazole is an attractive *alternative initial antifungal in the preterm* infant.
- It has an *excellent CNS penetration*.
- Visual disturbances are reported in adults.

E. Echinocandins

- Echinocandins block the synthesis of the fungal cell wall, by inhibiting the enzyme (1→3)-β-D-glucan synthase complexes.
- They are effective against *Candida* spp., *Aspergillus* spp., *Histoplasma*, and *Blastomyces*, and are not active against *Candida neoformans*, zygomycetes, and dimorphic fungi.

- They are an appropriate *alternative for systemic candidiasis* when there is *lack of response, resistance, or toxicity* to other antifungal agents.
- Among the echinocandins, *micafungin is the most studied in neonates* and the only one approved by both the EMA and the U.S. FDA for younger children.
- Compared to Amp B or fluconazole, micafungin is preferred as catheter lock, due to its ability to *penetrate the intraluminal biofilms*.
- Caspofungin and micafungin have extremely poor oral bioavailability and require parenteral administration once daily by slow intravenous infusion.

Important tips in managing fungal sepsis in neonates

- In case of systemic fungal infection, search for end-organ dissemination (CSF, eye, kidney, etc.).
- When systemic candidiasis is diagnosed, prompt catheter removal is recommended. In neonates, a delayed central venous catheter removal, when fungal infections occur, seems to be associated with significantly increased mortality.
- Duration of therapy is 2 weeks (3 weeks for meningitis) after documented clearance of *Candida* species from the bloodstream.

Suggested Readings

Antibiotics

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54 Intracranial Hemorrhage and White Matter Injury/Periventricular Leukomalacia

Janet S. Soul

KEY POINTS

- A large intracranial hemorrhage (ICH) of any type is an emergency that requires prompt stabilization with volume replacement, perfusion and respiratory support as needed, and urgent neuroimaging.
- Due to radiation exposure, computed tomography (CT) scanning should be reserved for urgent situations in which magnetic resonance imaging (MRI) is not possible.
- Neurosurgical consultation should be obtained for large ICH with mass effect, particularly if there are signs of brainstem dysfunction and/or increased intracranial pressure.
- Seizures are common but may be subclinical, so electroencephalogram (EEG) monitoring should be obtained for newborns with significant intraventricular, parenchymal, subarachnoid, or subdural hemorrhage.

I. OVERVIEW

The incidence of intracranial hemorrhage (ICH) varies from 2% to >30% in newborns, depending on the gestational age (GA) at birth and the type of ICH. Bleeding within the skull can occur in the following:

A. External to the brain into the epidural, subdural, or subarachnoid spaces

B. Into the parenchyma of the cerebrum or cerebellum

C. Into the ventricles from the subependymal germinal matrix or choroid plexus

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 the 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 ultrasound (US) is typically preferred for premature newborns and

critically ill newborns who are not stable for transport to MRI. 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 US is available/possible. The American Academy of Neurology (AAN) practice parameter states that all newborns with a birth GA of <30 weeks should undergo routine cranial ultrasound (CUS) between 7 and 14 days and optimally repeated between 36 and 40 weeks' postmenstrual age. Our local practice is to obtain a CUS on every newborn with a birth GA of <32 weeks and birth weight <1,500 g.

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, vasopressor 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 such as seizures or the development of posthemorrhagic hydrocephalus (PHH). In general, a large ICH is more likely to result in greater morbidity or mortality than a small one. However, the presence and severity of parenchymal injury, whether due to hemorrhage, infarction, or other neuropathology, is usually the best predictor of outcome.

II. 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. 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, although small, inconsequential SDH ("parturitional SDH") is fairly common in uncomplicated deliveries (the true incidence in apparently well newborns is unknown). SDH in the supratentorial space usually results from rupture of the 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 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 with SDH 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, as demonstrated by a cerebrospinal fluid (CSF) examination. Finally, a chronic subdural effusion may gradually develop over months, presenting as an 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, US imaging of structures adjacent to bone (i.e., the subdural space) is often inadequate. MRI has proven to be quite sensitive to small hemorrhage and can help establish the 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 often 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), vasopressors, 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, supportive care instead of surgical intervention should be utilized in the management of posterior fossa SDH. 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 an 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. Epidural hemorrhage (EH). EH is uncommon in newborns compared with in older infants and children. It 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. Similar to SDH, a small EH does not necessarily require surgical treatment but should still be monitored carefully with serial imaging to ensure that there is no progressive enlargement of the EH or other hemorrhage or brain injury.

III. 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 examination 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. This is quite different from SAH in adults, where the source of bleeding is usually arterial and therefore produces a much more emergent clinical syndrome. SAH should be distinguished from subarachnoid extension of blood from a germinal matrix hemorrhage (GVH)/IVH, which occurs most commonly in the preterm newborn. SAH may also result from extension of SDH or a cerebral contusion (parenchymal hemorrhage). Finally, 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 in the setting of a vaginal delivery (often assisted).

B. Clinical presentation. As with other forms of ICH, clinical suspicion of SAH may result 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 because of the lack of radiation and to determine whether there is any other parenchymal pathology. For example, SAH may occur in the setting of hypoxic-ischemic brain injury or meningoencephalitis, pathologies which are better detected by MRI than by CT or US. CUS is not sensitive for the detection of small SAH so should be used only if the patient is too unstable for transport for 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 hypoxia-ischemia or other significant neuropathology that will be the crucial determinant of a poor neurologic prognosis because a surgical procedure may not improve outcome if there is extensive brain injury in addition to the SAH. 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.

IV. INTRAPARENCHYMAL HEMORRHAGE

A. Etiology and pathogenesis

1. **Primary cerebral hemorrhage** is uncommon in all newborns, whereas cerebellar hemorrhage is found in 5% to 10% of autopsy specimens in the premature newborn. An intracerebral hemorrhage may occur rarely as a primary event related to 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, such as 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 (because venous infarctions are typically hemorrhagic) either in relation to a large GMH/IVH (preterm > term) or as a result of sinus venous thrombosis (term > preterm). From the arterial side, bleeding may occur secondarily into an arterial embolic infarction 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). IPH may be found occasionally in newborns undergoing extracorporeal membrane oxygenation (ECMO) therapy. Finally, cerebral IPH may occur as an extension of a large ICH in another compartment, such as large SAH or SDH, as rarely occurs 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 in term newborns and may be missed by routine CUS because the reported incidence

is higher in neuropathologic than in 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), and MRI is more sensitive for the detection of small posterior fossa IPH, SAH, or SDH. Intracerebellar IPH may be a primary hemorrhage or may result from venous hemorrhagic infarction or from extension of GMH/IVH or SAH (preterm > term), and small foci of cerebellar hemorrhage of unclear pathogenesis may be detected by MRI > US. It is difficult to determine the original source of cerebellar hemorrhage by US (and sometimes MRI); hence, the proportion of primary versus secondary cerebellar hemorrhage is unclear. Cerebellar IPH rarely occurs 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 differs depending 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 and should be managed as for a large posterior fossa SDH.

C. Diagnosis. MRI is the best imaging modality for IPH. In addition, magnetic resonance (MR) angiography/venography may be useful to demonstrate a vascular anomaly, lack of flow distal to an arterial embolus, 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 and prognosis

- 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.
- The long-term prognosis largely relates to the 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 a lifelong seizure disorder, 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 for those newborns who survive the newborn period.

V. GERMINAL MATRIX HEMORRHAGE/INTRAVENTRICULAR HEMORRHAGE

A. Etiology and pathogenesis. GMH/IVH is found principally in the preterm newborn; the incidence is currently 15% to 20% in newborns born at <32 weeks' GA but is uncommon in the term newborn. The etiology and pathogenesis are different for term and preterm newborns. In preterm babies, it is now well recognized that the "size of blood leak" is not associated with outcomes; the bleed is often the result of an ischemic area; it is the extent of the ischemic area (may not be detected in early stages on US) that matters.

- In the term newborn, primary IVH typically originates in the choroid plexus or in association with venous (±sinus) thrombosis and thalamic infarction and much less commonly in the small remnant of the subependymal germinal matrix. The pathogenesis of IVH in the term newborn is more 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.
- 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 risk factors that have been identified in the etiology of IVH, including maternal factors such as infection/inflammation and hemorrhage, lack of antenatal steroids (ANS), external factors such as neonatal transport to another hospital, and increasingly recognized genetic factors that predispose some newborns to IVH. These risk factors all contribute to the pathogenesis of GMH/IVH, which is largely related to intravascular, vascular, and extravascular factors (Table 54.1). The intravascular risk factors are probably the most important and are also the factors most amenable to preventive efforts.
  - 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. 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, normal saline, or hyperosmolar solutions such as sodium bicarbonate. Rapid infusions of such solutions are thought to be particularly likely to contribute to GMH/IVH. Briefer fluctuations in CBF has been demonstrated to be associated with GMH/IVH in preterm newborns. In one study, newborns with large fluctuations in CBF velocity by Doppler US were much more likely to develop GMH/IVH than newborns

Table 54.1. Factors in the Pathogenesis of GMH/IVH

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; GMH/IVH, germinal matrix hemorrhage/intraventricular hemorrhage

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 to be 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"). Such impaired autoregulation puts the newborn at an 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 may also contribute to GMH/IVH and can be caused by seizures, hypercarbia, anemia, and hypoglycemia, which result in a compensatory increase in CBF. In addition to cerebrovascular factors affecting arterial or venous flow, impaired coagulation and platelet dysfunction are intravascular factors that can contribute to the pathogenesis or severity of GMH/IVH.

- 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 in this area of relatively large-diameter, thin-walled vessels; all of these factors make the vessels particularly susceptible to rupture.
- Extravascular risk factors for GMH/IVH include deficient extravascular support and likely excessive fibrinolytic activity in preterm newborns (see Table 54.1).

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 pathogeneses of these two complications are discussed here.

1. **PVHI** has previously been considered an extension of a large IVH; hence, it was often referred to as a grade IV IVH. Although this designation is occasionally used in much of the literature, 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 separate lesion consisting of a venous hemorrhagic infarction. 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 the notion of venous obstruction underlying the pathogenesis of PVHI includes the observation that PVHI occurs on the side of the larger IVH, and Doppler US studies show 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 has been observed to remain intact in some cases, 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 IV IVH). Risk factors for the development of PVHI include low GA, low Apgar scores, early life acidosis, PDA, pneumothorax, pulmonary hemorrhage, and need for significant respiratory or blood pressure support.
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 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 an important role in the pathogenesis of PVD. High levels of TGF-β_1 are found in the CSF following IVH, particularly in newborns with PVD; TGF-β_1 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 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 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 a clinically silent syndrome** and thus is recognized only when a routine CUS is performed. The vast majority of these hemorrhages occur within 72 hours after birth, hence the use of routine CUS within 3 to 4 days (all will be captured by CUS at 7 to

14 days) after birth in many nurseries for newborns with a GA <32 weeks. Newborns with large IVH 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 (EEG).

a. 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 unrecognized such that newborns may be discharged home after birth and then present within the first week or so after birth with the earlier listed clinical signs.

b. PVD may develop over days to weeks following IVH and may present rarely with a severe presentation—splitting of sutures, decreased level of consciousness, increased apnea or worsening respiratory status, feeding difficulties, increasing head growth (crossing percentiles on the growth chart), bulging fontanelle, or impaired upgaze or sunsetting sign. However, PVD is most 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 relatively nonspecific. Thus, serial CUS scans are critical for the diagnosis of PVD in preterm newborns with known IVH. A 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 I to II IVH (Table 54.2) (up to 12%) but occurs in up to 75% of newborns with grade III IVH ± PVHI. The incidence of PVD is also higher with younger GA at birth. Ventricular dilation may proceed 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 (~15% of the latter group does not survive).

D. Diagnosis

1. The diagnosis of GMH/IVH is almost invariably made by real-time portable CUS in the premature newborn. We obtain routine CUS studies in all newborns born at <32 weeks' GA, but the GA threshold for obtaining screening US varies from 30 to 32 weeks among different institutions. A CUS may be considered in older 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. We perform routine CUS studies twice on 7th to 14th day and at 36th to 40th week postmenstrual age (or just prior to discharge) for newborns born at <32 weeks' GA (or birth weight <1,500 g). For unstable newborns in whom the CUS may change management, we also obtain a CUS in the first few days after birth. In a very sick,

very low-birth-weight newborn with encephalopathy, consideration should be given to performing a first CUS because a large IVH with/without additional intracranial pathology (e.g., PVHI) may be an important factor in appraising the family of potential neurodisability. Also, a large IVH in very sick, very preterm newborns may require earlier follow-up CUS studies to determine whether there is rapid 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 of GMH/IVH such as PVD and PVHI and for other lesions such as PVL or cerebellar hemorrhage. In addition, any preterm newborn who develops abnormal neurologic signs or a significant risk factor for IVH (such as pneumothorax, sepsis, sudden hypotension, or volume loss of any etiology) later in his or her 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 54.2. Grading of GMH/IVH should be assigned based on the earliest CUS obtained when the IVH itself is of maximal size. Notably, ventricular dilation that occurs days to weeks following GMH/IVH is **not** considered a grade III IVH if the original IVH grade was grade I or II; it 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

Table 54.2. Grading of GMH/IVH

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)

GMH/IVH, germinal matrix hemorrhage/intraventricular hemorrhage.

b. Laterality (or bilateral) 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, with specification of location and size of echogenicity

e. Presence or absence of ventricular dilation, with measurements of ventricles when enlarged

f. Presence or absence of any other ICH (e.g., SAH) or parenchymal abnormalities

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 MR venography sequences are included (see Table 54.2).

E. Management and prognosis

1. **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. Although antenatal administration of **ANS** has clearly been shown to decrease the incidence of GMH/IVH, antenatal phenobarbital and vitamin K have not been conclusively demonstrated to prevent GMH/IVH. Postnatal prevention of GMH/IVH should be directed toward minimizing risk factors outlined in section IV.A. In particular, infusions of colloid or hyperosmolar solutions should be given slowly when possible, and all efforts should be directed to avoiding hypotension and large fluctuations or sustained increases in arterial blood pressure or cerebral venous pressure. *Both prophylactic* ibuprofen and indomethacin given to close PDA have been associated with reduced severe IVH and PVHI in some studies, but no difference was shown in long-term neurologic outcome, and these drugs are not routinely recommended solely for the prevention of IVH. *Early treatment* of significant PDA may be associated with a decrease in IVH of severe grade. We do not routinely muscle relax our preterm newborns because of the many risks associated with this intervention but do provide sedation as needed. There is no clear evidence to support IVH reduction with delayed cord clamping. Umbilical cord milking (UCM) is associated with a higher risk of severe IVH. In another systematic review, UCM was associated with a decreased risk of IVH. Head positioning in neutral or tilting has no definite association with IVH. Use of tocolytics seems to be associated with a decrease in severe grades of IVH. Antenatal risk factors—inflammatory syndrome and abruptio placentae—increased the risk of severe IVH. Score for neonatal acute physiology - perinatal extension (SNAPPE) II at 12 hours was an independent predictor of IVH in babies <29 weeks at birth. Need to transport babies in the first 72 hours (compared to *in utero* transport) increases the risk of IVH. Metabolic acidosis in the first 72 hours correlated better with the risk of IVH

as compared to respiratory acidosis (CO_2 levels). In a multicentric study, many risk factors were recognized: Cesarean section before labor was protective, and early onset sepsis, PDA, low Apgar, need for ventilation, and inotropes all increased the risk of IVH.

All the risk factors and potential strategies to decrease IVH are derived from retrospective audits; prospective implementation has not shown clear benefits in most.

2. **Management of IVH.** Supportive care should be directed toward maintaining stable cerebral perfusion by maintaining normal blood pressure, circulating volume, 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.

3. **Management of PVD**

   a. Post-IVH care consists of careful monitoring of ventricle size by serial CUS and appropriate intervention when needed to reduce CSF accumulation, such as serial LPs to remove CSF, surgical interventions to divert CSF flow; medications to reduce CSF production are not recommended (Fig. 54.1). The goals of therapy are to reduce ventriculomegaly and remove blood products, both of which may contribute to the pathogenesis of brain injury, and potentially to prevent need for a permanent shunt. CSF removal has been shown to improve cerebral perfusion, metabolism, and neurophysiologic function in newborns with PVD. Evidence from numerous animal studies and some human data suggest that earlier treatment of PVD can improve neurologic outcome, although most human clinical trials of medications or interventions to treat PVD have not shown improved neurologic outcome.*

   b. In cases of slowly progressive PVD (over weeks), close monitoring of clinical status (particularly OFC, fontanelle, and sutures) and ventricle size (by CUS) may be sufficient. Many such cases will have spontaneous resolution of PVD without intervention or will prove to have stable ventriculomegaly. It is critical to determine by serial CUS which newborns have progressive dilation requiring therapy versus which newborns have stable ventriculomegaly (e.g., caused by atrophic ventriculomegaly associated with PVL).

   c. When serial CUS shows progressive 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). Notably, there is currently no consensus regarding the threshold for initiating intervention or the best management strategy. One retrospective study suggested that treatment initiated before ventricle size reached the 97th percentile + 4 mm and resulted in improved long-term neurologic outcome, but no prospective interventional trial (drug and/or procedure) has demonstrated a clear benefit of intervention on outcome. We typically begin therapy when progressive dilation persists for about 1 to 2 weeks in newborns with clinical signs, although the rate of ventricular dilation and size of ventricles are assessed in each case to decide

*Kestle JRW, Riva-Cambrin J. Prospective multicentre studies in pediatric hydrocephalus. *J Neurosurg Pediatr* 2019;23:135–141.

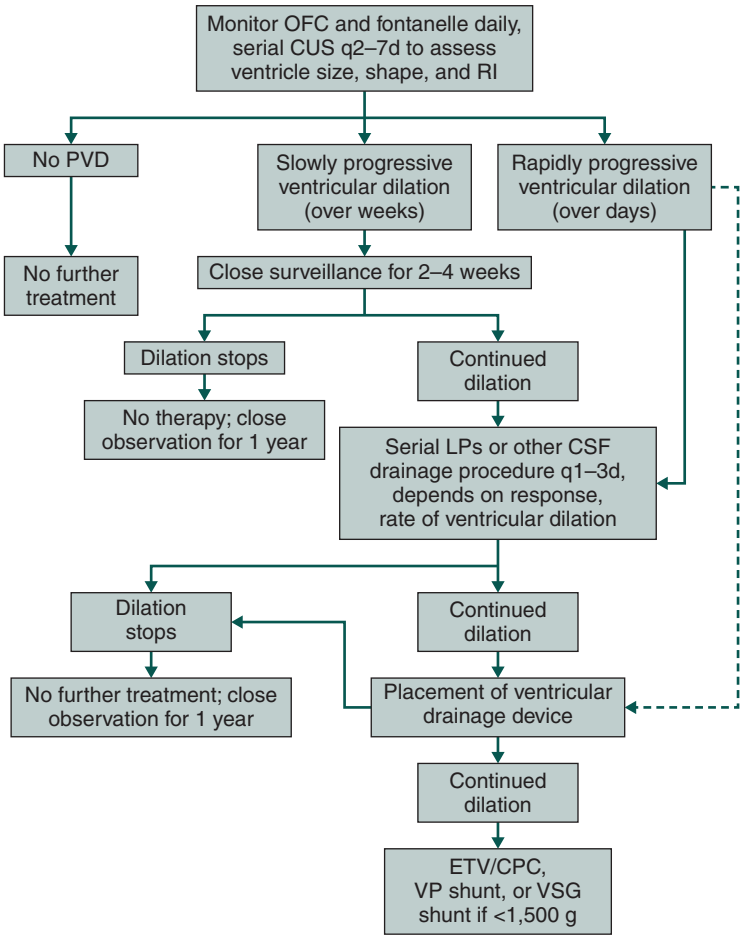

Figure 54.1. Suggested algorithm for management of posthemorrhagic ventricular dilation (PVD) following intraventricular hemorrhage (IVH). CSF, cerebrospinal fluid; CUS, cranial ultrasound; ETV/CPC, endoscopic third ventriculostomy combined with choroid plexus cauterization; LP, lumbar puncture; OFC, occipital–frontal circumference; RI, resistive index; VP, ventriculoperitoneal; VSG, ventriculosubgaleal.

whether therapy should be initiated sooner or later. We use a combination of measures of ventricle size, rate of PVD, resistive index (RI) (see the following text), and the newborn's clinical course to decide when to initiate treatment, rather than using a single measure of ventricle size as an upper limit (e.g., 97th percentile + 4 mm). Therapeutic LPs to remove CSF can be performed every 1 to 3 days (removing 10 to 15 mL of CSF per kg body weight), depending on the rate of ventricular dilation and the effectiveness of CSF removal. A CUS with Doppler performed before and after CSF removal is often helpful in establishing the diagnosis of PVD and determining the effect of CSF removal in decreasing ventricle size. If PVD is rapidly progressive, daily taps or early surgical intervention with a subgaleal shunt or external drain may be needed.

d. There is no evidence that repeated removal of CSF via LP, via ventricular puncture, or from a ventricular reservoir produces any benefit over conservative management in neonates with or at risk for developing PHH in terms of reduction of disability, death, or need for placement of a permanent shunt.

e. Measurement of the RI can be helpful in guiding management of PVD. The RI is a measure of resistance to blood flow and may indicate when intracranial compliance is low and cerebral perfusion may be decreased. Because persistent or intermittent decreases in cerebral perfusion may result in ischemic brain injury, we use the measurement of RI to help guide the treatment of PVD. RI is obtained by measuring systolic and diastolic blood flow velocities by Doppler US (usually in the anterior cerebral artery) and calculating the RI as given by the following formula:

$$\text{RI} = \frac{\text{systolic} - \text{diastolic}}{\text{systolic}}$$

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. Occasionally, values of RI >1 will be recorded, due to reversal of flow during diastole, which likely puts the newborn at 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. We typically consider a >30% increase in RI with compression compared to baseline RI, or a baseline RI >0.9, as an indication for the need 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 or use of high-frequency ventilation.

f. A combination of the newborn's clinical status, ventricular size and shape by serial CUS, measurement of ICP by manometry, RI by Doppler US, and response to CSF removal should be used to determine the need for and frequency of CSF removal procedures or other interventions to reduce intraventricular CSF volume and reduce the risk of ischemic brain injury (see Fig. 54.1).

g. Surgical treatment. If medical therapy does not successfully reduce ventricle size, and/or PVD is rapidly progressive, surgical intervention is indicated. A ventriculosubgaleal shunt (VSG), ventricular access device (reservoir), or external ventricular drain should be placed. We prefer to insert a VSG 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 VSG may be sufficient for adequate CSF drainage into the subgaleal space for days to weeks, although it may provide insufficient drainage or eventually become blocked by particulate matter. If there is insufficient CSF drainage by the VSG, CSF may be removed intermittently by a needle

placed in the reservoir of the VSG (or ventricular access device) every 1 to 3 days, as for serial LPs. External ventricular drains are less favored by our neurosurgeons because of the risk of infection, especially if the catheter is not tunneled subcutaneously, although they do provide the ideal therapy of *continuous* (rather than intermittent) CSF drainage.

h. Medications to decrease CSF production. Acetazolamide and furosemide are carbonic anhydrase inhibitors that can be used to decrease CSF production. However, their combined use often produces electrolyte disturbances and nephrocalcinosis and may be associated with a worse long-term neurologic outcome. For these reasons, the use of acetazolamide and furosemide together has fallen out of favor, and we rarely use these agents in our local practice. A large multicenter trial of these two agents used together showed no improvement in neurologic outcome compared with "standard therapy," although the standard therapy group was not managed according to a standardized protocol, and treatment was initiated only once the PVD was well established. Acetazolamide could be considered for cases where intermittent CSF removal is not possible by LP, ventricular tap, or surgical drainage procedure, or to reduce the frequency of intermittent CSF removal procedures, for example, in very small or critically ill newborns in whom a surgical procedure has an unacceptably high risk. However, the safety and efficacy of acetazolamide monotherapy for PVD has not been demonstrated in large studies, and pharmacotherapy alone is insufficient in most severe cases of PVD.

i. Fibrinolytic therapy alone has not been demonstrated to prevent PVD in five separate studies of different fibrinolytic agents. 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. However, when this very intensive high-risk therapy was tested in a larger multicenter trial, the side effects appeared to outweigh the benefit. Of 34 newborns treated with DRIFT in this second trial, 2 died and 13 received a ventriculoperitoneal (VP) shunt (44%), whereas of the 36 newborns treated with standard therapy (lumbar or ventricular taps), 5 died and 14 underwent a shunt placement (50%). Notably, 12 of 34 patients treated with DRIFT had a secondary IVH, whereas only 3 of 36 in the standard therapy group had further IVH. This second trial showed that DRIFT may have been helpful in reducing the incidence of severe cognitive disability to a subset of newborns, but the overall risks of the therapy were greater than in the pilot trial; thus, this therapy has not been widely adopted.

j. DRIFT was a challenging treatment requiring two external ventricular drains and measurement of ICP. The ventricular system was injected with recombinant tissue plasminogen activator and then flushed with artificial CSF for 2 to 7 days. Patient accrual to the study stopped early because two patients in the treatment group had rebleeds. Despite those rebleeds, the treatment group had a significantly lower incidence of death or severe disability at the 2-year follow-up. This benefit persisted at the 10-year follow-up.

k. If PVD has persisted and progressing for >4 weeks despite medical therapy as described earlier, a permanent shunt will usually be needed. However, a permanent VP shunt 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 VSG, external drain, or ventricular access device will be needed (if not already placed) until the newborn is large enough to undergo VP shunt placement. 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 for this procedure to avoid 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, and if CPC is performed. Depending on these factors, failure may occur in up to 60% of cases, usually within 6 months of the procedure, and a VP shunt will need to be placed. While relatively new, the combined ETV/CPC may offer improved outcomes for infants with hydrocephalus. Relative to shunt insertion and ETV alone, select patients undergoing ETV/CPC appear to undergo fewer repeat procedures for hydrocephalus. However, very young patients, those with postinfectious hydrocephalus, and patients with partial or incomplete CPC may respond less favorably to endoscopic treatment. Long-term and neurocognitive outcomes in patients undergoing ETV/CPC remain unclear and are the subject of ongoing clinical trials.

l. Monitoring. Rarely, 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).

m. Prognosis. The long-term prognosis for newborns with GMH/IVH varies considerably depending on the severity of IVH, complications of IVH or other brain lesions, the birth weight/GA, and other significant illnesses that affect the neurologic outcome. Several studies show that preterm newborns with even milder grades (I to II) of IVH have an increased risk of CP and/or cognitive impairment compared with 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. That being said, these cognitive impairments likely relate at least in part to coexisting cerebral WMI (i.e., PVL, see next section), 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 an 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 early CUS. Newborns with grade III IVH are clearly at a higher risk for cognitive and motor impairments, although these newborns frequently have complications of IVH or other neuropathologic lesions such as PVL that likely contribute significantly to their neurologic outcome. Notably, newborns with grade III IVH and those with PVHI ("grade IV IVH") are often grouped together in outcome studies. MRI has been demonstrated

to be superior to CUS in improving detection, classification, and, hence, prognosis of GMH/IVH and its associated complications as well as detecting other neuropathologic lesions such as periventricular WMI. Newborns with the two major complications of IVH, namely, PVHI and PVD, are at a 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.

n. Outcome in term newborns with IVH 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 a high risk for significant cognitive and/or motor deficits and epilepsy.

o. Future trends

i. Nasal application of breast milk in a group of preterm babies with severe IVH reduced porencephaly formation. The hypothesis is that milk has neurotrophins and mesenchymal stem cells that have good uptake from the nasopharynx.

ii. Erythrocyte-stimulating agents (erythropoietin [EPO]) used early in extreme preterm babies are associated with a decrease in IVH and PVL and a trend to better neurodevelopment at 18 to 22 months.

VI. PRETERM BRAIN INJURY/WHITE MATTER INJURY/PERIVENTRICULAR LEUKOMALACIA

A. Etiology and pathogenesis of preterm brain injury. PVL is the neuropathologic lesion underlying much of the cognitive, motor, and sensory impairments and disabilities in children born prematurely. A recent systematic review showed a high incidence of white matter damage at 40% in babies born before 28 weeks and 25% in those born before 32 weeks. The main risk factors were lower GA, intrauterine infection, preterm rupture of membranes, and chorioamnionitis. WMI is a term used increasingly in place of the traditional term PVL. It 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 and includes noncystic lesions. The incidence of cystic PVL has declined over the years, with a rate of <1% of preterm newborns born in 2000 to 2002 with birth weight ≤1,500 g in one center. An even more encompassing term, *encephalopathy of prematurity*,

was proposed by Volpe 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 is a term that 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. Note that WMI with a similar imaging pattern to PVL in the preterm newborn has also been reported in newborns born at term, particularly those with congenital heart disease.

The characteristic neuropathology includes bilateral areas of focal necrosis, gliosis, and disruption of axons, 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. A severe "anoxic" episode has occurred in most newborns and the lesion is consistently observed in the location of the border zone of the vascular supply. Two key features of the pathogenesis of PVL are (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 (which become cystic) and a diffuse white matter lesion. 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. Interestingly, 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 recent 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.

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 are the following: (i) hypoxia-ischemia, (ii) intrinsic vulnerability of cerebral white matter of the premature newborn, and (iii) infection/inflammation. There is evidence to suggest the presence of a pressure-passive circulation in a subset of premature newborns, predisposing these newborns to hypoxic-ischemic brain injury.

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.

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.

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 US 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.

Studies correlating US 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 for the noncystic form of PVL. 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 it is clear that 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 DEHSI represents an injury or altered development, e.g., myelination delay. ***The routine use of MRI scans to detect WMI or other lesions has not been recommended by practice guidelines.*** 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, although the timing of MRI has also been debated. A brain MRI is the most useful imaging modality to confirm clinically suspected WMI in an older infant or child born prematurely who presents with cognitive, motor, and/or sensory impairments. 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. Neuroimaging of preterm babies

has advanced hugely. It is possible to have quantitative (volumetric) analysis of various structures of the brain. It is also possible to assess the various connections and their normal or abnormal development.

C. 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. 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). A trial targeted management of cerebral tissue oxygenation saturation ($rStO_2$) using near-infrared spectroscopy (NIRS). Monitoring and interventions to maintain cerebral $rStO_2$ in the range of 55% to 85% reduced significantly (by 58%) the time preterm newborns spent hypoxic (mainly) or hyperoxic, with a trend to lower mortality and severe brain injury, but long-term neurologic outcome data are not yet available. Avoidance and prompt treatment of infection (including prompt delivery in the setting of chorioamnionitis) may also minimize PVL, although no studies have conclusively shown any effect of such interventions. Management of PVL after discharge from the NICU is directed at identification of any cognitive, sensory, or motor impairments, and appropriate therapies for any such impairments as described in the following text. Clinical trials of EPO in preterm newborns have not been associated with any change in the neurologic outcome.

D. Prognosis. PVL is associated with cognitive, behavioral, motor, and sensory impairments in children born at <32 weeks' GA.

1. A recent systematic review found that the risk of CP increased 10 times in infants with PVL and almost 20 times in those with cystic PVL.
2. There is an approximately 10% incidence of CP and up to 50% incidence of school difficulties in children born prematurely, more often in those with PVL/PVHI. The incidence of neurologic impairments increases with lower GA at birth. For example, one study of extremely low-birth-weight newborns (<1,000 g) showed that only 30% of such children were performing at level, without extra support at 8 years of age.
3. Similarly, the incidence of CP is much higher in children born extremely prematurely, occurring in approximately 20% of children born at ≤26 weeks' GA but in only 4% of children born at 32 weeks' GA. 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. When PVL is more severe and/or widespread, quadriplegia may result.

4. 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 cortical visual perceptual impairment that worsens 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.
5. Some children with severe PVL may also have epilepsy, requiring antiepileptic drugs. Together, these also influence scholastic performance of the child.
6. Nonhemorrhagic ventriculomegaly is also associated with poorer development outcomes.

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55 Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy

Anne R. Hansen and Janet S. Soul

KEY POINTS

- Therapeutic hypothermia (TH) for hypoxic-ischemic encephalopathy (HIE) is associated with decrease in mortality and neurodisability and must be started within 6 hours of birth for maximal efficacy.
- Cooling with non-servo methods with close temperature monitoring is an alternative in resource-limited settings.
- In HIE, seizures may be difficult to detect clinically; they are often subclinical (electrographic only) and abnormal movements or posture may not be seizures; conventional electroencephalogram (EEG) must be used.
- Careful management of ventilation, oxygenation, perfusion, metabolic state, and fluid balance is critical to optimizing outcome.
- A large number of neonates have poor outcomes despite being treated with TH.

I. PERINATAL ASPHYXIA. It refers to a condition during pregnancy and 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. The umbilical artery pH that defines asphyxia is not the major determinant of brain injury. Although the most widely accepted definition of fetal acidosis is a pH <7.0, the likelihood of brain injury is relatively low with this degree of acidosis. 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. These pathophysiologic terms describe 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 rigorous 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, muscle 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 examination, laboratory tests, imaging studies, or electroencephalograms (EEGs). *After the first hour or so of life*, 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 (including 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 IX.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 (e.g., pregnancy-induced hypertension, gestational diabetes, multiple gestation) with emphasis on risk factors associated with neonatal depression (exclude pertinent family history for causes other than HIE)
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 examination with emphasis on neurologic exam (exclude any dysmorphic features)
   b. Clinical course including presence or absence of seizures (and time of onset), oliguria, cardiorespiratory dysfunction, and treatment (e.g., need for pressor medications, ventilator support)
   c. Lab tests include blood gases, electrolytes, evidence of injury to end organs other than the brain (kidney, liver, heart, lung, blood, bowel), and tests to exclude inborn errors of metabolism, if suspected
   d. 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 developed countries with advanced obstetric/neonatal care and is inversely related to gestational age and birth weight (BW). It occurs in 0.5% of live births >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. The incidence of perinatal asphyxia is estimated to be much higher (10 to 15 times) in low- to middle-income countries (LMIC).

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. It is not possible, often, to estimate the timing of asphyxia in many cases. Asphyxia can also occur in the postpartum period, usually secondary to pulmonary, cardiovascular, or neurologic abnormalities.

A. 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, and compression
5. Abnormalities of umbilical vessels
6. Fetal factors. Anemia (e.g., from fetal–maternal hemorrhage), infection, cardiomyopathy, hydrops, and severe cardiac/circulatory insufficiency

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 the 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 the mother and the 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, and then stat cesarean section), it is thought that this diversion of blood flow to vital deep nuclear structures of the brain does not occur, which 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 the 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 a secondary energy failure that usually begins approximately 6 to 24 hours after the initiating insult. Cell death can be either immediate or delayed and either necrotic or apoptotic.

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 inotropic 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 because it can promote the formation of excess reactive oxygen species (e.g., superoxide, hydrogen peroxide, hydroxyl, singlet oxygen), 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-1β and tumor necrosis factor-α).

V. DIAGNOSIS

A. Perinatal assessment of risk includes awareness of pre-existing 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 not sufficient to diagnose HIE/perinatal asphyxia.

1. Other causes for low Apgar/need for resuscitation (but not asphyxia). The *differential diagnoses* for a term newborn with a low Apgar score include depression from maternal anesthesia or analgesia, birth trauma, infection, cardiac or pulmonary disorders, and 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 blood gas determination. The specific blood gas criteria that define asphyxia causing brain damage are uncertain; however, the pH and base deficit on the cord or first blood gas are helpful for determining which infants have asphyxia that indicates need for further evaluation for the development of HIE. In the randomized clinical trials of hypothermia for neonatal HIE, severe acidosis was defined as pH ≤7.0 or base deficit ≥12 to 16 mmol/L.

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 diagnosis of neonatal encephalopathy includes a number of etiologies in addition to perinatal hypoxia-ischemia. Asphyxia is likely, and other causes are less likely if the following are present:

1. Prolonged (>1 hour) antenatal acidosis
2. Fetal HR <60 beats per minute
3. Apgar score ≤3 at ≥10 minutes
4. Need for positive-pressure ventilation or first cry delayed >5 minutes
5. Seizures within 12 to 24 hours of birth
6. Burst suppression or suppressed background pattern on EEG or amplitude-integrated electroencephalogram (aEEG)

VI. NEUROLOGIC SIGNS.

The clinical spectrum of HIE is described as mild, moderate, or severe (Table 55.1). EEG is useful to provide objective data to grade the severity of encephalopathy.

A. Encephalopathy. Newborns with HIE must have abnormal consciousness by definition, whether mild, moderate, or severe. Mild 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 and severe encephalopathy are characterized by more impaired responses to stimuli such as light, touch, or even noxious stimuli. The background pattern detected by EEG or aEEG is useful for determining the severity of encephalopathy.

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 dysconjugate gaze, gaze preference, ocular bobbing or other abnormal patterns of bilateral 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. Over days to weeks, the initial hypotonia may

Table 55.1. Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy*

Stage	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
Level of consciousness	Hyperalert; irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control	Uninhibited, overreactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhea	Variable
Seizures	None	Common focal or multifocal (6–24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal (awake)	Early: Generalized low voltage, slowing (continuous delta and theta)	Early: Periodic pattern with isopotential phases

(continued)

Table 55.1. Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy*

Stage	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
		Later: Periodic pattern (awake); seizures focal or multifocal; 1.0–1.5 Hz spike and wave	Later: Totally isopotential
Duration of symptoms	<24 hours	2–14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5–7 days	About 50% die; remainder with severe sequelae

*The stages in this table are a continuum reflecting the spectrum of clinical states of newborns over 36 weeks' gestational age.
Source: From Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976;33:696–705.

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 24 hours after the HI insult. Seizures indicate that the severity of encephalopathy is moderate or severe, not mild.

1. Seizures may be subtle, tonic, or clonic. 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 abnormal movements or posture may not be seizure, EEG remains the gold standard for diagnosing neonatal seizures, particularly in HIE.
3. Seizures may compromise ventilation and oxygenation, especially in newborns who are not receiving mechanical ventilation. It is important to adequately support respiration to avoid additional hypoxic injury.

E. Increased intracranial pressure (ICP) resulting from diffuse cerebral edema in HIE often reflects extensive cerebral necrosis rather than swelling of intact cells and indicates a poor prognosis. Treatments (empiric fluid restriction/mannitol/frusemide) to reduce ICP does not improve outcome, and are not recommended.

VII. MULTIORGAN DYSFUNCTION. Other organ systems in addition to the brain usually exhibit evidence of asphyxial damage. In a minority of cases (<15%), the brain may be the only organ exhibiting dysfunction following asphyxia. In most cases, multiorgan dysfunction occurs as a result of 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).

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 the 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), poor production of clotting factors due to liver dysfunction, and poor production 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.

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 the placenta, lungs, GI tract, and kidneys. Other serum markers such as protein S-100, NSE, glial fibrillary acidic protein (GFAP), and urine markers have been measured in newborns with asphyxia and HIE.
2. *In practice, serum and urine markers of brain injury are not routinely 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.

3. Urine levels of β_2-microglobulin have been used as an indicator of proximal tubular dysfunction, *though not routinely*. This low-molecular-weight protein is freely filtered through the glomerulus and reabsorbed almost completely in the proximal tubule.

IX. BRAIN IMAGING

A. Cranial sonographic examination can demonstrate edema as loss of gray-white differentiation and small ventricles when severe, but it is generally *insensitive for the detection of HI brain injury,* particularly in the first days after birth. It may be useful to rule out large intracranial hemorrhage, particularly because this may be a contraindication to therapeutic hypothermia (TH).

B. CT may be used to detect cerebral edema, hemorrhage, and eventually HI brain injury. Because of the degree of radiation exposure, CT is indicated only if imaging is urgently needed to determine clinical treatment and MRI is not available or when the baby is not stable enough to leave the neonatal intensive care unit (NICU) for a longer period of time.

C. MRI. Conventional T1- and T2-weighted MRI sequences are the best modality for determining the severity and extent of irreversible HI brain injury, but the injury is not apparent on these sequences in the first days after the HI insult, unless the injury is older than suspected or very severe. These **conventional sequences are best for the detection of brain injury at 7 to 10 days** at the earliest, and a scan as late as 14 days or older may be needed to show the full extent of the injury, particularly if early MRI shows less injury than suspected by clinical examination or EEG findings.

1. **Diffusion-weighted imaging (DWI)** can show abnormalities within hours of an HI insult that may be useful in the diagnosis of 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*, 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, which can occasionally be found in association with HIE.

X. EEG AND aEEG. A full-array EEG uses about 16 electrodes and requires the expertise of a neurophysicist who is trained to interpret EEG. aEEG is a method of continuous tracing of EEG which evaluates long-term changes and trends in electrocortical background activity. In aEEG, the signals from one to two channels of continuous EEG are amplified, filtered, rectified, and compressed using a piecewise semilogarithmic transformation and are portrayed as a slow-trend display along with the raw EEG. It is useful for continuous monitoring of the brain function.

The analysis of the aEEG consists of looking at the background pattern, presence of seizure activity, and sleep–wake cycle. The background pattern is classified into the following:

- Continuous (upper margin >10 μV and lower margin >5 μV—normal pattern)
- Discontinuous (upper margin >10 μV and lower margin <5 μV—normal in preterm babies, moderately abnormal in term babies)
- Burst suppression (discontinuous activity with minimum amplitude without variability at 0 -1 μV, and bursts with amplitude >25 μV)
- Continuous low-voltage and isoelectric/flat trace

Although a full-array EEG has a better seizure detection rate, the advantages of aEEG over EEG include ease of operation and interpretation, immediate bedside interpretation, prolonged periods of monitoring, and condensed output.

aEEG is increasingly being used for select babies eligible for cooling, to detect subclinical seizure activity and as a long-term prognosticator. Although aEEG is not mandatory, the background pattern in the first 6 hours post asphyxia can be used as an adjunct in selecting babies who would benefit from TH. aEEG is also an excellent tool for early prognostication in babies with HIE. The recovery time to normal background pattern is the best predictor of poor outcome in both cooled and noncooled babies (96.2% and 90.9%, respectively). *Never developing sleep–wake cycling over 72 to 96 hours always predicted a poor outcome while infants treated with hypothermia have a good outcome if the background became continuous by 48 hours.*

XI. PATHOLOGIC FINDINGS OF BRAIN INJURY

A. 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 the hippocampus, Purkinje cells of the cerebellum, neurons of the thalamus and basal ganglia (particularly putamen), 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 severe hypotension. This injury reflects poor perfusion of the vulnerable periventricular border zones in the centrum semiovale and produces predominantly white matter injury, particularly in preterm newborns. In the term newborn, more severe, prolonged HI insults 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 the cortex in the depths of sulci) due to loss of perfusion in one or more vascular beds.

B. Neuropathology may reflect the type of asphyxial episode, 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 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 probably present in most cases.

XII. TREATMENT

A. Perinatal management of high-risk pregnancies

1. Fetal HR abnormalities may provide supporting evidence of asphyxia, especially if accompanied by the presence of thick meconium. However, they have limited value in assessing the duration or severity of an asphyxial event.
2. Measurement of fetal scalp pH is a better determinant of fetal oxygenation than 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 the progress of labor with awareness of other signs of *in utero* distress is important.
4. The presence of a constellation of abnormal findings 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 designed and placed in 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 (pulse oximetry). 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 radiant warmer is an effective way to initiate TH as soon as possible after the HI insult. Hyperthermia should always be avoided. It must be remembered that temperatures can drop to lower than recommended levels and fluctuate widely in passive cooling; these may be detrimental to long-term neurodevelopment.
4. **Perfusion.** Cardiovascular stability and adequate mean systemic arterial BP are important in order to maintain adequate cerebral perfusion pressure.
5. **Maintain physiologic 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. **Judicious fluid management** is needed, and 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. **Control of seizures.** Seizures generally start within 12 hours of birth, increase in frequency, and then usually resolve within days, although seizures may persist in severe cases. Seizures caused by HIE can be extremely difficult to control and may not be possible to eliminate completely with currently available anticonvulsants. 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. EEG is thus required to detect seizures and monitor the response to anticonvulsant therapy and is superior to aEEG for this purpose. There is increasing evidence that seizures exacerbate brain injury, but anticonvulsants are often incompletely effective, and it has not yet been proven that improved seizure control results in improved neurologic outcome. Metabolic perturbations such as hypoglycemia, hypocalcemia, and hyponatremia that may cause or exacerbate seizure activity should be corrected.

a. **Acute anticonvulsant management**

i. **Phenobarbital** is the initial drug of choice. It is given as a loading dose of 20 mg/kg intravenous (IV over 15 to 20 minutes). 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 12 to 24 hours after the loading dose. 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.

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 the *risk of hypotension is less 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 range of 20 to 25 mg/dL may be effective and consideration should be given to the measurement of the free phenytoin level.

iii. **Benzodiazepines** are considered third-line drugs and include lorazepam, which can be given in doses of 0.05 to 0.1 mg/kg/dose IV. Some clinicians use midazolam boluses and IV infusions to control seizures, but there are few data regarding the safety and efficacy of this treatment.

iv. **Levetiracetam** has been used recently because of its availability in IV form and relative safety and efficacy for various types of childhood epilepsy. There are several published series reporting benefit in newborns (but without continuous EEG monitoring to confirm efficacy), and there are few data regarding short- or long-term safety. In a recently published phase IIb randomized clinical trial, phenobarbitone was more effective than levetiracetam in the treatment of neonatal seizures (80% vs. 28% seizure free at 24 hours).

b. **Long-term anticonvulsant management.** Anticonvulsants can be weaned when the clinical examination and EEG indicate that the newborn is no longer having seizures. If a newborn is receiving more than one anticonvulsant, 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 is controversy regarding when phenobarbital should be discontinued, with some favoring discontinuation shortly before discharge and some favoring continued treatment for 1 to 6 months or more. Newborns who have a higher risk of developing epilepsy in infancy or childhood are those with a *large area of HI brain injury and those with a persistently epileptiform EEG.*

8. **Management of other target organ injury**

a. **Cardiac dysfunction** should be managed with the 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 continuous monitoring of systemic mean arterial BP, CVP (if available), and urine output. Newborns with cardiovascular compromise may require inotropic drugs such as dopamine (see Chapter 40) and may need afterload reduction (e.g., dobutamine or 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 the adequacy of preload (i.e., 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 and urine output (~60 mL/kg/day) and 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. Withholding feeds for long is neither necessary nor desirable. In profound shock or clinical signs of ileus (abdominal distension) and blood-stained stools, feeds may be withheld.

d. Hematologic abnormalities (see Chapters 42 to 47). Coagulation profile should be monitored with partial thromboplastin time (PTT) and prothrombin time (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 the measurement of transaminases (alanine aminotransferase [ALT], aspartate transaminase [AST]), clotting time (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.

XIII. NEUROPROTECTIVE STRATEGIES.

A number of neuroprotective strategies have been proposed and/or are being tested in animal or clinical human trials.

A. TH has been shown to decrease the risk of brain injury in newborns exposed to perinatal HI insult(s). 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.

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°C to 34°C).

1. **Inclusion criteria.** We offer total body cooling to newborns with HIE based on the following three criteria (*Note:* **A normal neurologic exam does not require confirmation by aEEG):**
   - **a.** Postmenstrual age (PMA) ≥36 weeks, BW ≥2,000 g
   - **b.** Evidence of fetal distress or neonatal asphyxia 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 the first hour of life
     - **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 examination and/or aEEG as follows:
     - **i. Primary method for determining neonatal encephalopathy is physical examination.**
     - **ii.** If the examination shows moderate or severe encephalopathy, aEEG should be performed to provide further assessment and monitoring.
     - **iii.** In circumstances in which physical examination is unreliable (e.g., muscle relaxants), an aEEG should be performed to determine whether there is encephalopathy.
     - **iv.** Patterns on aEEG that indicate moderate or severe encephalopathy include the following, with minimum recording time of 20 minutes:
       - **a)** Severely abnormal: Upper margin <10 μV
       - **b)** Moderately abnormal: Upper margin >10 μV and lower margin <5 μV
       - **c)** Seizures identified by aEEG
2. **Exclusion criteria.** (*Do not start/continue TH.*) Patients may be excluded from this protocol according to the judgment of the attending physicians. If an exclusion criterion is identified during therapy, the patient should be warmed according to the rewarming procedure described in the following text:.
   - **a.** Presence of lethal chromosomal abnormality (e.g., trisomy 13 or 18)
   - **b.** Presence of severe congenital anomalies (e.g., complex cyanotic congenital heart disease, major CNS anomaly)
   - **c.** Significant bleeding diathesis
   - **d.** Major intracranial hemorrhage

   Arterial access and central venous access should be obtained prior to the initiation of TH protocol if possible. Obtaining central access in the hypothermic state can be extremely challenging due to vasoconstrictive effects.

B. Other neuroprotective agents. Although TH has been proved to be an effective neuroprotective therapy with around 25% reduction in death and severe

disability, there still remain *a large number of neonates who have poor outcomes despite being treated with TH.* Numerous agents are being investigated for their neuroprotective role in HIE. While many are still in the preclinical phase (*N*-acetyl-L-cysteine, polyphenols, curcumin, osteopontin, interferon-β, c-Jun N-terminal kinases, and edaravone), several agents such as erythropoietin (Epo), melatonin, xenon, topiramate, magnesium sulfate, allopurinol, and stem cells are undergoing human trials. As TH has become the standard of care, any new agent will need to be assessed for neuroprotection along with TH. However, in resource-poor settings where it might not be possible to offer TH or presentation is often beyond 6 hours, there may be a need to evaluate other neuroprotective agents as a stand-alone therapy.

1. **Epo.** Several small studies have shown the benefit of Epo in babies with HIE when used both alone and in combination with TH. Currently phase III trials are evaluating Epo along with TH (HEAL—NCT 01913340; and PAEAN—NCT03079167and NEUREPO-NCT01732146), the results of which are expected over the next few years.
2. **Melatonin.** In addition to a number of preclinical studies, two small trials showed that melatonin has short-term benefits. Currently the MELPRO trial (NCT03806816) is recruiting patients.
3. **Xenon.** The Total Body hypothermia plus Xenon (TOBY-Xe) study which looked at the neuroprotection of xenon added to TH did not show differences in the primary outcome between the two groups (lactate to NAA ratio in the thalamus or in the fractional anisotropy in the posterior limb of the internal capsule). Lack of effect of xenon in this trial may have been related to the delayed administration of xenon to neonates with HIE or the lower dose used. The Xenon and Cooling Therapy in Babies at High Risk of Brain Injury Following Poor Condition at Birth (CoolXenon3) is an ongoing clinical trial evaluating the benefit of inhaled xenon gas treating newborn infants with HIE in combination with cooling (NCT02071394).
4. **Allopurinol.** There is an ongoing phase III trial—ALBINO trial—looking at the effect of postnatal allopurinol administered in addition to TH.
5. **Topiramate.** Two small studies have shown a reduction in seizures in the group that received topiramate, although there was no change in mortality or long-term disability.
6. **Stem cells.** Animal models of HIE have shown improvement in neuroprotection with stem cell treatment. Currently, there are ongoing trials with autologous cord blood and human placenta–derived stem cells in neonates with severe HIE (NCT02434965), umbilical cord milking for neonates with HIE (NCT02287077), and neural progenitor cell and paracrine factors to treat HIE (NCT02854579).

C. Equipment for TH. Servo-controlled devices available in the market include Tecotherm Neo, CritiCool, and Blanketrol III systems for whole body cooling and Olympic Cool-Cap for selective head cooling. These are automated and provide precise temperature control during the cooling phase and controlled rewarming with minimal interventions needed from the user. However, as the servo-controlled machines are expensive, several "low-technology" cooling devices

are available and being used in LMIC. These include ice gel packs and phase change material (PCM)–based MiraCradle-Neonate Cooler. Though labor intensive, low-technology devices have been shown to be safe and effective.

D. Safety monitoring of newborns during 72 hours of TH and rewarming

1. Temperature

a. Core temperature should be monitored continuously and documented every 15 minutes until 1 hour after the goal temperature of 33.5°C is achieved and then hourly. It is measured with an esophageal or rectal temperature probe.

b. During the rewarming procedure, core temperature should be monitored continuously and documented every hour.

2. Respiratory status

a. 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.

b. Due to minor differences between blood gases between 33.5°C and 37°C, ***there is no need to record the infant's core temperature on the blood gas requisitions.***

3. Cardiovascular

a. Vital signs should be monitored and documented.

4. Fluid, electrolyte balance, and renal/GI

a. 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 that are providing low-volume "trophic" or "gut priming" feeds of about 10 mL/kg/day if there are no direct contraindications such as hypotension.

b. 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 the ability to reach full goals.

c. To avoid cerebral edema in this at-risk population, goal Na level at the high end of the normal range. Because many of these patients have decreased urine output of multifactorial etiology, anticipating the need for relative fluid restriction will assist in avoiding serum Na below 140.

d. PT/PTT, international normalized ratio (INR), fibrinogen, and platelet count should be measured daily while cooled 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 requested for assistance.

5. Infectious disease

a. Antibiotics should be started after complete blood count (CBC) and blood culture drawn per routine.

b. If there are concerns regarding renal function, change from gentamicin to cefotaxime.

6. Neurologic status

a. Neurology consult should be requested as soon as possible, wherever available.

b. aEEG or, preferably, full EEG monitoring should be initiated on admission and continued through at least the first 24 hours, and 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 related to ischemia, hypothermia, and decreased mobility of the newborn.

c. Cranial ultrasound should be obtained as soon as possible after TH is initiated to assess for intracranial hemorrhage.

d. 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 the 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:

i. T1- and T2-weighted imaging to detect any irreversible injury or other congenital or acquired abnormalities of brain parenchyma

ii. DWI to detect evidence of acute HI injury

iii. Susceptibility-weighted imaging to detect hemorrhage

iv. Proton MRS to detect lactate or other metabolites suggestive of metabolic etiology other than HIE

v. MR venography or arteriography may be useful if there is evidence of focal venous or arterial ischemic injury suggestive of thromboembolic disease.

e. Early brain MRI obtained within the first 1 to 5 days after birth (or after HI insult) is useful for the following:

i. Detection of early restricted diffusion that indicates early HI injury

ii. To assess whether injury is already well established (e.g., antenatal as opposed to perinatal insult)

iii. To establish any potential etiology of encephalopathy besides HI

iv. To assess severity of any HI injury (this is especially important if there are clinical signs of severe encephalopathy and consideration of withdrawal of care)

Note: Early scans may underestimate HI injury, depending on the timing of insult and imaging.

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 will show increased diffusion in areas of established HI injury.

f. A recent meta-analysis showed that MRI in the first week was better predictive (higher sensitivity, specificity, and diagnostic odds ratio) than MRI done after 7 days. Most of the studies that were analyzed used a standard scoring system that incorporated DWI in the scoring. Two individual studies that looked at the timing of conventional MRI also found better prediction of outcome in early MRI. It is therefore recommended to ***perform MRI including DWI and H-MRS during the first week after birth using a standard scoring system*** (e.g., Barkovich, Rutherford, National Institute of Child Health and Human Development [NICHD], or Weeke), ***preferably after rewarming*** as TH slows the evolution of diffusion abnormalities. However, ***in a setting in which DWI and H-MRS are unavailable, conventional MRI should be done later (10 to 14 days)*** to delineate the full extent of the injury.

7. Pain and sedation

a. Goal sedation level during cooling should be established and measured with a sedation tool.

b. Sufficient sedation should be administered to optimize comfort and avoid shivering, which can increase the newborn's metabolism and temperature, thereby decreasing the efficacy of hypothermia therapy. Titrate to achieve goal sedation scores.

Stop cooling: At the end of 72 hours of induced hypothermia, the newborn is rewarmed at a rate of 0.5°C every hour until the patient reaches 36.5°C. This should take approximately 6 hours.

If a patient is discovered to meet an exclusion criterion or undergoes a major adverse event while undergoing hypothermia treatment, rewarm according to the same procedure.

8. Controversies in administering TH

a. Hypothermia of greater duration or depth. A question that arose following publication of the initial clinical trials of moderate hypothermia for 72 hours was whether cooling to a lower temperature and/or for a longer duration might be of greater benefit. A randomized trial addressing this question was published in 2014 and showed that neither cooling for 120 hours nor cooling to a temperature of 32°C offered additional benefit and instead showed a trend to worse outcome, with the trial being stopped early for futility.

b. Late initiation of hypothermia. There are data showing that hypothermia is associated with an improved outcome if started at <3 to 4 hours after birth, consistent with animal data, but it is unclear whether there is a benefit to hypothermia initiated >6 hours after birth. This question is being tested in an ongoing NICHD-funded trial, but in the meantime, centers such as ours do consider cooling infants beginning at 6 to 12 hours if other criteria are met.

c. Gestational age 34 to 36 weeks. It is currently unclear what the lowest gestational age is 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 US can be

performed early to rule out intraventricular hemorrhage, which occurs more commonly in preterm newborns.

d. Underlying medical conditions. There is also a controversy about providing hypothermia to newborns with underlying surgical or genetic conditions. This question is unlikely to be addressed in large clinical trials so requires careful clinical consideration.

e. Mild HIE. Likely the greatest difficulty is deciding whether to offer hypothermia to newborns who meet some but not all of the criteria, particularly those with a mild degree of encephalopathy. Although there are some objective entry 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 examination. The threshold for which hypothermia may provide benefit without adverse effects may be somewhat different from that which has been studied in clinical trials to date. Further data are clearly needed regarding the neurologic outcome of newborns with mild HIE and the risks and benefits of hypothermia for mild HIE.

XIV. OUTCOME IN PERINATAL ASPHYXIA

A. The overall mortality rate is approximately 20%. The frequency of neurodevelopmental sequelae in surviving newborns is approximately 30%. Treatment with TH is associated with about 25% reduction in the combined outcome of death and major disability, reduced from 61.4% to 46% with TH. Mortality alone decreased from 34.1% to 25.2% while major disability decreased from 24.9% to 19.1%. There are no good-quality studies with long-term outcomes from LMICs but meta-analyses suggest a reduction in mortality in babies cooled in low-resource settings. Several studies from LMICs have also shown improvement in short-term neurodevelopmental outcome and brain injury using MRI biomarkers with TH.

B. The risk of cerebral palsy (CP) in survivors of perinatal asphyxia is 5% to 10% compared to 0.2% in the general population. **Most CP is not related to perinatal asphyxia, and most perinatal asphyxia do not result in CP.**

C. Specific outcomes depend on the severity of the encephalopathy, the presence or absence of seizures, EEG results, and neuroimaging findings.

1. Severity of encephalopathy can be ascertained using the **Sarnat clinical stages of HIE** (see Table 55.1).

a. Stage 1 or mild HIE. <1% mortality, 98% to 100% of newborns will have a normal neurologic outcome.

b. Stage 2 or moderate HIE. 20% to 37% of newborns die or have abnormal neurodevelopmental outcomes. Prognosis can be refined by the use of EEG and MRI studies to detect the severity of encephalopathy and seizures, and the severity and location of HI brain injury. This group may benefit the most from TH.

c. Stage 3 or severe HIE. Death from effects of severe systemic asphyxia is more likely with severe HIE or from elective withdrawal of medical technology when there is severe brain injury that will result in severe neurologic

disability. Survivors are likely to have one or more major neurodevelopmental disability, such as CP, intellectual disability, visual impairment, or epilepsy.

2. The presence of seizures increases a newborn's risk of CP 50- to 70-fold. Mortality and long-term morbidity are the highest for seizures that begin within 12 hours of birth, are electrographic only, and/or are frequent.
3. Persistently low-voltage activity or isoelectric background in EEG is a prognostic indicator of poor neurologic outcome. Never developing sleep–wake cycling over 72 to 96 hours always predicted a poor outcome while infants treated with hypothermia have a good outcome if the background became continuous by 48 hours. Of note, some medications can transiently alter the neonatal EEG.
4. MRI adds a great deal of prognostic information to the clinical and EEG data because the pattern of HI brain injury by MRI generally correlates well with the 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 is usually associated with both intellectual and motor disability, but the severity can vary considerably depending on the regions involved and severity of injury to each region. Notably, discrete lesions in the subcortical nuclei or less severe watershed pattern/parasagittal injuries can be associated with a normal cognitive outcome and only mild motor impairments. Overall, motor outcome is easier to predict than cognitive or sensory outcome, and it can be very difficult to predict which infants 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.

Suggested Readings

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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 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 (EEG) is the gold standard for detection 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 per 1,000 live births. In neonates, the vast majority of seizures are symptomatic of underlying disorders, although primary epileptic disorders may also present in this age group. The occurrence of seizure may be the first clinical indication of a 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 may temporarily act 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 in older children. (iv) The immature brain may be more susceptible to developmental effects of anticonvulsant 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 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 an encephalopathic newborn. 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 clinical seizure patterns

1. **Focal clonic seizures.** This pattern may occur unilaterally, sequentially in different limbs, or simultaneously but asynchronously. The movement is rhythmic, biphasic with a fast contraction phase and a slower relaxation. 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 newborn), and/or pupillary dilatation. These are often also associated with hypertension.

   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

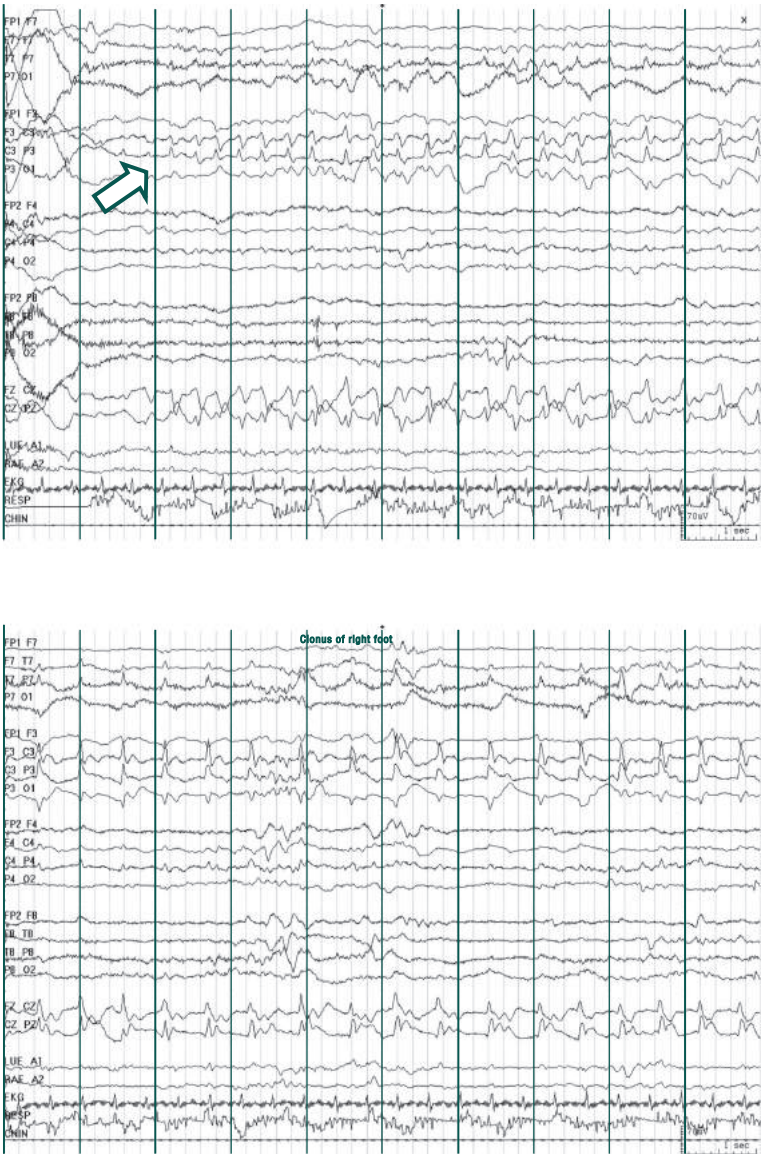

Figure 56.1. Left parasagittal neonatal seizure with focal clonic seizure. Electrographic seizure begins in the left parasagittal area (*open arrow*), and 12 seconds later, focal clonus of the right foot is noted.

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***

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 On 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.)

neonatal seizures. cEEG is particularly important given the high proportion of neonatal seizures that are subclinical (studies suggest that up to 80% of neonatal seizures are electrographic only) and would go undetected without continuous monitoring due to electroclinical uncoupling or 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 (aEEG) 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, sometimes, epileptic potential. 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.

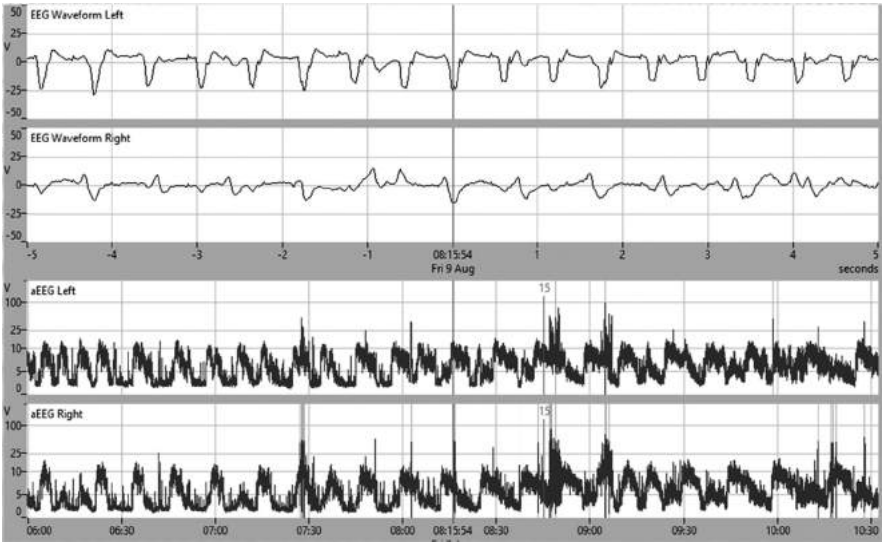

Figure 56.2. Seizures in term infants. Typical seizure: A sudden rise of the lower and upper margin followed by a short period of decreased activity.
Learning resource: Bruns N, Blumenthal S, Meyer I, Klose-Verschuur S, Felderhoff-Müser U, Müller H. Application of an amplitude-integrated EEG monitor (cerebral function monitor) to neonates. *J Vis Exp JoVE* [Internet]. 2017 Sep 6 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5752191/

2. **aEEG** 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 aEEG. 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 the response to therapies. Seizures occurring during recording of these 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). Some type of seizure etiology may cause a typical pattern on aEEG (e.g., epilepsy due to mutation in KCNQ2 gene which causes a decreased amplitude at the end of the seizure). The sensitivity of aEEG in detecting seizures is 30% for single seizures. This increases with the experience of the user, use of multichannel aEEG, increase in seizure duration to >30 seconds, and repetitive seizures. The specificity of seizure detection by aEEG is high.

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 the point of conception to the time of delivery), birth history,

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 the 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 raises suspicion of perinatal infarction. When seizures present after the first 48 hours of life, and particularly after a period of initial well-being, infection and metabolic disorders should be considered. Among seizures that occur early or late, cortical malformation, or neonatal epilepsy syndromes, which may be benign (e.g., benign familial neonatal seizures) or severe (e.g., early infantile epileptic encephalopathy[EIEE]), should be considered. 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 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 early suppression of the mental status, sometimes with coma and low tone, 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 anticonvulsant drugs 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 (TH) has become the standard of care in neonates with suspected hypoxic injury. TH 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. Although rare, the occurrence of a first neonatal seizure during rewarming has also been described.

2. **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 strokes, seizures may not always be preceded by encephalopathy. Asymmetries of the motor examination are often lacking in these infants, and diagnosis may be delayed until later in their first year if they do not present with neonatal seizures. Focal electrographic seizures as well as focal attenuation of EEG background activity and focal sharp waves support the clinical suspicion for infarction.

Table 56.2. Etiologies of Neonatal Seizures

Hypoxic-ischemic injury Perinatal asphyxia
Focal infarction Arterial Venous
Intracranial hemorrhage Intraventricular Parenchymal Subdural Subarachnoid
CNS infection as per regional patterns (*Escherichia coli,* Klebsiella, *Staphylococcus,* Pseudomonas, Acinetobacter, Candida, HSV, GBS, *Listeria monocytogenes*)
Malformations and other structural lesions Neuronal migration disorders Cerebral dysgenesis Neurocutaneous disorders, e.g., Sturge–Weber syndrome, tuberous sclerosis
Acute metabolic disorders Hypoglycemia 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's syndrome, EME)
CNS, central nervous system; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic epilepsy; GBS, group B *Streptococcus*; GLUT-1, glucose transporter-1; HSV, herpes simplex virus

3. **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. Normal delivery or deliveries with 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, the 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 the diagnosis important. In the term infant presenting with hemorrhage, sinovenous thrombosis should 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.

4. **Central nervous system (CNS) infection.** CNS infections account for about 5% of neonatal seizures. **Congenital intrauterine infections** such as with cytomegalovirus (CMV), toxoplasma, and rubella may present early (first 2 days) with seizures in severe cases while herpes simplex encephalopathy presents in the second or third week of life. 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** (causative organism in Asian region are mostly gram negative bacteria, *Staphylococcus aureus,* and Candida) is often complicated by meningitis and may be associated with seizures. In this setting, the newborn has often been well for a couple of days, only to deteriorate later with seizures occurring after the first 48 to 72 hours.

5. **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 <45 mg/dL (<2.6 mmol/L) in the first 24 hours and <50 mg/dL (<2.8 mmol/L) after 24 hours (see Chapter 24). 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.

   b. **Hypocalcemia.** Whole blood ionized calcium (iCa) is the best measure of calcium status in ill infants. Hypocalcemia is ionized calcium (iCa) <4.4 mg/dL (<1.1 mmol /L) in infants >1,500 gram birth weight and <4.0 mg/dL (<1 mmol/L) in infants <1,500 gram birth weight. **Early onset** hypocalcemia occurs in the first 3 days of life and is associated with

prematurity, infants of diabetic mothers, fetal growth restriction, and perinatal asphyxia. Most newborn 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's 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.

6. **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 the ophthalmic branch of the trigeminal 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.

7. **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 GLUT-1 deficiency, which impairs glucose transport across the blood–brain barrier, with resulting developmental delay and seizures. This illustrates the importance of identifying these disorders, because this disorder 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 coagonist 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-aminoadipic semialdehyde (α-AASA) dehydrogenase and accumulation of α-AASA in the 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 intravenous (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, identified by novel peaks in CSF chromatography (monoamine metabolites), 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.** Some of these patients also respond to a lysine-restricted diet.

8. **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 asymmetric). 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, although they may sometimes last few months. Some cases are associated with a mutation of the SCN2A gene. More severe epilepsy syndromes are also seen presenting in this period. These include the following:

   a. **Early myoclonic epilepsy** (EME), often presenting in the first few days of life with focal motor seizures and myoclonus, which may be subtle and erratic and usually affects the face and limbs. Tonic seizures appear relatively

late in this disorder. The seizures are very refractory to medications. The EEG is characterized by a burst-suppression pattern, which may be seen only in sleep, and, if present throughout the sleep–wake cycle, is exacerbated by sleep. This syndrome is often associated with underlying metabolic disorders, for instance, glycine encephalopathy (described earlier). Development is severely affected, and many infants die, often within their first year.

b. EIEE (Ohtahara's syndrome) is also associated with very refractory epilepsy. In contrast to EME, it is characterized by early onset of tonic spasms along with focal motor seizures. Myoclonus is rare in the early stages of this disorder. It, too, is associated with a burst-suppression pattern on EEG, which is relatively invariant. Whereas EME tends to be associated with underlying metabolic disorders, EIEE is more likely to be associated with structural lesions. Developmental prognosis is also poor in this syndrome, with many evolving to a chaotic epileptiform pattern known as hypsarrhythmia on EEG and accompanied by infantile spasms. Advances in the understanding of the complex molecular genetics of epilepsy have revealed associations between the earlier disorders and abnormality in a number of genes (e.g., ARX, STXBP1, KCNQ2, SCN2A). There is not a 1:1 phenotype:genotype relationship in this setting, and it may be that the same genetic disorder can be associated with either EME or EIEE, for as yet unknown pathophysiologic reasons. It is now possible, at some cost, to test arrays of genes implicated in particular clinical scenarios. The proportion of these cases for which a genetic diagnosis is possible continues to increase.

c. Malignant migrating partial seizures in infancy (Coppola's 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 anticonvulsant medications. Developmental status is acutely affected and prognosis for normal outcome is poor, although cases with less than devastating outcome have now been described. Although there is genetic heterogeneity, most are associated with mutations of the KCNT1 gene. There have been reports of response to quinidine in such patients, although a recent report of quinidine use in 40 patients with KCNT1 epilepsy showed seizure control in only 20% of patients.

Neonatal-onset epileptic encephalopathies related to **mutations of SCN2A and KCNQ2 genes respond better to sodium channel blockers such as phenytoin and carbamazepine.**

9. Other high-risk subpopulations

a. Extracorporeal membrane oxygenation (ECMO). Critically ill neonates requiring ECMO have been identified by recent guidelines as a population at a high risk for seizure due to the high risk of cerebral injury during the transition to ECMO. These patients typically remain paralyzed and sedated, further masking clinical signs of seizure. The pediatric Extracorporeal Life Support Organization (ELSO) registry reported a 11% incidence of ICH after neonatal respiratory ECMO and an incidence of EEG-detected seizures of 3% and 4% after respiratory and cardiac ECMO, respectively.

b. Congenital heart disease. Neonates that undergo surgery for congenital heart disease are known to be at risk for seizure 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 anticonvulsant treatment of ongoing seizures. Continuous aEEG monitoring especially in an asphyxiated newborn undergoing TH may help in both detection of seizures and prognosis. 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 limited. Head computed tomography (CT) and especially brain MRI are more helpful to confirm these disorders. 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 anticonvulsant 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 anticonvulsant drugs 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 anticonvulsant medications. Some newborns may not need treatment with anticonvulsant 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 events may be prolonged and refractory to treatment, and efforts to eliminate them may be limited by systemic vulnerability to the circulatory effects of anticonvulsant medications.

Adverse effects of anticonvulsants, aside from respiratory and cardiovascular suppression, are also of concern in the developing brain. In studies of normal immature animals, many anticonvulsants, 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 does not appear to have this effect.**

A number of factors alter the pharmacokinetics of the anticonvulsant drugs 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 anticonvulsant drugs so that changes in dosing are required to maintain therapeutic drug levels over the first weeks of life.

TH offered to a newborn with HIE has also been seen to alter the pharmacokinetics of certain anticonvulsants. Although one study showed that the severity of asphyxia and TH altered the clearance of phenobarbitone, most other studies showed no change in pharmacokinetics of phenobarbitone during TH. There was reduced clearance of midazolam and lidocaine during TH. Hence, there is a need for careful consideration and caution while using anticonvulsant during TH.

When anticonvulsant treatment is indicated, phenobarbital is the drug most commonly used as first-line therapy. Other options include fosphenytoin, leviteracetam, and benzodiazepines. A randomized control trial treatment with phenobarbital and phenytoin 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.

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 sulfate, 12.5% (125 mg/mL) 50–100 mg/kg IV; 50% (500 mg/mL) 0.2 mL/kg IM

IV, intravenous.

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 newborn 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 greater than 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 newborn. Onset of action is within minutes for both drugs; however, the 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. **Diazepam should be used with caution in newborns since its therapeutic dose may be higher than its toxic dose** and it may cause respiratory depression and circulatory collapse when used with phenobarbitone. The preservative in diazepam (benzoate) may also displace bilirubin from albumin predisposing to bilirubin encephalopathy. 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 anticonvulsant 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. It acts by binding to synaptic vesicle protein 2A,

inhibiting neuronal calcium release, and inhibits increased interneuronal synchronous activity. Its IV formulation, benign side effect profile, and limited interactions make it an attractive treatment option. Reported loading doses vary from 10 to 20 mg/kg to as high as 40 to 50 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, thrice daily dosing has been suggested. An ongoing phase II trial (LEVNEONAT-1) is looking at the optimal dosing in newborns for seizure control.

E. Topiramate. Topiramate is often used adjunctively after the acute phase of neonatal seizure for continued refractory neonatal seizures. It is thought to have neuroprotective properties. Studies of topiramate in human neonates are ongoing. One drawback is the lack of an IV preparation.

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. It can also cause arry thmias and bradycardia and the propensity to arry thmias is increased when there is concomitant use of phenytoin.

Orally administered anticonvulsants 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 (risk of hyperammonemia).

No guidelines exist as to the appropriate duration of anticonvulsant treatment for newborns with seizures, and there is wide variation in practice. There is a trend toward shorter therapy (around 72 hours), taking into account the short-lived nature of precipitating causes, the recovery from acute HIE in many instances, and the possible detrimental effect of anticonvulsants 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 the 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, occur at a high rate of up to 30% to 35%, with postneonatal seizures 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 examination, normal or mildly abnormal neonatal EEG background activity, and normal neuroimaging or abnormalities limited to extraparenchymal injury (Table 56.4).

Table 56.4. Anticonvulsant Drug Doses for Initial Management of Neonatal Seizures

Drug	Initial Dose	Maintenance
Phenobarbital	20 mg/kg IV Consider further 5-to 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	5 mg/kg/day divided BID to QID
Benzodiazepines	Lorazepam: 0.05–0.1 mg/kg IV Diazepam: 0.3 mg/kg IV Midazolam: 0.15 mg/kg bolus	
Levetiracetam	20–50 mg/kg bolus	20–80 mg/kg divided BID or TID

IV, intravenous; PE, phenytoin equivalent (1.5 mg fosphenytoin gives 1 mg of phenytoin).

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57 Neural Tube Defects

Anne R. Hansen and Benjamin Warf

KEY POINTS

- Prenatal repair can potentially improve the outcomes of neural tube defects, but is associated with a risk of maternal morbidity and preterm delivery.
- Preoperatively, minimize bacterial colonization and tissue damage by keeping the newborn in a prone position with a sterile saline–moistened gauze sponge placed over the defect covered by a plastic wrap.
- Administer intravenous antibiotics (ampicillin and gentamicin or as per local antibiotic policy) to diminish the risk of meningitis.
- Ensure that no latex equipment is used, to avoid the development of severe allergy to latex rubber following repeated exposure.
- After surgical closure of back, follow the baby for signs of hydrocephalus - bulging anterior fontanel, rapidly increasing head circumference, and rapidly progressive ventriculomegaly on ultrasound. Stridor and swallowing difficulties are ominous signs, suggestive of coning due to severe hydrocephalus.
- There is an increasing trend to avoid or delay VP shunt, benefits of shunt are not proven and risks of VP shunt are significant.

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 and the Arnold–Chiari II (ACII) malformation (malformation of the pons and medulla, with downward displacement of the cerebellum, medulla, and fourth ventricle into the upper cervical region), with associated aqueduct stenosis and hydrocephalus.

a. **Myelomeningocele** is the most common primary neural tube defect. It involves a saccular outpouching of neural elements (neural placode), typically through a defect in the bone and the soft tissues of the posterior thoracic, sacral, or lumbar regions—the latter comprising 80% of lesions. Arachnoid is typically included in the sac (meningo), which contains visible neural structures (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 the hydrocephalus and the malformation has been significantly re-evaluated 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 of anterior neural tube closure is an outpouching of the dura with or without the brain, noted in the occipital region, in 80% of cases and less commonly in the frontal, parietal, or temporal region. It may vary in size from a few millimeters to many centimeters.

c. **Anencephaly.** In the most severe form of this defect, the cranial vault and posterior occipital bone are defective, and derivatives of the neural tube are exposed, including both the brain and the bony tissue. The defect usually extends through the foramen magnum and involves the brainstem. It is not compatible with long-term survival. Rachischisis is a 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.** Five percent of all neural tube defects result from abnormal development of the lower sacral or coccygeal segments during secondary neurulation. This leads to defects primarily in the lumbosacral spinal region. These heterogeneous lesions are rarely associated with hydrocephalus or the Chiari II malformation, and the skin is typically intact over the defect. Because the hindbrain abnormality of the Chiari II malformation is evident on prenatal scans, this radiographic finding is useful in distinguishing open from closed neural tube abnormalities.

a. **Meningocele** is a spinal fluid-filled sac causing an outpouching of the skin and dura without involvement of the neural elements aside from a commonly associated dorsal band of neurovascular tissue adherent to the sac. Meningoceles may be associated with bone and contiguous soft-tissue abnormalities.

b. **Lipomeningocele** is a lipomatous mass usually in the lumbar or sacral region, occasionally off the midline, typically covered with full-thickness skin. Adipose tissue frequently extends through the defect into the spine and dura and adheres extensively to a distorted spinal cord or nerve roots.

c. Filum lipoma, **sacral agenesis/dysgenesis, diastematomyelia, and myelocystocele**, all may have varying degrees of bony involvement. Although rarely as extensive as with primary neural tube defects, neurologic manifestations may be present representing distortion or abnormal development of neural structures. These lesions may be inapparent on physical examination of the child, resulting in the use of the term *occulta* to describe them.

B. Etiologies. The exact cause of failed neural tube closure 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's syndrome (autosomal recessive syndrome of encephalocele, polydactyly, polycystic kidneys, cleft lip and palate), as well as other chromosome disorders. Although specific genes (particularly those in the folate–homocysteine pathway as well as genes involved in planar cell polarity) have been implicated as risk factors, the genetics is likely complex and multifactorial (see Chapter 10). In a systematic review pregestational diabetes, low birth weight, female gender, low paternal age, stressful life events, and low maternal education were modestly associated with NTD.

C. Epidemiology and recurrence risk. The incidence of neural tube defects varies significantly with geography and ethnicity. The worldwide incidence of spina bifida is approximately 4.63 per 10,000 births. In the United States, the overall frequency of neural tube defects is approximately 1 in 2,000 live births. The literature may underestimate the true prevalence 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 in 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's 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. Controlled, randomized 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. 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.

E. Clinical outcome. Clinically, spina bifida leads to difficulties with mobility and ambulation, which is largely dependent on the lesion level; by adulthood, independent ambulation is seen in 93% of patients with a sacral lesion, 91% with an L5 lesion, 57% with an L4 lesion, and no patients with an L1–3 or thoracic lesion. Sensory deficits and orthopedic abnormalities, such as talipes (clubfoot), kyphosis, and scoliosis, can also occur. Most patients with spina bifida experience neurogenic sphincter dysfunction resulting in impaired bladder and bowel control.

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 on 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 Arnold–Chiari malformation has a sensitivity of >90%. The Chiari malformation is seen as a flattened cerebellum 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), but an appreciation of the level of disruption can be helpful in that higher spinal levels within the thoracolumbar range portend a correspondingly higher level of neurologic deficit. Some patients with higher thoracic or cervical lesions, however, have remarkable preservation of function; often, restitution of the spinal cord below the lesion is evident by MRI in these cases.

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 cerebrospinal fluid (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 the ventricular size. Assess the intracranial pressure (ICP) with the baby sitting upright by palpating the anterior fontanel and tilting the head and torso forward until the midportion of the anterior fontanel is flat. The fontanels may be quite large and the calvarial bones widely separated (see Chapter 54).
3. **Eyes.** Abnormalities in conjugate movement of the eyes are common and include esotropias, esophorias, and abducens paresis.
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 the 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. Carefully examine deep tendon reflexes (see 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 (manual pressure on the abdomen at the location of the bladder) 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 [VSD]), 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.

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 ham-strings	—	Knee jerk	May ambulate with braces and crutches
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: From Noetzel MJ. Myelomeningocele: current concepts of management. *Clin Perinatol* 1989;16:311–329.

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 this hospitalization.
6. **Physical therapy.** Involve physical therapists in planning for outpatient physical therapy programs.
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

1. **Rationale**. Both clinically and in animal models, the neurologic effects of spina bifida have been shown to worsen throughout gestation. These observations led to the development of a "two-hit" hypothesis, in which the final neurologic deficit results from a combination of the primary failure of neural tube formation and later injury from trauma and amniotic fluid toxicity. The corollary of this theory is, therefore, that earlier repair, while still *in utero*, should result in an improved outcome for the patient.
2. **Open fetal repair**. *In utero* open fetal repair of spina bifida was first performed in 1994. Observational studies have found that *in utero* repair is associated with lower rates of ventriculoperitoneal (VP) shunting and consistent reversal of hindbrain herniation. Long-term effects remain uncertain. The Management of Myelomeningocele Study (MOMS), a randomized clinical trial comparing outcomes after *in utero* and postnatal surgery, was conducted by three US centers

already performing fetal spina bifida repair. Fetal surgery was offered in the trial between 19+0 and 25+6 weeks of gestation. A standardized method of repair was agreed across the three centers; this included a maternal laparotomy and stapled hysterotomy and layered neurosurgical repair as performed in postnatal surgery. The results of the study are shown in Table 57.2.

As is clearly evident from the results, prenatal surgery improved the outcomes of neural tube defects but was associated with significantly increased maternal and prematurity-related risks. Preterm delivery as well as uterine scar dehiscence/rupture risk was increased in these women even in subsequent pregnancies.

3. **Mini-hysterotomy.** A less invasive alternative is the use of a "mini-hysterotomy," i.e., a uterine opening with a diameter of less than 4 cm, as opposed to 8 cm in open repair. Through this opening, a standard multilayer microsurgical repair is performed. In a case series of 45 patients, there was a reduced rate of preterm rupture of membranes (23%), a slightly higher gestational age at delivery (35 weeks), and a 95% intact hysterotomy site at delivery.
4. **Fetoscopic repair.** Fetoscopic repair has also been tried in many centers but does not yet clearly confer a fetal benefit equal to open repair and appears to be associated with higher rates of prematurity and preterm rupture of membranes.

Table 57.2. Summary of Main Risks and Benefits of Prenatal Surgery from the Management of Myelomeningocele Study (MOMS)

Outcome	Prenatal Surgery, *n* (%)	Postnatal Surgery, *n* (%)	*P* Value
Fetal benefits			
Shunt placement at 12 months	40 (44)	77 (84)	<0.0001
Hindbrain herniation at 12 months	45 (64)	66 (96)	<0.001
Independent walking at 30 months	39 (44.8)	21 (23.9)	0.01
Maternal risks			
Pulmonary edema	5 (5.5)	0 (0)	0.03
Placental abruption	6 (6.6)	0 (0)	0.01
Blood transfusion at delivery	8 (8.8)	1 (1.1)	0.02
Spontaneous membrane rupture	40 (44.0)	7 (7.6)	<0.0001
Chorionic membrane separation	30 (33.0)	0 (0)	<0.0001
Fetal/neonatal risks			
Bradycardia during repair	8 (10)	0	0.003
Perinatal death	2 (3)	2 (2)	1.00
Average gestational age at birth	34.1 ± 3.1	37.3 ± 1.1	<0.001
Respiratory distress syndrome	16 (21)	5 (6)	0.008

B. Perinatal. *Cesarean section prior to the onset of labor is the preferred mode of delivery* because it decreases the likelihood of rupturing the meningeal sac and is associated with improved neurologic outcome.

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 result from premature fusion of the posterior fossa leaving insufficient space for the cerebrum, cerebellum, and brainstem. 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 majority of the time.
   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. **Meningitis.** Administer intravenous antibiotics (ampicillin and gentamicin or as per local antibiotic policy) to diminish the risk of meningitis, particularly due to group B streptococci (Gram-negative microbes are common in Asian setting, making cefotaxime or meropenem the preferred antibiotic). 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 a 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 whether 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 equipment should be used.
6. **Surgical treatment.** Open defects must be urgently closed 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 meningomyelocele 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 rare occurrence of intracranial hypertension can be initially controlled by ventricular puncture or continuous ventricular drainage. If hydrocephalus is severe from birth, it can be treated at the same time as the back closure. Because hydrocephalus often progresses following closure of the back in untreated patients, anterior fontanel tension and head circumference should be carefully monitored. Due to experience with prenatal closure and known complications with permanent shunting, increasingly, practitioners are trying to delay or avoid permanent shunting and to consider such alternatives as endoscopic third ventriculocisternostomy with choroid plexus cauterization (ETV-CPC). Regardless of the planned strategy for dealing with hydrocephalus, close monitoring is important.

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, and then the placode is rolled into a more normal shape and gently held in this configuration with fine, pial sutures. The edges of what would have been dura mater are identified, isolated, and closed over the placode, and then the skin is closed with the goal of attaining a well-vascularized, watertight closure.

7. **Management of hydrocephalus.** A systematic review of large number of neural tube defects showed no difference in outcomes when VP shunt was done simultaneously with the local repair of defect versus delayed shunt. The current trend is to avoid VP shunts as far as possible due to lack of evidence of benefit to development in long term and risks of malfunction and infection necessitating second surgery. The threshold for VP shunt is higher, larger ventricles sizes are observed conservatively. ETV-CPC, is an alternative to VP shunt, creating an internal rerouting of CSF flow while decreasing CSF production. This combination of procedures may eliminate the need for shunts in about 75% of the infants with myelomeningocele requiring hydrocephalus treatment. This has become our primary initial treatment for the majority of these patients.

D. 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 a 20% to 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. Acute deterioration in feeding skills may, as with stridor, signal the need for assessing the status of hydrocephalus and, less commonly, consideration of posterior fossa decompression.

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 urodynamic studies. It 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 the spine. Abnormalities in vertebral bodies, absent or defective posterior arches, and evidence of kyphosis are common.

d. Evidence of dysplasia of the 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 should not 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 (available online at www.sbaa.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 for those with myelomeningocele. 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, psychiatry, gastroenterology, endocrinology, pulmonary medicine, and physical, occupational, and speech language pathology.

1. Neurosurgical issues. In one cohort study of myelomeningocele patients, 86% underwent VP shunt, the large majority of whom required additional shunt revision. Release of tethered cord was required in 32%, and scoliosis was diagnosed in 49%, of whom approximately half required a spinal fusion procedure. 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 unshunted child, shunt malfunction or infection in the shunted child, or failure of ETV-CPC to adequately address the problem. 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, and paralysis of upward gaze

ii. New onset of respiratory complications, particularly stridor from vocal cord paralysis, and 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 shunt malfunction but may also disappear without treatment. After insuring 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.

c. Seizures remain a risk, and families should be familiar with signs and symptoms to monitor as well as an initial treatment approach.

2. **Motor outcome.** This depends more on the level of paralysis and surgical intervention than 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 observation. 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, and 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. One study found that although 37% of individuals with myelomeningocele required additional assistance with school work or attended special education classes, 85% were attending or had graduated from secondary school or college.

4. **Hearing and vision** status must be formally reassessed to rule out any contribution to learning difficulties.

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 the risk of aspiration with oral feeds.
   b. *Arm span may be a more accurate reflection of growth than measurement of height* because growth below the waistline is usually disproportionately slow or distorted by lower extremity or spinal deformities.
   c. Skin fold 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.

   These services should be established through District Early Intervention Centers (DEIC)
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

James R. Kasser

KEY POINTS

- **Foot deformity:** Club feet, fixed deformities of the feet, or vertical talus at birth should be treated with exercise or early casting.
- **Hips:** Hip instability should be treated (splint) in the newborn only if severe or if persistent at 2 to 8 weeks. Early splint application does not benefit since it increases the risk of avascular necrosis.
- **Neonatal compartment syndrome:** It presents with upper extremity swelling and ulceration or bulbous skin lesion requiring emergency treatment.

I. INTRODUCTION.

This chapter considers common musculoskeletal abnormalities that may be detected in the neonatal period. Consultation with an orthopedic surgeon is often required to provide definitive treatment after the initial evaluation.

There is a significant change in guideline on screening newborns for dislocatable hip, early treatment using Pavlik harness is not preferred. Decision to treat unstable hips is deferred till 3 to 4 months age.

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** but may be secondary to muscle adaptation from an abnormal *in utero* position of the head and neck.

1. **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 mass is frequently found in the SCM muscle. This mass gradually disappears and the muscle fibers are partially replaced by fibrous tissue, which contracts and limits head motion. Because of 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 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.

3. **Treatment.** Most infants will respond favorably to positioning the head in the direction opposite to that produced by the tight muscle. ***Most infants require no active treatment.*** Padded bricks or sandbags can be used to help maintain the position of the head until the child is able to move actively to free the head. Passive stretching by rotating the head to the ipsilateral side and tilting it toward the contralateral side also may help. The torticollis in most infants resolves by the age of 1 year. Helmets are sometimes used to treat persistent head asymmetry after a few months of age. Patients who have asymmetry of the face and head and limited motion after 1 year should be considered for surgical release of the SCM muscle.

B. Differential diagnosis. Torticollis with limited motion of the neck may be due to a congenital abnormality of the cervical region of the spine. Some infants with this disorder also have a tight SCM muscle. These infants are likely to have significant limitation of motion at birth, generally not seen in CMT. Radiologic evaluation of the cervical region is necessary to make this diagnosis. Beyond the newborn period, infection in the retropharyngeal area may present with torticollis. The neck mass seen in torticollis in the SCM muscle may be differentiated from other cervical lesions by ultrasonography.

III. POLYDACTYLY

A. Duplication of a digit may range from a small cutaneous bulb to an almost perfectly formed 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 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. ***Do not tie off digits on the radial side of the hand (thumb) or the medial border of the foot.***

2. When duplicated digits contain bone or muscle attached by more than a small bridge of the 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. FRACTURED CLAVICLE (see Chapter 6)

A. The clavicle is the site of the most common fracture associated with delivery.

B. Diagnosis is usually made soon after birth, when the infant does not move the arm on the affected side or cries when that arm is moved. There may be

tenderness, swelling, or crepitance at the site. Occasionally, the bone is angulated. Diagnosis can be confirmed by radiographic examination. A "painless" fracture discovered by radiography of the chest is more likely a congenital pseudarthrosis (nonunion). Most pseudarthroses occur on the right side or are bilateral. There are case reports of left side involvement with dextrocardia and cervical ribs.

C. The clinical course is such that clavicle fractures heal without difficulty. **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. We usually pin or tape the infant's sleeve to the shirt and put a sign on the baby to remind personnel to decrease motion of the clavicle. No reduction is necessary. If the fracture appears painful, a wrap to decrease motion of the arm is useful.

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. 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. Congenital scoliosis is differentiated from **infantile scoliosis**, in which no vertebral anomaly is present. Infantile scoliosis often improves spontaneously, although the condition may be progressive in infants who have a spinal curvature of >20°. If the scoliosis is progressive, treatment is indicated and magnetic resonance imaging (MRI) of the spine looking for spinal cord pathology should be done. Rarely, severe congenital scoliosis may be termed *thoracic insufficiency syndrome* and be associated with pulmonary compromise.

B. Clinical course. Congenital scoliosis will increase in many patients. Bracing of congenital curves is usually not helpful. Body casts for correction of the deformity are beneficial, allowing growth at the chest and lungs. Surgical correction with chest expansion or limited fusion may be indicated before the curve becomes severe. Many patients with congenital curves have renal or other visceral abnormalities. Abdominal ultrasonography is used to screen all such patients.

VI. DEVELOPMENTAL DYSPLASIA OF HIP. Screening of newborns is associated with overtreatment:

Screening hips of all newborn babies by clinical examination or by ultrasound (or directed ultrasound for high-risk babies) does not seem to benefit (by decrease in the need for late surgical treatment); on the contrary, the number of neonates treated (overtreated) is likely to be more. Some of these treated neonates are at risk of avascular necrosis. Currently, there is no evidence-based recommendation of clinical/ultrasound screening of hips of all newborn. When examined, mild dislocation (Barlow's test) must be observed and decision to treat taken after 2 to 8 weeks.

A. Examination and screening

1. Ortolani's test, performed gently, is useful to detect developmental dysplasia of the hip (DDH) till the baby is 3 months old.
2. Mild DDH (Barlow's test) is not an indication for referral for ultrasound or to an orthopedician. Such referrals will result in overtreatment.
3. Ultrasonographic examination of the hip is useful for diagnosis in high-risk cases (physical examination finding + family history or female breech).

Ultrasonography is delayed as a screening technique until 1 month 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 calcified and is recommended after 4 to 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 increases the incidence of DDH.

B. There are three types of congenital dislocations.

1. The **classic DDH** is diagnosed by the presence of Ortolani's sign. The hip is unstable and dislocates on adduction and also on extension of the femur but readily relocates 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 usually 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 2 to 8 weeks of life should be treated with a splint that keeps the hips flexed and abducted. The Pavlik harness has been used effectively to treat this group of patients, with approximately 80% success rate. Ultrasonography is used to monitor the hip during treatment as well as to confirm the initial diagnosis. Failure of Pavlik harness was associated with severity of hip dislocation and with age at initiation of treatment.
2. The **teratologic type of dislocation** occurs very early in pregnancy. The femoral head does not relocate on flexion and abduction; that is, Ortolani's sign is not present. If the dislocation is unilateral, there may be asymmetry of the gluteal folds and asymmetric motion with limited abduction. In bilateral dislocation, the perineum is wide and the thighs give the appearance of being shorter than normal. This may be easily overlooked, however, it requires 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 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. Treatment of the dysplasia is with the Pavlik harness, but after the age of 8 months, other methods of treatment 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. The latter two abnormalities are more serious and require more extensive treatment.

A. Congenital genu recurvatum is secondary to an *in utero* position with hyperextension of the knee. This can be treated successfully by repeated cast changes, with progressive flexion of the knee until it reaches 90° of flexion. Minor degrees of recurvatum can be treated with passive stretching exercises. It may be associated with DDH.

B. All infants with **hyperextension of the knee** should have a 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 subluxed knee with dislocation, the tibia is completely anterior or anterolateral to the femur. The tibia is shifted forward in relation to the femur and is frequently lateral as well.

Congenital fibrosis of the quadriceps is frequently associated with the fixed dislocated knee and open reduction is essential, as attempted treatment of the dislocated knee by stretching or by repeated cast changes is hazardous and may result in epiphyseal plate damage.

C. Treatment. Hyperextended or subluxed knees are treated with manipulation and splinting after delivery with progressive knee flexion and reduction. Fixed dislocation of the knee will require open reduction but not in 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 probably caused by an *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 definitely identified but is probably related to an *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 is necessary 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 leg. Structural changes in the bones do not seem to be present. The sequela to this deformity appears to be a valgus or pronated foot that is more severe 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 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*; a fixed or rigid calcaneovalgus deformity probably represents a congenital vertical talus. It may also be related to a short tibia with posteromedial bow.

C. Congenital clubfoot is a deformity with a multifactorial etiology. It occurs with a 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. **There are three and sometimes four components to the deformity.** 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.
2. Treatment should be started early within a few days of birth. An effective method of treatment consists of manipulation and application of either tapes or plaster or fiberglass casts that are changed weekly. The Ponseti's 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. Physical therapy and splinting are used in a newborn with complex medical problems as initial management.

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. This is a very rare but potentially devastating condition if diagnosis is delayed. 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 the 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 the evolution of neonatal compartment syndrome. Intrauterine abnormalities or birth trauma may be related to this abnormality.
2. **Treatment.** If recognized early, treatment with emergency fasciotomy or revascularization of the limb has been beneficial. Prolonged ischemia results in scarring (known as Volkmann's ischemic contracture of muscle), nerve injury, permanent disability, and potential loss of a portion of the extremity.

Suggested Readings

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59 Osteopenia (Metabolic Bone Disease) of Prematurity

Steven A. Abrams

KEY POINTS

- Metabolic bone disease of prematurity (MBDP) remains a common problem for very preterm infants. The most common cause is inadequate dietary minerals.
- Other factors which may contribute to MBDP include use of loop diuretics, steroids, chronic immobility, and, in some cases, vitamin D deficiency.
- Prevention of MBDP is best done by the use of human milk fortifiers and specialized preterm and transitional formulas, and limiting the use of diuretics that cause calcium excretion, such as furosemide.

I. GENERAL PRINCIPLES

A. Definition. Metabolic bone disease of prematurity (MBDP) is the undermineralization of the preterm infant's skeleton arising from inadequate calcium and phosphate mineral, both prenatally and postnatally.

1. MBDP 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 is estimated to occur in 16% to 40% of VLBW infants and extremely low-birth-weight (<1,000 g) babies. 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 100 to 130 mg of calcium and 60 to 70 mg of phosphorus/kg/day. Poor mineral intake and absorption after birth result in undermineralized new and remodeled bone (Table 59.1).
   a. Diets low in mineral content. These diets predispose preterm newborns to metabolic bone disease of prematurity (MBDP).
   b. Unsupplemented human milk. In this circumstance, urinary calcium loss increases, suggesting a phosphorus deficiency, an issue that is greater than the calcium deficiency.
   c. Long-term use of parenteral nutrition

d. 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.

e. Furosemide therapy. This causes renal calcium wasting but is not likely the principal contributor to osteopenia for most preterm infants.

f. Long-term steroid use. Steroids can cause increased bone resorption and reduced bone formation. They can also reduce gut absorption of minerals.

2. Vitamin D deficiency. Vitamin D deficiency is not a major factor for MBDP. It may be ideal to maintain 25-hydroxy vitamin D levels more than 50 nmol/L.

II. DIAGNOSIS

A. Clinical presentation

1. Osteopenia (characterized by bones that are undermineralized or "washed out") develops during the first postnatal week. Signs of rickets (epiphyseal dysplasia and skeletal deformities) usually become evident after 6 weeks postnatal age or by term-corrected gestational age. The risk of bone disease is greatest for the sickest, most premature infants.

B. History

1. History of VLBW, especially <26 weeks or 800 g birth weight, prolonged parenteral nutrition, or long-term steroids is very common.

2. Rapid increase in alkaline phosphatase (ALP) value is common.

3. A history of a fracture noticed by caregivers or incidentally on x-rays taken for other purposes may be seen.

Table 59.1. Risk Factors for Metabolic Bone Disease of Prematurity

Prematurity, low gestational age, and birth weight **SGA**	**Optimize Timing of Delivery of Preterm Baby**
Feeding practices	Delayed enteral feeding Prolonged total parenteral nutrition, NEC/bowel perforation Use of unfortified human milk
Drugs	Corticosteroids, loop diuretics (furosemide), methylxanthines
Vitamin D deficiency	Exclusive breast milk feeding Malabsorption of vitamin D and calcium (e.g., cholestasis, short gut syndrome)
Prolonged immobilization	Paralysis/sedation, infants with neuromuscular disorders
Aluminum-containing parenteral nutrition	

NEC, necrotizing enterocolitis; SGA, small for gestational age.

C. Physical examination

1. **Infants with MBDP demonstrate few symptoms or signs until late into the disease process.** 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.

D. Laboratory studies

1. **Laboratory evaluation.** The earliest indications of osteopenia are often a decreased serum phosphorus concentration and an increased ALP activity. Serum phosphate level <5.6 mg/dL (<1.8 mmol/L) is associated strongly with radiologic evidence of rickets. However, it is often difficult to distinguish the normal rise in ALP activity associated with rapid bone mineralization from the pathologic increase related to early osteopenia. ALP increases over the first 3 weeks of life and reaches peak at 6 to 12 weeks of age. ALP >500 IU is suggestive of impaired bone homeostasis and values >700 IU/L are associated with bone demineralization, despite the absence of clinical signs. Combination of serum phosphate level <5.6 mg/dL (<1.8 mmol/L) and ALP level >900 IU/L in preterm infants (<33 weeks) indicates low bone mineral density (BMD) and has a sensitivity of 100% and specificity of 70% for MBDP.

   In this circumstance, decreased bone mineralization observed on a radiograph confirms the diagnosis.

   a. Serum calcium level (low, normal, or slightly elevated) is not a good indicator of the presence or severity of MBD; it is often maintained normal, despite MBD.

   b. Serum ALP level (an indicator of osteoclast activity) is often but not invariantly correlated with disease severity (>1,000 IU/L in severe rickets).

   c. Normal neonatal range of ALP is much higher than in adults. Values of 400 to 600 IU/L are common in VLBW infants with no evidence of osteopenia.

   d. Hepatobiliary disease also elevates ALP level. Determining bone isoenzymes may be helpful but is not usually clinically necessary.

   e. Solitary elevated ALP 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.

   f. Serum 25(OH)D levels do not need to be routinely assessed in preterm infants. Optimal levels in infants are unknown as are functional outcomes at any level. When assessed, targets of >20 ng/mL are reasonable based on very limited evidence. There is no evidence that levels of 12 to 20 ng/mL lead to worsened osteopenia in preterm infants.

   g. An elevated serum parathyroid hormone (PTH) level may be indicative of osteopenia but is not commonly used as a screening tool and may be related to vitamin D status. Elevated PTH levels not only indicate secondary hyperparathyroidism but in association with kidney tubular reabsorption of phosphate (TRP) can also differentiate the underlying cause of hypophosphatemia. A high PTH with low TRP (normal 75% to 85%) indicates calcium deficiency while a normal or low PTH with high TRP indicates phosphate deficiency.

h. Urinary biomarkers. Measurement of TRP is an important second-line investigation. The normal range of TRP is 75% to 91% and a value above 95% is a significant marker of insufficient phosphate supplementation. Tubular phosphorus reabsorption is calculated by the following formula:

$$1 - \left[\frac{\text{urinary phosphorus}}{\text{urinary creatinine}}\right] \times \left[\frac{\text{serum creatinine}}{\text{serum phosphorus}}\right] \times 100$$

Similarly, urinary calcium or phosphate to creatinine ratios may be useful markers for MBD, but these ratios are highly dependent on the dietary intake and also affected by diuretic or methylxanthine use.

E. Imaging

1. **Radiographic signs** include widening of epiphyseal growth plates; cupping, fraying, and rarefaction of the metaphyses; 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.** Measurement of bone mineral content by densitometry or ultrasonography remains investigational in preterm infants. Dual-energy x-ray absorptiometry (DEXA) is a gold standard technique to assess BMD, adaptable in preterm infants. It expresses the bone mineral content as grams of hydroxyapatite per centimeter squared. DEXA values are a function of the size of the bone being measured, its volume, and its density.

     Quantitative ultrasound (QUS) measures both bone mineral content (BMC) and organic matrix. It is a portable modality of investigating MBD in preterms and usually performed on the tibia. Two parameters are evaluated by QUS: speed of sound (SOS) and bone transmission time (BTT). SOS, used most commonly, decreases in preterm infants from birth to term-corrected age and is suggestive of decreased BMC.

III. MANAGEMENT

A. Prevention of metabolic bone disease of prematurity

1. Early enteral feeding. In VLBW infants, early enteral feeding significantly enhances the establishment of full-volume enteral intake, leading to increased calcium accumulation and decreased osteopenia.
2. Fortified breast milk or specialized preterm formula. Mineral-fortified human milk or "premature" formulas are the appropriate diets for preterm infants weighing <1,800 to 2,000 g; their use at 120 kcal/kg/day can prevent and treat MBDP.
3. Decrease the duration of total parenteral nutrition.
4. Provide an appropriate amount of minerals and vitamin D. The recommended calcium, phosphate, and vitamin D are given in Table 59.2.

Table 59.2. Calcium, Phosphate, and Vitamin D Supplementation in Preterm Infants <1,500 g

	TPN During First Week	TPN After First Week (Fluid Intake 140 to 150 mL/kg/day)	Full Enteral Feeding (Breast Milk/Formula)
Calcium	40 to 120 mg/kg/day (1 to 3 mmol/kg/day)	75 to 90 mg/kg/day (1.8 to 2.2 mmol/kg/day)	140 to 160 mg/100 kcal (AAP) 70 to 140 mg/100 kcal (ESPGHAN)
Phosphate	31 to 71 mg/kg/day (1.0 to 2.2 mmol/kg/day)	60 to 70 mg/kg/day (1.9 to 2.2 mmol/kg/day)	95 to 108 mg/100 kcal (AAP) 50 to 86 mg/100 kcal (ESPGHAN)
Vitamin D	160 to 280 IU/day	160 to 280 IU/day	200 to 400 IU/day (AAP)

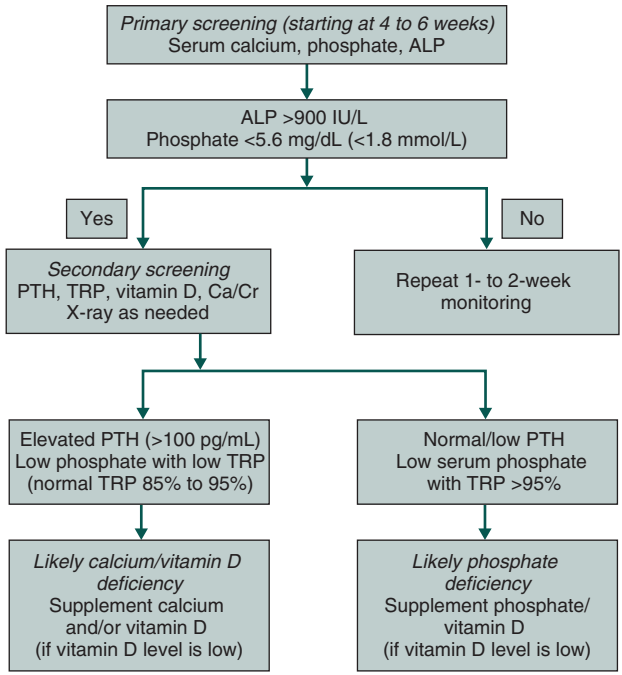
AAP, American Academy of Pediatrics; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; TPN, total parenteral nutrition.

5. Ensure optimal enteral and parenteral calcium and phosphate ratios.
6. Avoid prolonged use of loop diuretics, postnatal steroid therapy, and antacid in neonates.
7. 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.
8. Avoid nonessential handling and vigorous chest physiotherapy in preterm infants with severely undermineralized bones. Recent data suggest that daily passive physical activity (range of motion, 5 to 10 minutes) may enhance both growth and bone mineralization.
9. At hospital discharge, VLBW infants who are formula fed may benefit from the use of a transitional formula that has calcium and phosphorus contents midrange between that of preterm formulas and that of formulas designed for full-term infants. Such infants may need additional vitamin D to achieve an intake of 400 IU/day.

B. Treatment of metabolic bone disease of prematurity

1. Management is based on what the biochemical parameters are pointing to—predominantly calcium or predominantly phosphorus deficiency (Flow chart 59.1).
2. In case of primary phosphate-deficient state (low serum phosphate for age and normal plasma PTH level), phosphate supplementation can be initiated (0.5 to 1.0 mmol/kg/day in two to three divided doses). Calcium supplementation may be necessary in order to maintain optimal enteral calcium to phosphate intake ratios (1.5:1 to 1.7:1 on a milligram-to-milligram basis).

   Avoid giving the two supplements simultaneously or with meals, to avoid precipitation.



Flowchart 59.1. Diagnosis and management of metabolic bone disease.

3. In a primarily calcium-deficient state (low PO_4, elevated ALP and PTH, normal/low calcium), calcium supplementation at daily doses of 0.5 to 1.5 mmol/kg in two to four divided doses is required to normalize elevated plasma PTH, thus reversing the resultant bone resorption and hypophosphatemia.

   Conversely, in this primarily calcium-deficient state, phosphate supplementation will result in binding to ionized calcium, therefore causing a further increase in PTH and in fact exacerbation of MBDP. Therefore, the common practice of *universal phosphate supplementation of all neonates with MBDP should be discouraged without prior measurement of plasma PTH.*

4. Vitamin D supplementation is necessary in infants with MBDP. High doses of vitamin D may be required in case of vitamin D deficiency/insufficiency (<50 nmol/L).

5. Active vitamin D analogues (alfacalcidol, calcitriol) are rarely used in neonatal practice to treat MBDP.

6. Infants at risk of cholestasis and malabsorption may benefit from additional supplementation with fat-soluble vitamins and use of specialized formula to facilitate fat absorption.

7. Monitor 1 to 2 weekly with calcium, phosphate, serum ALP, and PTH and adjusting phosphate and calcium dose if applicable.

C. Postdischarge. Breast milk fortification or postdischarge preterm formulas are indicated until 40 to 52 weeks post-conceptional age or up to 6 months in cases

of poor growth velocity. VLBW infants who are discharged exclusively on breast milk need mineral supplementation if ALP is >800 to 1,000 IU.

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60 Inborn Errors of Metabolism

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KEY POINTS

- Early diagnosis and institution of therapy are mandatory to prevent death and ameliorate complications from many inborn errors of metabolism (IEMs), but neonates with IEMs usually present with nonspecific signs. Therefore, a high index of suspicion and newborn screening are necessary.
- After performing the initial metabolic workup, you can narrow the differential diagnosis by the following categorizations:
  - In metabolic acidosis with hyperammonemia, consider an organic acidemia (or pyruvate carboxylase deficiency if lactate is also very high).
  - In hyperammonemia with respiratory alkalosis, consider a urea cycle defect.
  - In hypoglycemia without ketosis, consider fatty acid oxidation defects.
  - In hypoglycemia with ketosis and elevated lactate, consider fructose-1,6-bisphosphatase deficiency and glycogen storage disease type I.
  - In liver failure, galactosemia and tyrosinemia type I should be evaluated.
  - In cardiomyopathy, consider glycogen storage disease type II and fatty acid oxidation defects.
- When managing acute metabolic decompensation, make sure of the following:
  - Provide adequate calories, at least 20% above what is normally needed.
  - Use insulin infusion to reverse catabolism.
  - Limit the enteral feeding restriction to 24 to 48 hours and introduce enteral feeding with the appropriate formula early (after 24 to 48 hours).

I. INTRODUCTION. Inborn errors of metabolism (IEMs) are a group of disorders each of which results from deficient activity of a single enzyme in a metabolic pathway. Although IEMs are individually rare, they are collectively common, with an overall incidence of more than 1:1,000. More than 500 IEMs have been recognized, more than 100 of which can present clinically in the neonatal period.

IEMs can present in the fetal life, in the neonatal period, or later in childhood and even adult age groups. Most commonly, neonates with IEMs are healthy at birth with signs typically developing in hours to days after birth. The signs are usually nonspecific and may include decreased activity, lethargy, poor feeding, vomiting, respiratory distress, or seizures. These signs are common to several other neonatal conditions, such as sepsis and cardiopulmonary dysfunction. Therefore, maintaining a high index of suspicion is important for early diagnosis and the institution of

appropriate therapy, which are mandatory to prevent death and ameliorate complications from many IEMs.

The vast majority of IEMs are inherited in an autosomal recessive manner. Therefore, a history of parental consanguinity or a previously affected sibling should raise the suspicion of IEMs. Some IEMs, such as ornithine transcarbamylase (OTC) deficiency, are X-linked. In an X-linked disorder, typically affected males have a severe disease, whereas affected females either are asymptomatic or have a milder disease. So, the severely affected family member could be a maternal uncle or a brother, whereas the mildly affected member could be a mother or a sister. IEM can be inherited by autosomal and X-linked dominant inheritance as well.

II. CLINICAL PRESENTATION

A. Spectrum of clinical presentation. IEM can present in various patterns in the neonatal age group. Recognition of these patterns can aid in earlier identification of these diseases as the laboratory investigation can be targeted toward the underlying causes of the presentation. The clinical presentation of IEM in the neonatal age group can be broadly categorized into six patterns (discussed according to age of presentations):

1. **Fetal presentation**. It can present with features of increased fetal movements (which could be due to seizures) and hydrops fetalis (nonimmune), or can be suspected by antenatal ultrasound findings (callosal dysgenesis, holoprosencephaly, brain atrophy, subcortical cysts, cerebellar hypoplasia, ventriculomegaly, etc.).
2. **Floppy neonates**. These neonates can present with marked hypotonia and antenatal- or neonatal-onset seizures, or may have some dysmorphic features. Typical example includes peroxisomal disorders.
3. **Congenital malformations**. It is a rare presentation of IEM. Peroxisomal disorders, congenital disorders of glycosylation (CDG), cholesterol biosynthetic disorders, homocystinuria, pyruvate dehydrogenase (PDH) deficiency, etc., can present with dysmorphic features.
4. **Intoxication**. This is the most common presentation of IEM in the neonatal age group. Characteristically neonates of this phenotype are asymptomatic for the first 1 or 2 days of life and then deteriorate very rapidly beginning with altered higher mental functions, refusal of feeds, vomiting, and altered breathing patterns, and display abnormal neurologic examination. They have a relentless downhill course unless the offending agent is removed, and specific treatments are instituted. This presentation would most likely be confused with sepsis. Three most common IEMs that present this way include organic acidemia, urea cycle disorder (UCD), and aminoacidopathies.
5. **Energy failure**. This is one of the most perplexing presentations and can be present in a variety of ways from the time of birth to infancy or even later. Typical examples include mitochondrial respiratory chain defects, fatty acid oxidation defects (FODs), and congenital hyperlactatemia.
6. **Predominant visceral involvement**. This presentation mainly involves extensive involvement of one organ system (most commonly liver and heart) with collateral effects on other systems. Three main clinical groups of hepatic

symptoms can be identified: liver failure (jaundice, coagulopathy, elevated transaminases, hypoglycemia, and ascites), cholestatic jaundice, and hepatomegaly with or without hypoglycemia. Some IEMs can present predominantly with cardiac diseases, including cardiomyopathy, heart failure, and arrhythmias.

B. Major organ system involvements in IEM. Neonates with IEMs present with four major system involvements in the beginning of manifestation of the disease, i.e., neurologic, hepatic, cardiac, and dermatologic manifestations. Failure to recognize the disease leads to a rapid downhill course leading to multiorgan dysfunction and death. IEMs presenting as involvement of various organ system are given next.

1. Neurologic manifestations. Deterioration of consciousness is one of the common neonatal manifestations of IEMs that can occur due to metabolic derangements, including metabolic acidosis (see section IV), hyperammonemia (see section V), and hypoglycemia (see section VI). Neonates with these metabolic derangements typically exhibit poor feeding and decreased activity that progress to lethargy and coma. Other common neurologic manifestations of IEMs in the neonatal period are seizures (see section VII), hypotonia (see section VIII), and apnea (Table 60.1).

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 ■ GLUD1-related hyperinsulinemic hypoglycemia ■ Carbonic anhydrase VA deficiency ■ Hypoglycemia ■ Disorders of gluconeogenesis ■ Hyperinsulinemic hypoglycemia ■ Pyruvate carboxylase deficiency
Seizures ■ Holocarboxylase synthetase deficiency/biotinidase deficiency ■ Pyridoxine-dependent epilepsy ■ Pyridoxal phosphate-responsive epilepsy ■ Glycine encephalopathy ■ Mitochondrial diseases ■ Zellweger's syndrome ■ Sulfite oxidase/molybdenum cofactor deficiency

(continued)

Table 60.1. Inborn Errors of Metabolism Associated with Neurologic Manifestations in Neonates *(Continued)*

■ Purine and pyrimidine metabolism disorders ■ Disorders of creatine biosynthesis and transport ■ Neurotransmitter defects ■ Congenital disorders of glycosylation ■ Folate metabolism disorders ■ Serine deficiency ■ Disorders leading to severe hypoglycemia and hypoglycemic seizures
Hypotonia ■ Mitochondrial diseases ■ Zellweger's syndrome ■ Glycine encephalopathy ■ Sulfite oxidase/molybdenum cofactor deficiency
Apnea ■ Glycine encephalopathy ■ MSUD ■ Urea cycle disorders ■ Disorders of pyruvate metabolism ■ Fatty acid oxidation defects ■ Mitochondrial diseases ■ Asparagine synthetase deficiency

2. **Liver dysfunction (see section IX).** Galactosemia is the most common metabolic cause of liver disease in the neonate. The hepatic involvement could be in various forms: (i) liver failure can be caused by galactosemia, tyrosinemia type I, neonatal hemochromatosis, mitochondrial hepatopathies, etc.; (ii) neonatal cholestasis—which can be caused by lysosomal acid lipase deficiency, α_1-antitrypsin deficiency, and mitochondrial hepatopathies; and (iii) hepatosplenomegaly with or without hypoglycemia—which may be seen in Gaucher's disease, Niemann–Pick disease, GM1 gangliosidosis, and Wolman's disease (Table 60.2).
3. **Cardiac dysfunction (see section X).** Heart involvement can present as cardiomyopathy, which can be seen in respiratory chain disorders, Pompe's disease, fatty acid oxidation disorders, CDG, and glycogen storage diseases (Table 60.3).
4. **Dermatologic manifestations.** Conditions such as holocarboxylase synthetase (HCS) deficiency, biotinidase deficiency, Hartnup's disease, and mevalonate kinase deficiency can present with typical dermatologic manifestations. The dermatologic manifestations include exfoliative dermatitis, alopecia, erythroderma, and conditions mimicking acrodermatitis enteropathica.
5. **Other manifestations.** An abnormal urine odor is present in some IEMs in which volatile metabolites accumulate (Table 60.4). Some IEMs can present with facial dysmorphism (Table 60.5), and others can present with hydrops fetalis (Table 60.6).

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's syndrome ■ α_1-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's disease)
Tricarboxylic acid cycle defects: α-Ketoglutarate dehydrogenase deficiency
Mitochondrial diseases
Congenital disorders of glycosylation singular

III. EVALUATION AND MANAGEMENT. Early diagnosis and the institution of appropriate therapy are mandatory in IEMs to prevent death and ameliorate complications. However, their diagnosis is generally delayed due to rarity of these disorders coupled with their nonspecific presenting signs. Therefore, a high index of suspicion is required for early diagnosis of IEMs. Management of suspected IEMs should be started even before birth.

A. Before or during pregnancy. Three important components of history taking should include consanguinity, obstetric history, and pedigree charting. History of consanguinity, obstetric history suggestive of unexplained neonatal deaths, mental retardation, or developmental delay, and pedigree charting suggestive of

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	Dysmorphic Features
Zellweger's 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 the nearly 100 disorders
Miller's syndrome (dihydroorotate dehydrogenase deficiency)	Micrognathia, cleft lip/palate, malar hypoplasia, eyelid coloboma, downslanted palpebral fissures, and absence of fifth digits

involvement of relatives in past three generations should raise the suspicion about possibility of IEM. Following steps should be taken under such circumstances:

1. Clinical reports and hospital charts should be reviewed.

Table 60.6. Inborn Errors of Metabolism Associated with Hydrops Fetalis

Lysosomal disorders ■ Mucopolysaccharidosis types I, IVA, and VII ■ Sphingolipidosis: GM1 gangliosidosis, Gaucher's disease, Farber's disease, Niemann–Pick disease type A, multiple sulfatase deficiency ■ Lipid storage disorders: Wolman's disease, Niemann–Pick disease type C ■ Oligosaccharidosis: Galactosialidosis, sialic acid storage disease, mucolipidoses I (sialidosis), mucolipidoses II (I cell disease)
Zellweger's syndrome
Glycogen storage disease type IV
Congenital disorders of glycosylation
Mitochondrial diseases
Neonatal hemochromatosis

2. Prenatal genetic counseling regarding the possibility of having an affected infant
3. The parents and relatives can be screened for possible clues of an IEM.
4. When a diagnosis of previous sibling is known, intrauterine diagnosis by measurement of abnormal metabolites in the amniotic fluid, by enzyme assay or DNA analysis of amniocytes or chorionic villus cells, or by targeted/whole exome sequencing can be carried out.
5. Antenatal ultrasound to identify fetal abnormalities including features of hydrops fetalis
6. Planning to deliver the baby in a facility equipped to handle potential metabolic or other complications
7. Management plan should be clearly stated which should include any special planning during resuscitation, feeding plan, laboratory evaluation plan, and provision of supplements/drugs.

B. Initial evaluation. When an IEM is suspected in a neonate, a careful physical examination seeking any of the signs of IEM needs to be performed; nonmetabolic causes of symptoms such as infection, asphyxia, or intracranial hemorrhage need to be evaluated; and the newborn screening program should be contacted for the results of the screening and for a list of the disorders screened. Initial laboratory studies should be obtained immediately once IEMs are suspected (Table 60.7). Recognition of patterns of IEMs helps in prioritizing laboratory investigations. The results of these tests can help to narrow the differential diagnosis and determine which specialized tests are required.

1. **Complete blood cell count.** Neutropenia and thrombocytopenia may be associated with a number of organic acidemias. Neutropenia may also be found with glycogen storage disease type Ib and mitochondrial diseases, such as Barth's syndrome and Pearson's syndrome.
2. **Electrolytes and blood gases** are required to determine whether an acidosis or alkalosis is present and, if so, whether it is respiratory or metabolic (including

Table 60.7. Laboratory Studies for a Newborn Suspected of Having an Inborn Error of Metabolism

Initial laboratory studies
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

anion gap). A persistently high anion gap metabolic acidosis with normal tissue perfusion may suggest an IEM (e.g., organic acidemia or pyruvate metabolism defects). It is important to remember that most metabolic conditions result in acidosis in late stages as encephalopathy and circulatory disturbances progress. For example, a case of UCD presenting in multiorgan failure is likely to reveal metabolic acidosis instead of respiratory alkalosis. A mild respiratory alkalosis in nonventilated babies suggests hyperammonemia.

3. **Glucose.** Hypoglycemia is a critical finding in some IEMs. It can manifest as a result of poor feeding or can result from energy deficiency or metabolic derangements interfering with metabolic processes. Requirement of glucose infusion rate of >8 mg/kg/minute helps to differentiate the latter two conditions from hypoglycemia occurring as a result of poor feeding.
4. **Blood ketone levels.** Measurement of blood ketones is critical in cases presenting with hypoglycemia. Some point-of-care glucometer devices can measure blood ketone levels.
5. **Plasma ammonia level** should be determined in all neonates suspected of having an IEM. Early recognition of severe neonatal hyperammonemia is crucial because irreversible damage can occur within hours. Care must be exercised in proper sample transport and early processing to avoid spurious results.

6. **Plasma lactate level.** A high plasma lactate can be secondary to hypoxia, cardiac disease, infection, or seizures, whereas primary lactic acidosis may be caused by disorders of gluconeogenesis, pyruvate metabolism, and mitochondrial diseases. Some IEM (fatty acid oxidation disorders, organic acidemias, and UCDs) may also be associated with a secondary lactic acidosis. Persistent increase of plasma lactate above 3 mmol/L in a neonate, who did not suffer from asphyxia and who has no evidence of other organ failure, should lead to further investigation for an IEM. Specimens for lactate measurement should be obtained from a central line or through an arterial stick because the use of a tourniquet during venous sampling may result in a spurious increase in lactate.
7. **Liver function tests.** Some IEMs are associated with liver dysfunction.
8. **Urine for reducing substances, pH, and ketones.** Reducing substances are tested by the Clinitest reaction that detects excess excretion of galactose and glucose but not of fructose. A positive reaction with the Clinitest should be investigated further with the Clinistix reaction (glucose oxidase) that is specific for glucose. Reducing substances in urine (Benedict's test) can be used as screening for galactosemia; however, this test is not very reliable because of high false-positive and false-negative rates. Urine pH <5 is expected in cases of metabolic acidosis associated with IEM; otherwise, renal tubular acidosis is a consideration. In neonates, the presence of ketonuria is always abnormal and an important sign of metabolic disease.
9. **Coagulation studies.** These should be performed in babies with clinical bleeding and IEM in whom liver failure is suspected.
10. **Plasma amino acid analysis.** Plasma amino acid analysis is indicated for any infant suspected of having IEM. Recognition of patterns of abnormalities is important in the interpretation of the results.
11. **Urine organic acid analysis** is indicated for patients with unexplained metabolic acidosis, seizures, hyperammonemia, hypoglycemia, and/or ketonuria.
12. **Plasma carnitine and acylcarnitine profile.** Carnitine transports long-chain fatty acids across the inner mitochondrial membrane. An elevation of carnitine esters may be seen in FODs, organic acidemias, and ketosis. In addition to patients with inherited disorders of carnitine uptake, low carnitine levels are common in preterm infants and neonates receiving total parenteral nutrition (TPN) without adequate carnitine supplementation. Several metabolic diseases may cause secondary carnitine deficiency.
13. **Imaging.** Ultrasound should be performed to identify fluid in serous cavities in hydrops fetalis and identify visceral involvement in infiltrative disorders (e.g., glycogen storage disorder). Echocardiography, ECG, and x-ray chest need to be performed to identify cardiac involvement, wherever myocardial involvement is suspected. MRI is needed to diagnose cerebral edema, e.g., in maple syrup urine disease (MSUD), or can help in the identification of characteristic lesions, e.g., basal ganglia involvement.
14. **Other investigations.** Renal function tests and serum electrolytes should be performed in all sick neonates. Microbiological investigations should be performed before the initiation of antibiotics. Cerebrospinal fluid (CSF) analysis should be performed in hemodynamically stable neonates. CSF lactate should be analyzed in cases of suspected mitochondrial disorders.

The clinicians need to prioritize the investigative workup due to availability of a wide range of available investigations and limitations of blood sampling in vulnerable sick neonates. Recognizing the pattern of clinical presentation is helpful in choosing the necessary investigations. Generally, the investigations can be divided into first line, second line, and third line. The first-line investigations include blood glucose estimation, blood gas analysis, serum ammonia, serum lactate, liver and renal function tests, urine reducing substances, full blood count, and blood ketones (all these tests can be done in hospital labs with a short turnaround time). Tandem mass spectrometry (TMS) and analysis of urine organic/amino acids should be planned in the first-line investigations (the tests may be performed in a reference, outsourced lab; these take time and hence early testing is helpful). Second-line investigations include imaging studies and identification of the suspected analyte, e.g., plasma carnitine/acylcarnitine profile, biotinidase levels, CSF lactate/amino acids, blood/urine succinylacetone levels, and 2,4-dinitrophenylhydrazine reagent test. Third-line investigations include enzyme assays and DNA mutational analysis.

C. Management of acute metabolic decompensation. Several IEMs can present with acute metabolic decompensation during the neonatal period, such as urea cycle defects and organic acidemias. The principles of managing acute metabolic decompensation are as follows:

1. **Decrease production of the toxic intermediates** by holding enteral intake for 24 to 48 hours and suppressing catabolism. Reversal of catabolism and promotion of anabolism can be achieved by the following:
   - **a.** Remove the source of the offending agent, which is enteral feed in many IEMs. As it is difficult to establish the type of IEM at the time of presentation, it is best to stop feeds in the initiation of treatment.
   - **b.** Providing adequate caloric intake through initiation of maintenance fluids containing 10% dextrose or appropriate glucose infusion rate as required.
   - **c.** Administering insulin. Insulin is a potent anabolic hormone and can be administered as a continuous infusion (0.05 to 0.1 unit/kg/hour) with adjusting the intravenous (IV) glucose to maintain a normal blood glucose.
   - **d.** Providing adequate hydration and treating infections aggressively.
   - **e.** Introducing enteral feeding as early as possible. The period of enteral feed restriction should not exceed 24 to 48 hours; after that, a special formula appropriate for the suspected IEM should be introduced if there are no contraindications for enteral feeding.
2. **Elimination of toxic metabolites** by the following:
   - **a.** IV hydration, which can promote renal excretion of toxins.
   - **b.** The use of specific medications that create alternative pathways. For example, carnitine can bind organic acid metabolites and enhance their excretion in urine in organic acidemias. Another example is sodium benzoate, which is used in glycine encephalopathy and urea cycle defects, because it binds to glycine-forming hippurate, which is excreted in urine.
   - **c.** Hemodialysis/hemofiltration may be employed in cases of unresponsive hyperammonemia (>500 mg/dL) in urea cycle defects and hyperleucinemia in MSUD.

d. Renal replacement therapy (RRT). In the absence of hemodialysis (hemofiltration) facilities, RRT can be achieved by peritoneal dialysis (PD) or continuous renal replacement therapy (CRRT). Although many units describe PD as inadequate, this is easy to set up and available in all neonatal intensive care units (NICUs) unlike extracorporeal (hemo) dialysis. Case series published from Italy and Turkey show good outcomes with PD.[*,†]

e. Double-volume exchange transfusion (DVET). It should be considered in neonates presenting with high levels of jaundice. It is not very helpful in removing toxic metabolites, but can be considered as a desperate measure where facilities of RRT are not available.

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. If hypernatremia is a problem, potassium acetate can be used in the maintenance fluid. Caution must be exercised in preterm neonates due to risk of intraventricular hemorrhage (IVH).
4. **Correction of hypoglycemia** (see Chapter 24)
5. **Calories.** Calories provided during a period of decompensation, in order to support anabolism, should be at least 20% greater than those needed for ordinary maintenance. Adequate calories can be achieved parenterally by IV glucose and intralipid and enterally by giving protein-free formula or special formula appropriate for the IEM. One must remember that withholding natural protein from the diet also eliminates this source of calories, which should be replaced using other dietary or nutritional (non-nitrogenous) sources.
6. **Lipids.** To supply extra calories, the neonate can be supplied with lipids in the form of oral medium-chain triglycerides (MCTs) or parenteral intralipid. However, before feeding MCT, it is very important to be certain that the infant does not have a medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency; otherwise, this could provoke a very severe metabolic crisis.
7. **Protein.** All natural proteins should be withheld for 24 hours while the patient is acutely ill. Afterwards, amino acid supplementation may be important in facilitating clinical improvement by promoting anabolism, but it should be implemented only under the supervision of a physician/dietitian with expertise in IEMs. Special parenteral amino acid solutions and specialized formulas are available for many disorders when individuals with IEMs require prolonged parenteral nutrition.
8. **L-Carnitine.** Free carnitine levels are low in organic acidemia because of increased esterification with organic acid metabolites. Carnitine supplementation may facilitate excretion of these metabolites. Diarrhea is the primary adverse effect of oral carnitine.

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*Bilgin L, Unal S, Gunduz M, Uncu N, Tiryaki T. Utility of peritoneal dialysis in neonates affected by inborn errors of metabolism. *J Paediatr Child Health* 2014;50(7):531–535.

†Pela I, Seracini D, Donati MA, Lavoratti G, Pasquini E, Materassi M. Peritoneal dialysis in neonates with inborn errors of metabolism: is it really out of date? *Pediatr Nephrol Berl Ger*. 2008;23(1):163–168.

9. **Cofactor supplementation.** Pharmacologic doses of appropriate cofactors may be useful in cases of vitamin-responsive enzyme deficiencies. The following supplements should be started in acute decompensations:
   a. **Hyperammonemia**. L-Arginine (300 mg/kg/day) and L-carnitine (100 to 300 mg/kg/day) IV or oral
   b. **Organic acidemia**. Carnitine (100 to 300 mg/kg/day), biotin (10 mg/day orally), vitamin B_{12} (1 to 2 mg/day intramuscular), and thiamine (300 mg/day)
   c. **Congenital lactic acidosis**. Thiamine (300 mg/day), riboflavin (100 mg/day), coenzyme Q (5 to 15 mg/kg/day), and L-carnitine (100 mg/kg/day)
10. **Antibiotics.** For certain organic acidemias (propionic acidemia [PA] and methylmalonic acidemia [MMA]), gut bacteria are a significant source of organic acid synthesis (propionic acid). Eradicating the gut flora with a short course of a broad-spectrum antibiotic (e.g., neomycin, metronidazole) enterally may speed the recovery of a patient in acute metabolic decompensation.
11. **Neonatal seizures.** In case the seizures are refractory to two or three anticonvulsants, IV pyridoxine (100 mg) should be instituted under electroencephalogram (EEG) guidance. If seizures are unresponsive to pyridoxine, biotin and folinic acid should be tried.
12. **Treatment of precipitating factors.** Infection should be treated as per usual protocols. Excess protein ingestion should be discontinued.

D. Monitoring the patient. Neonates with IEMs should be monitored closely for any mental status changes, overall fluid balance, evidence of bleeding (if thrombocytopenic), and symptoms of infection (if neutropenic). Biochemical parameters need to be followed including electrolytes, glucose, ammonia, blood gases, complete blood cell count, and urine for ketones.

E. Recovery and initiation of feeding

1. The neonate should be kept nothing by mouth (NPO) until his or her mental status is more stable. Anorexia, nausea, and vomiting during the acute metabolic decompensation period make significant oral intake unlikely.
2. If the neonate is not significantly neurologically compromised, consideration should be given to provide the neonate (orally or by nasogastric/gastric tube) with a modified formula preparation containing all but the offending amino acids. When the neonate is able to take oral feedings, a specific diet must be used. The diet should be individualized for each child and his or her metabolic defect, e.g., in galactosemia, the infant should be fed a lactose-free formula.

F. Long-term management. Several IEMs require dietary restrictions (e.g., leucine-restricted diet in isovaleric acidemia [IVA]). If hypoglycemia occurs, then frequent feeding and the use of uncooked cornstarch are advised. Cofactors are used in vitamin-responsive IEMs (e.g., pyridoxine in pyridoxine-dependent epilepsy). Examples of other oral medications used in chronic management of IEMs are carnitine for organic acidemias, sodium benzoate for urea cycle defects, and nitisinone (NTBC) in tyrosinemia type I.

G. Asymptomatic newborn with positive family history of IEM. Such newborn should be investigated and treated as a suspect IEM, if not investigated in the fetal

life. If a neonate is suspected to have IEM of "intoxication" pattern, avoid giving full feeds. Start partial feeds with protein intake 0.5 to 1.0 g/kg/day and rest through oral dextrose feeds or IV fluids. If the baby remains well including laboratory investigations, feeds should be increased with repeat metabolic screening and close clinical monitoring. Screening must be performed by TMS and urine organic acid tests, as early as possible. Further management should be guided by the reports of laboratory tests including provision of appropriate formulas.

IV. INBORN ERROR OF METABOLISM WITH METABOLIC ACIDOSIS. Metabolic acidosis with a high anion gap is an important laboratory feature of many IEMs including MSUD, organic acidurias, fatty acid oxidation disorders, disorders of pyruvate metabolism, glycogen storage diseases, and mitochondrial diseases (Table 60.1). The presence or absence of ketosis in metabolic acidosis can distinguish certain groups of disorders from each other (Fig. 60.1).

A. Maple syrup urine disease

1. An autosomal recessive disorder due to the deficiency of branched-chain α-ketoacid dehydrogenase (Fig. 60.2)
2. **Manifestations.** Severe form of MSUD presents during the first week of life with poor feeding, vomiting, irritability, ketosis, lethargy, seizures, hypertonicity, opisthotonus, coma, and maple syrup odor of urine and cerumen (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), depressed alanine levels, and the presence of branched-chain ketoacids and hydroxy acids in urine organic acid analysis. Leucine is the primary neurotoxic metabolite. Most newborn screening programs include MSUD. The ketoacids can be identified by the Dinitrophenylhydrazine (DNPH) test (adding few drops of 2,4-dinitrophenylhydrazine reagent to urine gives yellow precipitates). In acute states, MRI can detect cerebral edema (most prominent in the cerebellum, internal capsule, cerebral peduncle, and midbrain). Enzyme assay and molecular genetic tests are available.
4. **Management.** Management of acute presentation includes holding protein intake and suppressing catabolism with glucose and insulin infusions. Isoleucine and valine supplementation (20 to 120 mg/kg/day) and adequate caloric intake also are needed. The dose can be adjusted to keep normal plasma amino acid levels. Hemodialysis/hemofiltration/PD may be considered for rapid correction of hyperleucinemia (renal clearance of leucine is poor). Thiamine (10 mg/kg/day) trial for 4 weeks can be considered. Long-term management requires a branched-chain amino acid–restricted diet.

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 acidemia in the neonatal period, IVA, PA, and MMA, result from enzymatic defects in the branched-chain amino acid metabolism (Fig. 60.2).
2. **Manifestations.** Organic acidemias can present in the neonatal period with lethargy, poor feeding, vomiting, truncal hypotonia with limb hypertonia,

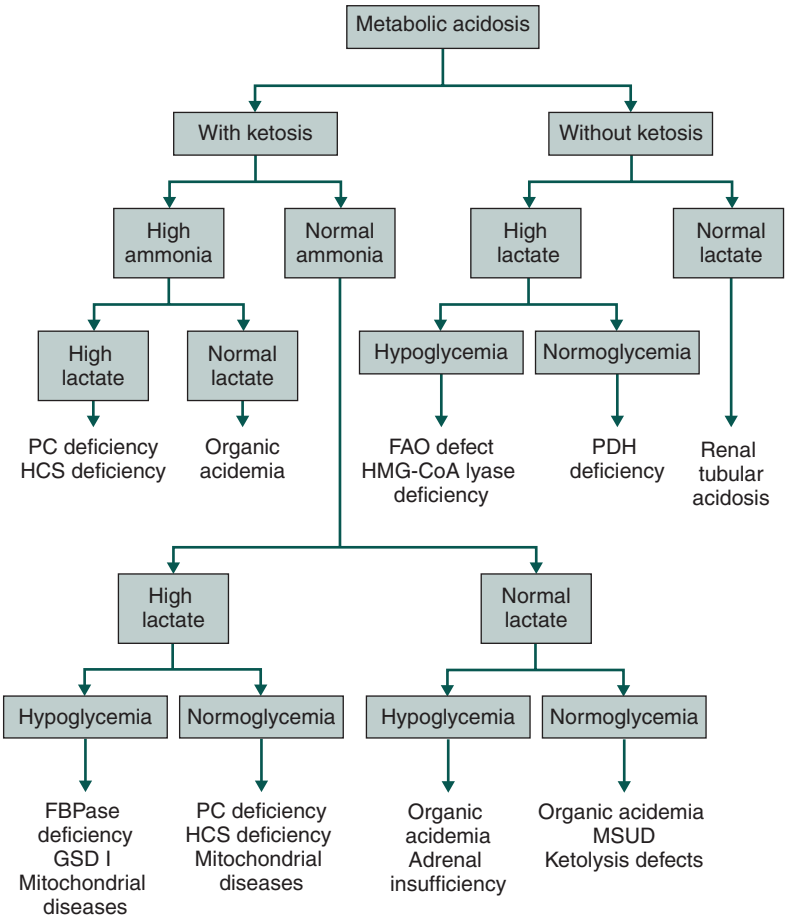

Figure 60.1. Approach to neonatal metabolic acidosis. Note that although a significant elevation in lactate is more associated with mitochondrial diseases and pyruvate metabolism disorders, milder lactate elevations can be seen in organic acidemias and MSUD. FAO, fatty acid oxidation; FBPase, fructose-1,6-bisphosphatase deficiency; GSD I, glycogen storage disease type I; HCS, holocarboxylase synthetase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MSUD, maple syrup urine disease; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase.

myoclonic jerks, hypothermia, cerebral edema, coma, multiorgan failure, and unusual odor (Table 60.4).

3. **Diagnosis.** Laboratory tests usually reveal high anion gap metabolic acidosis and occasionally hyperammonemia, hyperglycinemia, hypoglycemia, neutropenia, thrombocytopenia, pancytopenia, and elevated transaminases. The specific diagnosis can be reached by performing urine organic acid analysis and serum acylcarnitine profile (Table 60.8). Neuroimaging may reveal cerebral atrophy, delayed myelination, and abnormalities of the basal ganglia, especially globus pallidus. Enzyme assays and molecular genetic tests are available for

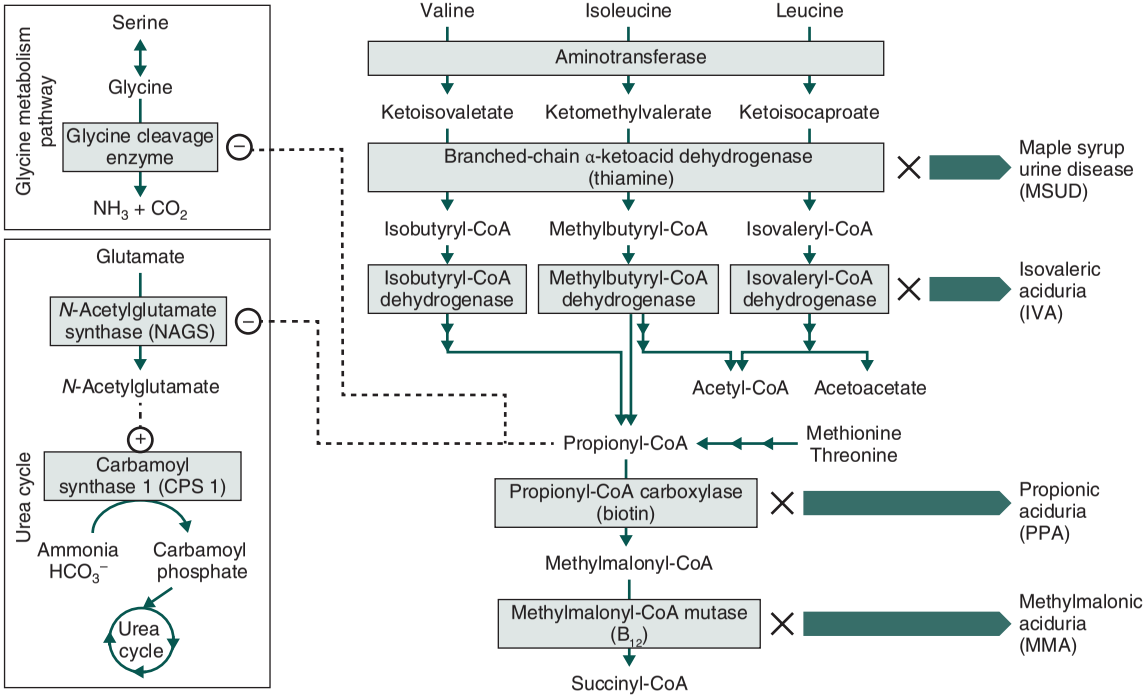

Figure 60.2. Branched-chain amino acid metabolism and enzyme defects associated with inborn errors of metabolism. Note that propionic acid inhibits glycine cleavage enzyme and *N*-acetylglutamate synthetase resulting in elevated glycine and hyperammonemia in propionic and methylmalonic acidemias. ⊖, negative effect/inhibition; ⊕, positive effect/acceleration.

Table 60.8. Biochemical Diagnosis of Organic Acidemias

Organic Acidemias	Enzymes	Urine Organic Acid Analysis	Plasma Acylcarnitine Profile
Propionic acidemia (PA)	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.

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. Biotin (10 mg/day orally), vitamin B_{12} (1 to 2 mg/day intramuscular), and thiamine (300 mg/day) should be initiated. Hemodialysis/RRT may be considered if these measures fail. Chronic treatment includes oral carnitine and dietary restrictions. 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 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.
5. Prenatal diagnosis is possible through measurement of pathogenic variants on genomic sequencing or analysis of enzymatic activity on cultured amniotic cells or uncultured chorionic villi.

C. Defects of pyruvate metabolism can present with severe neonatal metabolic acidosis with elevated lactate and include PDH, pyruvate carboxylase (PC), and 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 (Table 60.5).
   - **c. Diagnosis.** Very high lactate in various body fluids is suggestive of the diagnosis. The diagnosis is confirmed by enzyme studies and molecular genetic testing.

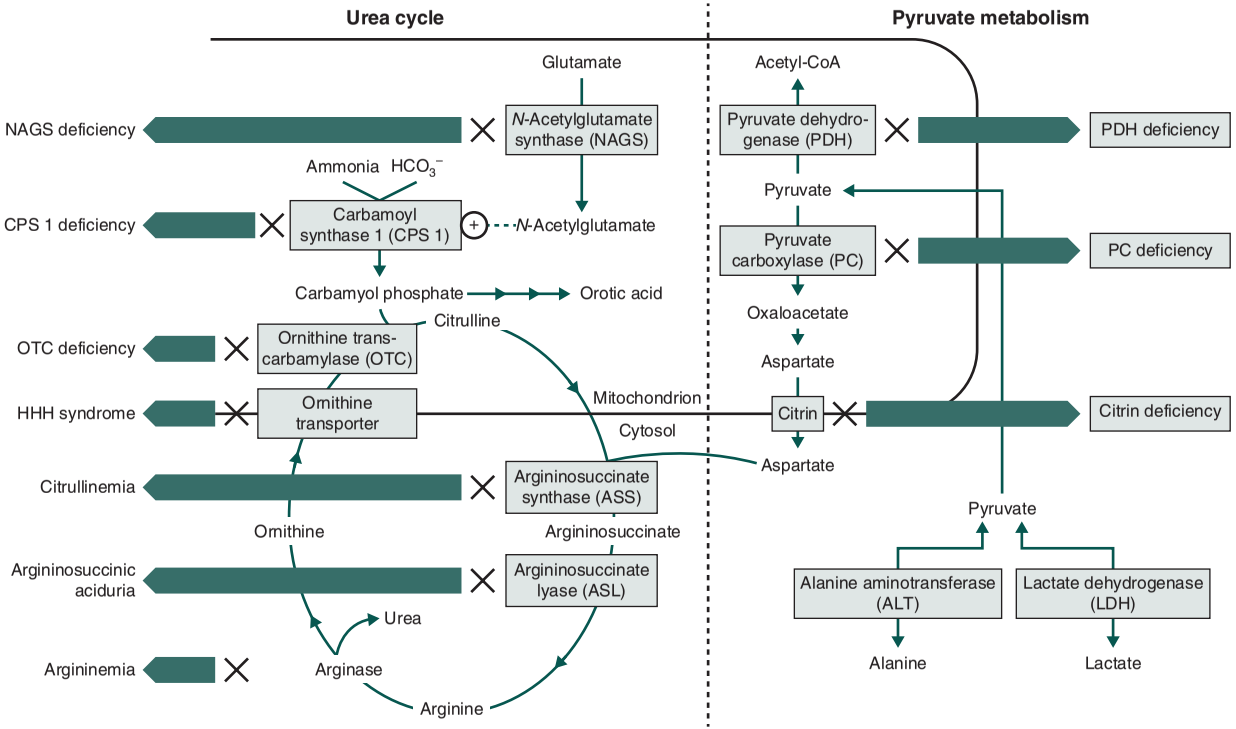

Figure 60.3. Metabolic pathways for urea cycle and pyruvate with the related inborn errors of metabolism. HHH, hyperornithinemia-hyperammonemia-homocitrullinuria.

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. Thiamine, a cofactor for PDH, can be used (10 mg/kg/day). Dichloracetate may be a potential treatment for these patients; however, the experience with this drug is limited and there is potential of peripheral neuropathy with its prolonged use.

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 enzyme studies and molecular genetic testing.

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 (5 to 20 mg/day). Improvement in metabolic abnormalities can be achieved by aspartate and citrate supplements.

3. HCS deficiency

a. HCS deficiency (multiple carboxylase deficiency) is an autosomal recessive disorder due to the 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 and/or propionylcarnitine. Prenatal diagnosis is possible in cases of known pathogenic variant. Affected mothers can be treated with high-dose biotin, though with unproven efficacy.

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. INBORN ERROR OF METABOLISM WITH HYPERAMMONEMIA. It is essential to measure ammonia in every sick neonate, whenever an IEM or septic workup is

considered. Early recognition of severe neonatal hyperammonemia is crucial because irreversible damage can occur within hours. Hyperammonemia can be caused by IEMs or acquired disorders (Table 60.9). It is the principal presentation for most

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 transcarbamoylase (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 respirator chain defects

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
  - Neonatal sepsis
  - Infection with urease-positive bacteria (with urinary tract stasis)
  - Reye's syndrome
- Medications (valproic acid, cyclophosphamide, 5-pentanoic acid, asparaginase)
- Technical
  - Inappropriate sample (e.g., capillary blood)
  - Sample not immediately analyzed

HHH, hyperornithinemia-hyperammonemia-homocitrullinuria.

UCDs. However, hyperammonemia with ketoacidosis suggests an underlying organic acidemia. Therefore, 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 in UCDs where glutamine is elevated.

A. Urea cycle disorders

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 (Fig. 60.3).
2. **Manifestations.** UCDs can present at any age. Neonates with severe forms of UCDs typically present with rapidly progressive symptoms appearing between 48 and 72 hours of life after a short, symptom-free interval. These symptoms include poor feeding, vomiting, lethargy, hypotonia, hypothermia, and

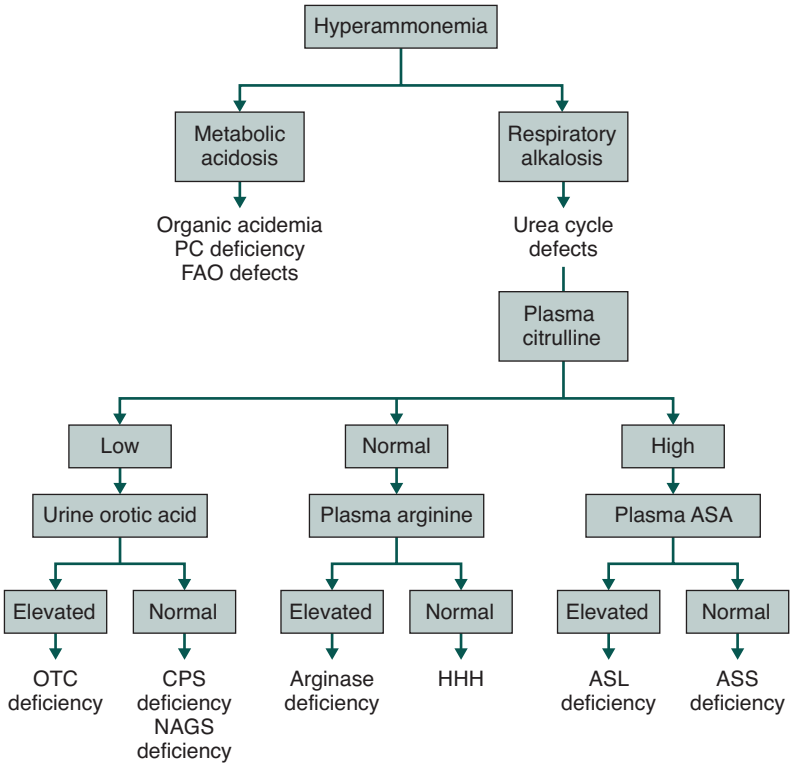

Figure 60.4. Approach to the investigation of neonatal hyperammonemia. ASA, argininosuccinic acid; ASL, argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase; CPS, carbamyl phosphate synthetase; FAO, fatty acid oxidation; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PC, pyruvate carboxylase.

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 higher than 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 help in reaching the diagnosis (Fig. 60.4). The diagnosis is confirmed by enzyme assay and/or molecular genetic testing. Newborn screening programs that have expanded metabolic screening typically detect citrullinemia, argininosuccinic aciduria, and argininemia but *not* OTC or carbamoyl phosphate synthetase (CPS) deficiencies.

4. **Acute management.** Prompt correction of hyperammonemia is critical to minimize neurologic injury:

   a. Decreasing the production of ammonia from protein intake and breakdown. Suppression of catabolism can be achieved through the use of glucose infusion, insulin infusion, and intralipid administration. Protein intake can be completely restricted for 24 to 48 hours, followed by introducing an essential amino acid formula to maintain the appropriate levels of essential amino acids, which is necessary to reverse the catabolic state.

   b. Removing ammonia. IV ammonia-scavenging drugs (Ammonul) should be started for ammonia levels above 300 µmol/L. 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 as loading and maintenance as well. The L-arginine doses are 200 mg/kg for loading and similar dose for maintenance in CPS and OTC deficiencies and 600 mg/kg in argininosuccinate synthase (ASS) and argininosuccinate lyase (ASL) deficiencies. L-Arginine hydrochloride is not used 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 should be considered if ammonia is very high (>500 mmol/L). However, while preparing for dialysis, the glucose, insulin, and ammonia scavenger therapy should be maintained. Hemodialysis is preferred over PD because it is much more effective at removing ammonia. If there is no provision to perform hemodialysis or PD, exchange transfusion can be tried.

   c. Reduce the risk for neurologic damage 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/kg/day with half of the required protein provided from essential amino acids formula and half from regular infant formula.

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 in *N*-acetylglutamate synthase (NAGS) deficiency and can be tried in individuals with CPS deficiency.

e. Triggers that can precipitate metabolic crisis (such as infection, fasting) should be avoided.

f. In children with severe types of UCDs, liver transplantation can be considered.

VI. INBORN ERROR OF METABOLISM WITH HYPOGLYCEMIA. Hypoglycemia is a frequent finding in neonates. The suspicion of an IEM should be raised if it is severe and persistent without any other etiology (see Chapter 24). The presence or absence of ketosis can help in guiding the diagnostic workup (Fig. 60.5).

A. Defects of fatty acid oxidation. FODs can present in the neonatal period with hypoketotic hypoglycemia. The diagnosis is based on the abnormalities found in acylcarnitine profile (Table 60.10), enzyme studies, and molecular genetic testing. Expanded newborn screening programs detect most FODs.

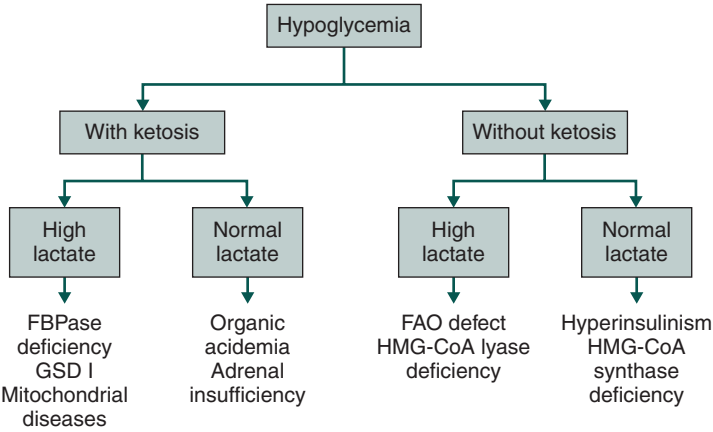

Figure 60.5. Approach to persistent hypoglycemia in the newborn with suspected inborn errors of metabolism. FAO, fatty acid oxidation; FBPase, fructose-1,6-bisphosphatase; GSD I, glycogen storage disease type I; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

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 (tertadecanoylcarnitine) ■ C14:1 (tetradecanoyl) ■ C12 (dodecanoylcarnitine)
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Elevated: ■ C6 (hexanoylcarnitine) ■ C8 (octanoylcarnitine) ■ C10 (decanoylcarnitine) ■ C10:1 (decanoyl)
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	Elevated: ■ C4 (butyrylcarnitine)
Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency	Elevated: ■ C14OH (hydroxytetradecanoyl) ■ 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.

1. Long-chain FODs include very long-chain acyl-coenzyme A dehydrogenase (VLCAD), long-chain hydroxyacyl-coenzyme A dehydrogenase (LCHAD), trifunctional protein (TFP), and carnitine palmitoyltransferase II (CPT II) deficiencies.
   a. **Manifestations.** Infants with the severe forms typically present in the first months of life with cardiomyopathy, arrhythmias, hypotonia, hepatomegaly, and hypoglycemia.
   b. **Management.** Hypoglycemia should be treated with glucose infusion and avoided by frequent feeding. Diet restrictions with a low-fat formula and supplemental MCTs should be initiated early. Cardiac dysfunction is reversible with early intensive supportive care and diet modification.
2. **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. Laboratory manifestations. Neonates have hypoketotic hypoglycemia, elevation of hepatic enzymes, and altered coagulogram. There can be mild metabolic acidosis and hyperammonemia. Urinary organic acid profile shows medium-chain dicarboxylic acids in symptomatic neonates. The neonates have secondary carnitine deficiency. Newborn screening can detect MCAD deficiency. Diagnosis can be confirmed by sequencing.

c. Management. Feeds should not be missed in neonates as fasting precipitates the crisis. Hypoglycemia should be treated with glucose infusion and avoided by frequent feeding. Uncooked cornstarch also can be used to prevent the hypoglycemia.

B. Disorders of ketone body metabolism. Ketone bodies (acetoacetate and β-hydroxybutyrates) are important fuel for many tissues during fasting. Ketone bodies are synthesized with the help of enzymes 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase and HMG-CoA lyase and catabolized by enzymes succinyl-coenzyme A oxoacid coenzyme A transferase (SCOT) and β-ketothiolase. (Fig. 60.6). Disorders of ketone body synthesis (ketogenesis) present typically 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. Blood lactate and ammonia concentrations are normal, and urine is negative for ketone bodies.

b. Diagnosis. Urine organic acid analysis shows dicarboxylic aciduria without ketosis. The diagnosis can be confirmed molecularly by genetic testing. Absence of acylcarnitines differentiates this condition from fatty acid oxidation.

c. Management. Hypoglycemia should be treated with glucose infusion and avoided by frequent feeding.

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. Hyperammonemia should be treated promptly. Carnitine is also used. Long-term management includes avoiding fasting, carnitine, and low-fat, protein-restricted diet.

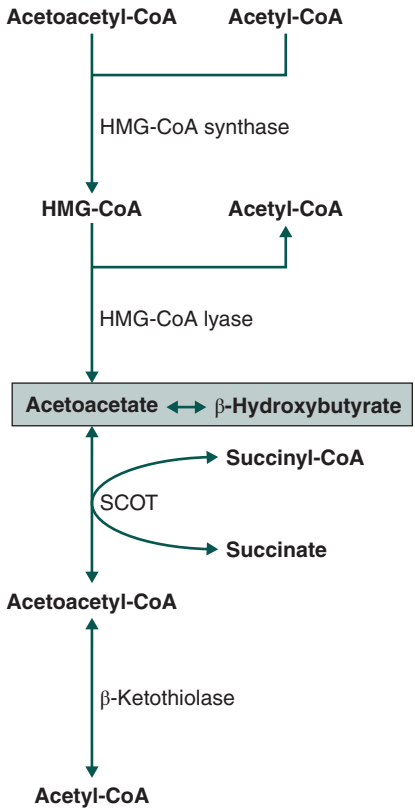

Figure 60.6. Ketone body (acetoacetate and β-hydroxybutyrates) synthesis and degradation. HMG-CoA. 3-hydroxy-3-methylglutaryl coenzyme A; SCOT, succinyl-coenzyme A oxoacid coenzyme A transferase.

C. Fructose-1,6-bisphosphatase deficiency. Deficiency of fructose-1,6-bisphosphatase (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 enzyme assay and molecular genetic testing.
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 enzyme assay and molecular genetic testing.
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 starch, and intragastric continuous feeding if needed. The diet should be low in fat, sucrose, and fructose and high in complex carbohydrate.

VII. INBORN ERROR OF METABOLISM WITH NEONATAL SEIZURES.

The possibility of IEMs should always be considered in neonates with unexplained and refractory seizures (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, and cutaneous symptoms, including skin rash, alopecia, and recurrent viral or fungal infections.
3. **Diagnosis.** The diagnosis is established by assessing the biotinidase enzyme activity in blood. Molecular genetic test can also be performed. 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 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. Antiquitin functions as a piperideine-6-carboxylate (P6C)/α-aminoadipic semialdehyde (AASA) dehydrogenase; therefore, its deficiency results in the accumulation of AASA and P6C. The latter binds and inactivates pyridoxal phosphate, which is a cofactor in neurotransmitter metabolism.
2. **Manifestations.** Newborns with pyridoxine-dependent epilepsy present soon after birth with irritability, lethargy, hypotonia, poor feeding, and seizures that are typically prolonged with recurrent episodes of status epilepticus.
3. **Diagnosis.** The diagnosis is established clinically by showing a response to pyridoxine. Administering 100 mg of pyridoxine IV while monitoring the 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, ASAA, and P6C 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 the 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 during the first day of life with lethargy, hypotonia, and refractory seizures that are not responsive to pyridoxine.
3. **Diagnosis.** Diagnosis is established by the demonstration of 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 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. EEG shows a characteristic burst-suppression pattern. Many infants die within a few weeks of life, typically from apnea; survivors develop profound psychomotor retardation. In transient glycine encephalopathy, which is secondary to the immaturity of glycine cleavage enzymes, laboratory and clinical abnormalities return to normal 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). Enzyme assay and molecular genetic testing 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 the 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 deficiency.** Adenylosuccinate lyase (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. INBORN ERROR OF METABOLISM WITH HYPOTONIA.

Hypotonia is a common symptom in sick neonates. Some IEMs can present predominantly as hypotonia in the neonatal period (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 the 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, and 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 the skeletal muscle, skin fibroblast, or liver tissue, but this

Table 60.11. Mitochondrial Syndromes Associated with Neonatal Presentation

Barth's syndrome ■ Hypertrophic cardiomyopathy ■ Skeletal myopathy ■ Neutropenia ■ Affects male individuals (X-linked)
Pearson's 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 functions return to normal after 3–4 months

may be nondiagnostic. Molecular testing for mitochondrial DNA content and sequencing for mitochondrial DNA and known mitochondria-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's syndrome

1. Zellweger's syndrome is a disorder of peroxisomal biogenesis. Peroxisomes are cell organelles that possess anabolic and catabolic functions, including synthesizing plasmalogens, which are important constituents of cell membranes and myelin, β-oxidation of very long-chain fatty acids (VLCFAs), oxidation of phytanic acid, and formation of bile acids.
2. **Manifestations.** Neonates with Zellweger's 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 (Table 60.5).
3. **Diagnosis.** Biochemical abnormalities include elevated phytanic acid and VLCFAs and low plasmalogens. Many proteins are involved in peroxisomal

biogenesis. Therefore, complementation analyses allow the determination of which protein is defective, and molecular genetic analysis for the responsible gene can be performed for molecular confirmation.

4. **Management.** There is no effective treatment, and management is largely symptomatic.

IX. INBORN ERROR OF METABOLISM WITH LIVER DYSFUNCTION. Several IEMs can have hepatic manifestations in the neonatal period (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 (Table 60.11).

A. Galactosemia (see Chapter 26)

1. Galactosemia is an autosomal recessive disease due to the 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 a standard lactose-containing formulas or breast milk. 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 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 the deficiency of fructose-1,6-biphosphate aldolase (aldolase B) which is 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 enzyme assay and molecular genetic testing.
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 the 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 (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.** NTBC (1 to 2 mg/kg/day divided in two doses) and tyrosine-restricted diet are effective at preventing symptoms if instituted early in life.

D. Neonatal intrahepatic cholestasis caused by citrin deficiency

1. Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) is an autosomal recessive disorder due to the deficiency of citrin which is a mitochondrial aspartate–glutamate carrier (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. It 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 (Table 60.3).

A. Glycogen storage disease type II (Pompe's disease)

1. Glycogen storage disease type II (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.

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 an infant is dying or has died of what may be a metabolic disease, it is important to make a specific diagnosis in order to help the parents with genetic counseling for future reproductive planning. Sometimes, families will not permit a full autopsy, but will allow the collection of some premortem or immediately postmortem specimens that may help in the diagnosis. 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. Cerebrospinal fluid, 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, but 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. A full autopsy should be done if permitted.

XII. ROUTINE NEWBORN SCREENING.

Each state in the United States mandates the disorders evaluated in its own newborn screening program. Recent advances have enabled tandem mass spectrometry (MS/MS) to be applied to the newborn screening specimen. This technique is currently being used in all states to offer screening for many treatable IEMs. A list of what each state screens for may be found on the individual state governmental website or in aggregate on the national newborn screening and genetic resource center website (http://genes-r-us.uthscsa.edu/). Currently, there are no national recommendations on newborn screening in India. Very 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: http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm. 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
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)

(continued)

Table 60.12. Newborn Screen Primary Analytes and the Suspected Diagnoses *(Continued)*

Analyte	Condition
	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

CoA, coenzyme A; DC, dicarboxylic; GALT, galactose-1-phosphate uridyltransferase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

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61 Thyroid Disorders

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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.
- Timely initiation of treatment of congenital hypothyroidism is critical in determining long term outcome.
- Fetal and neonatal hyperthyroidism occurs in approximately 1% to 2% of infants born to mothers with Graves' disease.
- Neonatal hyperthyroidism is uncommon (accounting for ~1% of hyperthyroidism in children) 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 such as the United States. 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 the mother and the fetus. 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 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 due to 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), and 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 –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 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 on 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 trimester-specific normal ranges of 0.1 to 2.5 milliunits/L in the first trimester, 0.2 to 3 milliunits/L in the second trimester, and 0.3 to 3 milliunits/L in the third trimester. Achieving this goal often requires an L-thyroxine dose of 20% to 50% higher than in the nonpregnant state.

E. Screening of all pregnancies for thyroid dysfunction. Thyroid disorders in pregnant women can lead to poor pregnancy and fetal outcomes. Hypothyroidism is seen in 2.5% to 12% and hyperthyroidism in 0.1% to 2% of pregnant women. Up to 18% of all pregnant women are thyroid peroxidase antibody (TPO Ab) or thyroglobulin antibody (Tg Ab) positive. ***TPO Ab positivity adversely*** modulates the impact of maternal thyroid status on ***pregnancy and on the developing fetus***. Serum TSH is the principal determinant of maternal thyroid status. The use of population-based trimester-specific reference range of TSH is the best way to screen for hypothyroidism or hyperthyroidism during pregnancy. Considering the high prevalence of thyroid disorders among pregnant women, universal screening of all pregnancies with TSH is desirable. However, cost-effectiveness and practicality question the feasibility of such an approach. There is insufficient evidence to recommend for or against universal screening for abnormal TSH

levels in early pregnancy or preconception, except in women planning assisted reproduction or those known to be TPO positive. Universal screening to detect low free T4 (FT_4) is not recommended. The American Thyroid Association (ATA) 2017 guidelines recommend that all women seeking pregnancy should undergo clinical evaluation and assessment of TSH and TPO Ab status if risk factors are present. The risk factors are age above 30, high body mass index (BMI), infertility, bad obstetric history, diabetes mellitus, positive family history of thyroid disorders, and history of prior thyroid disease or surgery. Women with overt or subclinical hypothyroidism or those at risk for hypothyroidism (euthyroid women with TPO Ab or Tg Ab positive, post hemithyroidectomy, or treated with RAI) should be monitored with TSH measurement every 4 weeks until midgestation and at least once near 30 weeks' gestation. The ATA revised guidelines in 2017 recommend the **TSH upper cutoff limit of 0.5 milliunit/L less than the preconception TSH value or 4.0 milliunit/L** when local population-specific, trimester-specific reference range is not available. Pregnant women with TSH level above 2.5 milliunit/L should be evaluated for TPO Ab status and if positive should be considered for L-thyroxine (L-T_4) therapy.

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 whether fetal goiter is due to MMI- or PTU-induced fetal hypothyroidism or due 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 remain 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 in 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 milliunits/L at 6 hours of life. TSH then declines rapidly over 24 hours, and 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. This drop in thyroid hormones occurs due to many factors such as poorly developed hypothalamic–pituitary axis, immaturity of the thyroid gland, decreased hepatic TBG production, and increased tissue utilization of T_4. The process is further accentuated by complications of prematurity. 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. Recent studies indicate a higher prevalence across the world than was previously believed. Possible reasons are improved testing strategies and increase in the number of preterm births. In the United States, the incidence is approximately 1/2,500. CH is more common among Hispanic (1/1,600) and Asian Indian infants but less common among non-Hispanic black infants (1/11,000). Incidence of CH in a recent multicentric study

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 (milliunits/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

TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone.
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.

from Asian countries is 1 in 1,470 infants in Japan, 1 in 2,080 infants in China, 1 in 2,700 infants in Turkey, and 1 in 1,130 infants in India. 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** (see Table 61.2)
   a. **Thyroid dysgenesis.** Abnormal thyroid gland development is the cause of permanent CH in about 70% 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 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}Tc) 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 30% of permanent CH cases. Most are recessive and carry a 25% recurrence risk in subsequent siblings. The most common defect is abnormal TPO activity, which results in impaired organification of iodine. Additional defects affect other key steps in thyroid hormone synthesis such as Tg synthesis, iodine trapping, hydrogen peroxide generation, and iodotyrosine deiodination. **Pendred's 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 1/25,000 to 1/16,000. Affected infants usually have other pituitary

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 has 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

(*Continued*)

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
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 Tg synthetic defect, ↑ in other forms of dyshormonogenesis.
†Treat with iodine, not L-thyroxine.
MMI, methimazole; NB, newborn; PTU, propylthiouracil; TBG, thyroxine-binding globulin; Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

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 substantial 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 seaweed (e.g., in Korea). In infants with hypothyroidism due to iodine excess, goiter may be present, T_4 is low, and TSH is elevated. RAI and ^{99m}Tc 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 (THOP) is the most common pattern of thyroid dysfunction seen in preterm infants born before 31 weeks' gestation. It is characterized by low serum T_4 and free T_4 levels with concurrent normal or low levels of TSH. THOP is observed in up to 50% of infants born before 28 weeks' gestation. Low T_4 and T_3 in extreme preterm infants can be due to many reasons such as loss of maternal and placental transfer of T_4, immaturity of HPT axis, immature thyroid hormone synthesis, and insufficient or excessive iodine intake.

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 school failure. It is generally agreed that THOP cannot be considered physiologic. But there is paucity of evidence to support the treatment of this condition

with thyroid hormones. Several randomized, placebo-controlled trials have been conducted with different L-T_4 dosages ranging from 4 to 20 μg/kg/day and for varying durations from 2 to 6 weeks. Some of these studies show better mental and psychomotor development following thyroid hormone (TH) treatment among children born at 25 to 26 weeks' gestation and better motor development in those born at 27 to 28 weeks' gestation. However, children born after 29 weeks' gestation had a worse outcome with treatment. There is no clear evidence of correlation between TH supplementation and neurologic outcome later in life. TH supplementation may even be detrimental in some infants.

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 –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 (ELBW) infants (<1,000 g, reported incidence 1/58), very low-birth-weight (VLBW) infants (<1,500 g, reported incidence 1/95), and 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). ***Some screening programs require repeat testing at 2 to 6 weeks of age for infants at high risk for delayed TSH elevation, and a few programs require repeat testing for all infants.***

B. Diagnosis. Over 95% of newborns with CH are asymptomatic at birth, but universal newborn screening (NBS) 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 NBS for CH.

1. **NBS for CH** is routine in most developed countries but is not yet performed in many 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. In India, many states and private sector hospitals have started universal screening, but it is not a national recommendation yet.
2. **Both FT_4 and TSH may be measured** in all cases for infants in the neonatal intensive care unit (NICU), infants weighing <1,500 g, infants with a family history or clinical signs of hypothyroidism, or if a previous specimen was unsatisfactory (e.g., collected too early, incorrect technique). Infants with abnormal screening test results should be evaluated in consultation with a pediatric endocrinologist (see section VI.B.5 and Fig. 61.1).
3. **A filter paper blood spot specimen/serum sample** should be sent from all newborns, ideally between 48 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-positive 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, 6, and 10 weeks of age** due to the risk of delayed TSH elevation (see section VI.A.3).
4. **Screening schedule in preterms.** Various studies have reported a higher prevalence of CH (both transient and permanent) in preterms, LBW infants, and VLBW infants. Incomplete development of the HPT axis in this group of neonates often delays the rise of TSH levels. Routine NBS may fail to identify these infants with CH. Various strategies have been proposed to avoid missing such cases of CH including rescreening at-risk neonates, lowering the screening cutoff of TSH, using cutoffs according to the gestational age, and using both TSH and T_4 levels. The ***ideal solution may be to repeat screening*** by both TSH and FT_4 simultaneously in preterms, LBW infants, and VLBW infants at the **ages of 2, 6, and 10 weeks**. TSH of 10 milliunits/L should be the cutoff level in such cases. However, in developing countries like India, where universal NBS has not yet come into practice, burdening an already hard-driven system at the cost of missing a few term infants with severe CH may be difficult. A more practical approach in such a situation would be to screen these high-risk newborns 2 weeks after the initial screen or at 2 weeks of age.
5. **If clinical signs of hypothyroidism** are present (e.g., constipation, hypothermia, poor tone, mottled skin, prolonged jaundice, poor feeding, large tongue, open posterior fontanel), 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

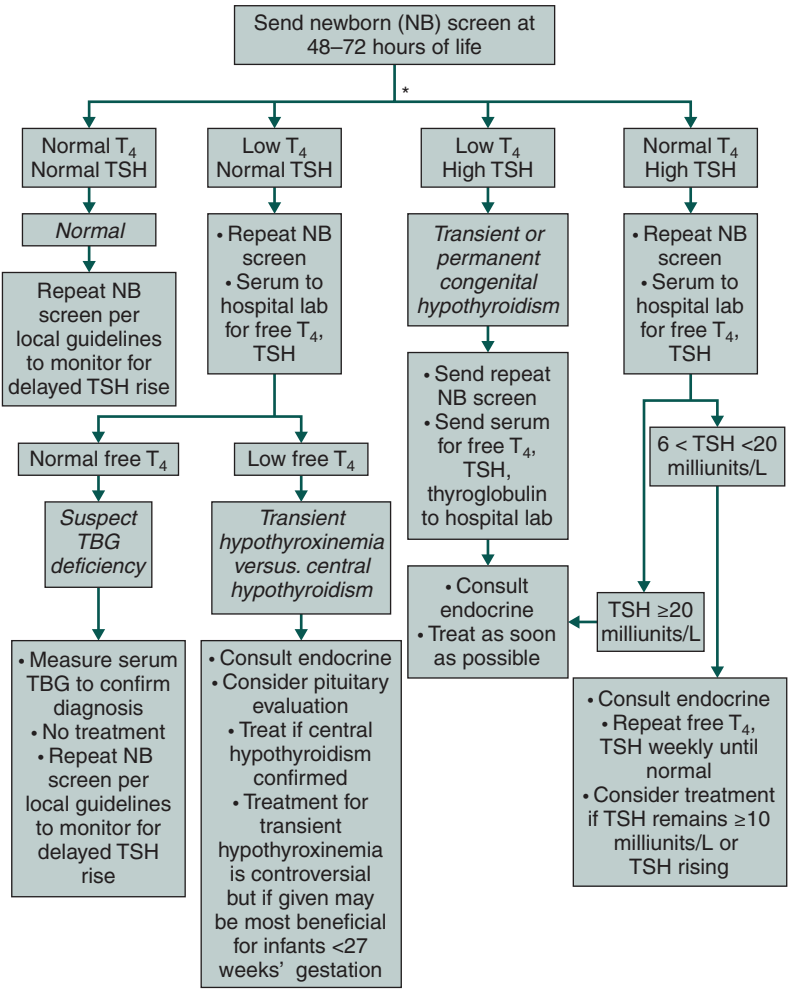

Figure 61.1. Suggested approach to follow-up of newborn screening for hypothyroidism in the hospitalized preterm infant. (*) In the United States, screening protocols and cutoff values vary slightly by state. TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone. (Modified from Brodsky D, Ouellette MA, eds. *Primary Care of the Premature Infant*. Philadelphia, PA: Elsevier Saunders; 2008).

screening programs may miss infants with central (pituitary) hypothyroidism. Acquired hypothyroidism (e.g., due to postnatal excess iodine exposure) will also be missed on NBS.

6. **Follow-up of NBS 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. Thyroid function tests should be repeated on a serum sample within 24 hours. Most infants with an initial TSH level >50 milliunits/L have a permanent form of CH. If the initial TSH is 20 to 40 milliunits/L, the CH may be transient. If it is not possible to see the patient promptly, therapy should be initiated as soon as the diagnosis is confirmed. If total T_4 is low but the TSH level is not elevated, a serum-free T_4 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 T_4 and free T_4 are low but TSH is not elevated, central hypothyroidism or THOP 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}Tc** 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 THOP 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 milliunits/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.

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 higher doses 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 with an aim to maintain TSH in age-specific reference ranges, and total T4 (TT_4) or FT_4 in the upper half of the specific reference range. Monitoring of L-T_4 treatment is based on periodic measurements of serum FT_4 (or TT_4) and TSH concentration. Blood samples for FT_4 or TT_4 measurement are collected ***before or at least 4 hours after*** the last L-T_4 administration. All babies initiated on treatment must be periodically assessed for growth and neurodevelopment.

2. Rapid normalization of thyroid hormone levels maintaining a relatively high FT_4 concentration during the first year of life leads to better intellectual outcomes. Ideally, T_4 level will normalize within 1 week and TSH level within 2 weeks of starting therapy. The first follow-up examination with FT_4 estimation is done 1 to 2 weeks after starting L-T_4 treatment. Two-weekly follow-up with FT_4 or TT_4 and TSH level estimation is recommended till the TSH level

is normalized. Follow-up is continued every 1 to 3 months until 1 year of age. Children between the ages of 1 and 3 should undergo clinical and laboratory evaluation every 2 to 4 months. After age 3, follow-up is recommended at 3- to 12-monthly intervals until growth is complete. Thyroid function tests are done at more frequent intervals if compliance is doubtful or abnormal values are obtained. Tests are repeated 4 to 6 weeks after any change in L-T_4 dose or formulation. Universal hearing screen and regular hearing assessment throughout childhood is recommended. Clinical examination to rule out a cardiac anomaly is advised for infants with CH.

3. 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.
   a. **L-Thyroxine** tablets should be crushed and fed directly to the infant, mixed in a small amount of juice, water, or breast milk. Soy-based formulas, ferrous sulfate, calcium supplements, and fiber interfere with absorption and should be administered at least 2 hours apart from the L-thyroxine dose. There are no commercially available liquid preparations of L-thyroxine in the United States.
   b. The effect of THOP on the neurodevelopmental outcome is uncertain. Therefore, the current recommendation is to supplement T_4 in preterm infants with THOP only if the condition is associated with elevated TSH levels. Repeat T_4 and TSH screening is crucial to avoid missing cases of CH which require T_4 treatment.
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 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.

It is uncommon (accounting for <1% of hyperthyroidism in children) and is almost always transient. Most newborns with hyperthyroidism are born to mothers with active Graves' disease. However it 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 stimulating antibodies and cause hyperthyroidism in the newborn. 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 5% develop hyperthyroidism.

B. Pathogenesis. Most neonatal hyperthyroidism result from transplacentally acquired maternal TSH receptor–stimulating antibodies. Rarely, both TSH receptor–stimulating and –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 may follow initial hypothyroidism caused by transplacental passage of MMI or PTU, which are typically cleared within the first week of life.

C. Clinical findings. Neonatal thyrotoxicosis 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 thyrotoxicosis 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, high titers of TSH receptor–stimulating antibodies, elevation of total and free T_4 levels, and suppression of TSH.

D. Treatment

1. **MMI** (0.5 to 1 mg/kg/day in three divided doses) is used to treat neonatal thyrotoxicosis. 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 thyroxine 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 one 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 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.

E. 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, persistent 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 less than 30 mg per day or of PTU less than 300 mg. **MMI is preferred in lactating women** over PTU 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

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62 Neonatal Effects of Maternal Diabetes

Terri Gorman

KEY POINTS

- The majority of infants of diabetic mothers are born to women with gestational diabetes; pregestational type 2 diabetes is also on the rise.
- Pregestational diabetes has a strong association with congenital abnormalities, perinatal mortality, and prematurity. The neonatal morbidities are proportional to periconceptional glycemic control.
- Frequent neonatal morbidities associated with diabetes in pregnancy include macrosomia, postnatal hypoglycemia, prematurity, and birth trauma.
- Prenatal hyperglycemia exposure leads to increased postneonatal metabolic complications including obesity, impaired glucose metabolism, and potential decrements in neurodevelopmental outcomes later in life.

I. BACKGROUND. Diabetes in pregnancy is associated with increased risks of fetal, neonatal, and lifelong complications in the offspring. 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 offsprings. Diabetes mellitus (DM) complicates 6% to 7% of pregnancies in the United States.

II. CLASSIFICATION OF DIABETES IN PREGNANCY. Pregnancy itself is characterized by an increased insulin resistance state and as gestation increases, it progresses with a peak insulin resistance during the third trimester. This is due to the actions of various placental hormones including human placental lactogen, progesterone, estrogen,

Table 62.1. White's 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	C_1: Onset at 10–19 years of age
	C_2: Duration 10–19 years
Class D	D_1: Onset before 10 years of age
	D_2: Duration 20 years
	D_3: Calcification of vessels of the leg (macrovascular disease)
	D_4: Benign retinopathy (microvascular disease)
	D_5: 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 from Hare JW. Gestational diabetes. In: *Diabetes Complicating Pregnancy: The Joslin Clinic Method*. New York, NY: Alan R. Liss; 1989.

prolactin, placental growth hormone, tumor necrosis factor alpha, and cortisol. Normally the decreased insulin sensitivity is associated with increased insulin secretion. But in gestational diabetes mellitus (GDM), this is not adequate and hyperglycemia develops over the course of pregnancy most commonly diagnosed at 24 to 28 weeks' gestation, during the routine screening. This chapter will review the effects of both DM diagnosed before conception (pregestational diabetes) and diabetes diagnosed during pregnancy, most specifically diagnosed in the second to third trimesters (GDM). Of all the cases of DM in pregnancy, around 80% to 90% are GDM.

A. Pregestational diabetes. Pregestational diabetes is present in 1% to 2% of all pregnancies and 13% to 21% of diabetes in pregnancy. This includes women with type 1 diabetes and type 2 diabetes who have been diagnosed and treated prior to conception. Type 2 pregestational diabetes mellitus (PGDM) is now

more common than type 1 as 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 (HbA1c) levels is very important to improve maternal and neonatal outcomes. Therefore, preconception counseling should be an important part of maternal management for all women with preexisting DM. Unfortunately, only less than one-third of women with type 1 or 2 DM actively seek preconceptual counseling. The impacts of PGDM should be discussed during routine gynecologic or primary care visits.

Obstetric 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 the third trimester.

Women with type 2 DM tend to have milder disturbances in glucose, in general, and their neonatal outcomes are similar to those with type 1 DM. But women with type 1 DM are more likely to have pregestational microvascular complications, increased risk of hyperglycemia and hypoglycemia, as well as diabetic ketoacidosis, which is more likely lead to fetal growth restriction.

1. **Maternal complications.** Obstetric complications of pregestational diabetes include miscarriage, preeclampsia, gestational hypertension, polyhydramnios, preterm delivery, infections, injuries (laceration of the introitus), 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 twofold to fourfold higher in pregestational diabetes, 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 HbA1c levels correlates directly with the frequency of anomalies. The rate of congenital anomalies in nondiabetic women with HbA1c of 5.5% is 2%; this number rises to 2.7% with HbA1c 6.2%, 4% with HbA1c 7.6%, and 10% to 25% with HbA1c ≥10%. With good glycemic control, with HbA1c less than 7%, the rate of congenital malformations in pregestational diabetes can fall to approximate levels of nondiabetic mothers, and a 30% reduction in risk can occur for every 1% lowering of HbA1c.

   Congenital anomalies in order of prevalence include congenital heart disease, central nervous system (CNS) defects, urogenital defects, limb defects, and orofacial clefts. Rarely, yet highly associated with DM, sacral agenesis/caudal dysplasia (15% to 25% of all cases result from DM), though not pathognomonic, is one of the classic findings of diabetic embryopathy. Most prevalent cardiac defects include tetralogy of Fallot, transposition of the great arteries, septal defects, and anomalous pulmonary venous return. Ventricular septal defect (VSD) and transposition of the great arteries (TGA) are increased fivefold

in insulin-dependent diabetes. CNS defects include anencephaly, spina bifida, encephalocele, hydrocephaly, and anotia/microtia. Prenatal folic acid 1 mg should be given for a minimum of 3 months to reduce the incidence of neural tube defects.

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 pregestational diabetes plus preexisting vascular or renal disease such as hypertension and preeclampsia, there is a 6- to 10-fold higher risk relative to in those without vascular disease of having a fetus with growth restriction. Asymmetric IUGR is common and thought to be due to uteroplacental vasculopathy.
4. **Further complications.** The earlier discussed complications are much more specifically associated with pregestational diabetes. Other complications that overlap with diabetic fetopathy that occurs due to glycemic derangements later in the pregnancy will be addressed later in this chapter.

B. GDM. GDM is defined as any carbohydrate intolerance of variable severity that starts or is first diagnosed during pregnancy. This does not exclude the possibility of some undiagnosed pregestational diabetes. 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. The risk of developing GDM increases from as low as 4% if the woman is underweight to more than 15% if she is morbidly obese. 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 must 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 (obese, poor physical activity, previous large-for-gestational-age [LGA] baby, DM in a first-degree relative, polycystic ovarian disease [PCOD], hypertension, etc.) should be screened at the first prenatal visit (Table 62.2). Women at risk for undiagnosed type 2 DM typically warrant screening on the first prenatal visit for potential preexisting glucose intolerance; for all other women, screening by glucose challenge is performed at 24 to 28 weeks.

   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. 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 glucose level check (100-g 3-hour diagnostic oral glucose tolerance test).

   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

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.

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). The WHO recommends the diagnosis of GDM using 75 g of glucose through oral glucose tolerance test irrespective of the last meal with a threshold of 2-hour blood sugar >140 mg/dL. The American College of Obstetricians and Gynecologists (ACOG, 2019) also recommends this at the first visit and if negative, to repeat at 24 to 28 and 32 to 34 weeks.

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.

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.

Modified dietary interventions were associated with less macrosomia (relative risk 0.49 [95% CI 0.27, 0.88]; P = 0.02). When compared to insulin and oral hypoglycemic agents, lifestyle changes (including healthy eating, physical activity and self-monitoring of blood sugar levels) was the only intervention that showed possible health improvements for women and their babies. Lifestyle interventions may result in fewer babies being large. Exercise reduced GDM by half in nonobese women. Previously, oral antidiabetic agents were felt to be contraindicated due to concern for fetal anomalies. However, careful studies have shown that glyburide and metformin are safe to use and can assist in achieving targeted glycemic control. Insulin and oral antidiabetic agents have equivalent efficacy in achieving target glucoses. 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 stimulated glucose uptake in peripheral tissues. These oral antidiabetics are now becoming the therapy of choice in women with GDM for whom diet alone cannot achieve glycemic targets. Obstetric decision making regarding use of oral hypoglycemic agents depends on the gestational age, glycemic control, and fetal growth patterns on ultrasound. Approximately 15% of GDM women will require oral antidiabetic agents or insulin to achieve glycemic control. 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. In a recent study, in obese GDM mothers, the maternal cholesterol levels and placental vascular dysfunction was higher with insulin use when compared to diet management. It is proposed that cholesterol levels must also be targeted in GDM management. Although the choice of therapy to manage hyperglycemia may not yet be optimized, there is no doubt that uncontrolled hyperglycemia is associated with poorer perinatal outcomes. For every mmol/ L rise in fasting sugars in the mother the odds of large for gestation baby was twice.

A systematic review and meta-analysis of randomized trials comparing glyburide, metformin, and insulin in women with gestational diabetes presented convincing evidence that glyburide performed less well than either metformin or insulin, with higher rates of both macrosomia and neonatal hypoglycemia. In a recent meta-analysis of randomized trials limited to women with gestational diabetes, it was found that, compared with insulin, metformin reduced gestational weight gain, birth weight, and risk for macrosomia, but the risk for a LGA infant was similar. Recent studies suggest that infant and childhood adiposity was more in fetuses exposed to metformin when compared to insulin. The neonates had lower birth weight and rapid gain of weight in infancy, this traditionally is associated with risk of cardiovascular illness in adulthood. Thus, it is evident that diet and exercise were associated with significant decrease in GDM, and that both insulin and oral hypoglycemic agents can have long-term effects on childhood and may be even till adult life.

III. MATERNAL MANAGEMENT AND DELIVERY. Maternal prenatal management is vital to outcomes for both the mother and the infant and typically will include the following objectives:

A. Close follow-up with obstetrician every 1 to 2 weeks during the first and second trimesters and weekly from 28 to 30 weeks onward with close attention to glucose management

B. Consultation with a registered dietitian and preferably maternal–fetal medicine and endocrinology based on local referral practices as well as disease severity

C. Routine level 2 ultrasound at 16 to 18 weeks with specific attention paid to the potential for congenital anomalies in the pregestational diabetic as well as an ultrasound in the late second to early third trimester (at approximately 22 weeks) as indicated by clinical glucose control both for estimation of fetal growth and to evaluate for fetal cardiac hypertrophy. Thereafter, fetal growth is evaluated every 4 weeks on an average to aid in delivery planning.

D. Nonstress testing (NST) biophysical profile evaluation, and amniotic fluid index, especially in women with poor glycemic control, is recommended by the ACOG, commonly conducted at 28 to 34 weeks' gestation. The risk of stillbirth is increased within 1 week of a reactive NST. So patients with DM and GDM requiring medication will require twice-daily testing.

E. The timing of delivery is guided by the risk of intrauterine fetal demise (IUFD) and macrosomia versus the risk of neonatal complications due to prematurity. The well-controlled group (see the subsequent text) can be managed expectantly until at least 39 weeks. However, expected management is not recommended beyond the due date, and women with DM are good candidates for induction at 40 weeks. Poorly controlled group should be delivered at late preterm or early term. Induction of labor for suspected macrosomia has not been found to reduce birth trauma but may increase rates of cesarean section.

F. Antenatal steroids. Women with GDM who deliver before 34 weeks should receive antenatal steroids.

G. Cesarean delivery should be considered if the estimated fetal weight is >4,500 g in women with diabetes.

H. Glucose monitoring should be done four times daily. For the well-controlled group, fasting in the morning will be less than 95 mg/dL, at 1 hour after meals will be 140 mg/dL, or at 2 hours after meals will be 120 mg/dL. Glucose monitoring can be done at 1 or 2 hours after every meal.

I. Low-dose aspirin may be required in pregestational diabetes to decrease the risk of preeclampsia.

IV. FETAL AND NEONATAL EFFECTS OF MATERNAL DIABETES MELLITUS. The risk of developing complications varies with the time of onset of DM, degree of maternal hyperglycemia/hyperinsulinemia, length of fetal exposure to hyperglycemia, and severity of maternal disease. Cardiac and renal complications in the mother have significant neonatal and obstetric effects.

A. Fetal effects of maternal DM. In the first trimester, thus primarily in women with pregestational diabetes, maternal hyperglycemia will cause a diabetic embryopathy resulting in congenital anomalies outlined earlier and increased risk of spontaneous abortion.

Maternal hyperglycemia in the second and third trimesters will result in a diabetic fetopathy characterized by fetal hyperglycemia, hyperinsulinemia, and

macrosomia. Chronic fetal hyperinsulinemia causes increased metabolic rates in the fetus that lead to increased oxygen consumption. The oxygen needs may not be met by the placenta flow leading to fetal hypoxemia. This contributes to increased mortality, metabolic acidosis, and increased erythropoiesis in the fetus. Increased erythropoietin synthesis causes polycythemia and increased catecholamine production. Increased catecholamines contribute to fetal hypertension and cardiac hypertrophy. Also, polycythemia will cause redistribution of iron stores from developing organs to the red blood cell (RBC) mass which can affect cardiac and neurodevelopment.

Hyperinsulinemia has been linked to impaired lung maturation, increasing the risk for respiratory distress in the newborn. It will also cause 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 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, obstetric and neonatal outcomes were worse in infants of diabetic mothers (IDMs) who are LGA relative to infants of nondiabetic mothers who are LGA.

According to the **Fidgety Fetus Hypothesis**, the fetal activity has an important role in determining the birth weight. Increased fetal activity, either due to increased maternal glucose levels or due to intrinsic factors, can reduce the impact of maternal hyperglycemia on birth weight. A relatively less active fetus appears to be at a higher risk for glucose-mediated macrosomia. Although normoglycemia is the goal of therapy in all women with diabetes, in those women whose fetuses manifest less movement, increased surveillance and treatment of hyperglycemia is of utmost importance. An indicator of fetal movement together with the indicators of maternal glycemia can be effectively utilized to improve the predicted birth weights in pregnancies that are complicated by diabetes.

Stillbirth. The greatest risk of stillbirth is among women with vascular disease, hypoglycemia, diabetic ketoacidosis (DKA), macrosomia, polyhydramnios, and preeclampsia. It increases with poor glycemic control. The main cause of stillbirth is thought to be chronic intrauterine hypoxia. Hyperinsulinism in fetus causes increase in oxygen consumption and decrease in arterial oxygen content. Maternal uterine blood flow does not increase enough to allow for enhanced oxygen delivery to the increased metabolic needs of the baby.

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 an 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 as her early conception Hb A1C rises above 6. It should be below 7. In women with type 1 DM, mortality is largely attributable to complications of prematurity and congenital anomalies. Before using insulin, stillbirth occurred in 30% of cases. For those with type 2 DM, mortality is attributable to stillbirths, birth asphyxia or hypoxic ischemic encephalopathy, and intra-amniotic infections. The

greatest risk is with vascular disease, hypoglycemia, DKA, polyhydramnios, and preeclampsia, due to underlying chronic hypoxia.

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 leading to preterm delivery. In the recent past, more infants were electively induced prior to 39 weeks due to concern for macrosomia. But with obstetrical efforts to curtail unnecessary late preterm and early term inductions, the incidence of late preterm IDMs is expected to fall.

3. **Macrosomia.** Macrosomia is defined by the ACOG as birth weight more than 4,500 g for IDM. Macrosomic IDM babies may have a higher incidence of respiratory distress (RD), hypoglycemia, birth injury, and feeding problems when compared to non-IDM macrosomic babies.

4. **Birth injury.** Typically the fetuses of diabetic mothers have a normal growth of lean body mass, but there is a higher fat deposition in the subcutaneous tissues of the abdomen and shoulder. Shoulder dystocia usually becomes an emergency because of the risk of hypoxia, hypoperfusion, and birth injury. With a BW > 4000 g, there was an increased risk of shoulder dystocia, brachial plexus injury, and birth fractures, which had OR 9.54, 11.03, and 6.43, respectively. The corresponding values for pregnancies with a BW >4500 g were: 15.64, 19.87, and 8.16. (confidence intervals have been omitted). Brachial plexus injury is most common followed by clavicle or humerus fracture and cephalhematoma. Abdominal organ injury, external genitalia hemorrhage, facial palsy, ocular hemorrhage, subdural hemorrhage, etc., are other possibilities.

5. **Large for gestational age (LGA).** A LGA infant is defined as having a birth weight >90th percentile for gestational age and the condition occurs in 36% to 47% of IDMs, relative to in 7% to 9% of infants of nondiabetic women. Due to the distribution of size in IDMs, they have a threefold increased risk of shoulder dystocia and 10-fold increase in brachial plexus injury.

6. **Respiratory distress.** The odds of RDS was 1.5 times in babies with gestational DM and higher (2.66) for pregestational diabetes mellitus. 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. Lung maturation can be delayed up to 10 days among infants of mothers with poor glycemic control. This 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 two to three times more frequently in IDMs, with both increased rates of cesarean section and inherent reduced fluid clearance. Cardiac disease, diaphragmatic paralysis, meconium aspiration, pneumomediastinum, pneumothorax, polycythemia, hypoglycemia, etc., are the other causes of RD, which should be considered.

7. **Hypoglycemia.** It 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 their infants experience hypoglycemia after birth. As Pederson noted in 1952, in his hyperglycemia–hyperinsulinemia 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 as 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 (GIRs) 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. The value of blood sugar in neonates will depend on the maternal glucose control in the later half of pregnancy and labor. Severe, prolonged symptomatic hypoglycemia can result in permanent neurologic injury; thus, timely screening and intervention is important to long-term outcomes (see Chapter 24). So monitor the neonates postnatally till proper metabolic stability is achieved.
8. **Hypocalcemia.** It is defined as total serum calcium <7 mg/dL (1.8 mmol/L) or ionized calcium <4 mg/dL (1 mmol/L), and it 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). It is more common in mothers with poor glycemic control. Exact etiology is unclear, although hypoxia, preterm birth, hypomagnesemia, hypoparathyroidism, hyperphosphatemia, abnormal vitamin D metabolism, hypercalcitoninemia, etc., have been implicated. 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.
9. **Hypomagnesemia.** It is defined as serum magnesium concentration <1.5 mg/dL (0.75 mmol/L), and it 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, it is typically transient and 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.

10. **Hyperbilirubinemia.** It occurs in approximately 25% of IDMs. Contributing factors include prematurity, macrosomia, and polycythemia. Fetal exposure to oxidative stress and excess insulin and insulin growth factors are also proposed as the reason. All IDMs should undergo routine screening for jaundice with either transcutaneous or blood testing, with phototherapy as indicated (see Chapter 26).

11. **Polycythemia.** It is defined as a central venous hematocrit >65%, and occurs in 5% of IDMs. In one series, 17% of IDMs had hematocrits >60%. Polycythemia is due to increased erythropoietin resulting from chronic fetal hypoxemia. A smaller contributing factor may be 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 due to the lower incidence, but infants should be screened if maternal control was known to be 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.

12. **Renal vein thrombosis (RVT).** It 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.

13. **Small left colon syndrome.** It is a rare form of bowel obstruction, and is 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 alternative differential diagnosis includes Hirschsprung's 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. This can often be treated conservatively with enemas.

14. **Cardiomyopathy.** It can be of congestive or hypertrophic type. Hypertrophic cardiomyopathy is characterized by thickening of the intraventricular septum and/or ventricular walls, with a reduction in size of the ventricular chambers of the heart. It occurs with increased frequency in PGDM and GDM but has been shown to be more prevalent in pregestational diabetes (as high as 40% in one series) even in the setting of strict glycemic control. The hypertrophy can be detected in the late second to early third trimester; thus, careful ultrasound screening or fetal echocardiography with concentration on ventricular size is recommended. Fetal hyperinsulinism triggers an increase in 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. 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. For infants with diffuse hypertrophy and outflow tract obstruction such as a subaortic stenosis causing congestive cardiac failure, 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. Digoxin is also avoided.

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.

15. **Poor feeding.** Poor feeding is a significant issue especially in poorly controlled IDMs, leading to prolonged hospital stays and interruption of parent-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. Excellent 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-mother bonding.

A. Delivery room care. Proper assessment of the need for neonatal resuscitation should be made based on the 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 an 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, are 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 ≥45 mg/dL prior to routine feedings. Prefeed glucose values 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, administration of IV glucose is required. 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. It 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 an 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 in Denmark to be 4 times greater in offspring of GDM women and 2.5 times in offspring of PGDM women.

B. Obesity. Multiple studies have shown an association between DM and obesity in the offspring. Although the 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 a higher BMI, a 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. Both type 1 and type 2 DM are known to be influenced by genetics, with type 1 diabetes occurring four times more often in offspring of women with type 1 DM. The lifetime risk of an offspring of a woman with 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 infants of mothers with well-controlled DM are similar to those of infants of nondiabetic mothers.

Increasing Hb 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

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63 Differences in Sex Development

Jonathan M. Swartz and Yee-Ming Chan

KEY POINTS

- Differences in sex development (DSD) are a heterogeneous group of disorders characterized by atypical development of genetic, gonadal, and/or anatomic sex.
- DSD frequently present in the newborn period with atypical (ambiguous) genitalia. The rapid evaluation of infants with atypical genitalia is critical to identify and, if necessary, treat salt-wasting congenital adrenal hyperplasia, which is potentially life-threatening.
- The main goal of sex assignment 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 term *disorders of sex development* (DSD) was introduced to replace older terms such as *ambiguous genitalia*, *pseudohermaphroditism*, and *intersex* to denote atypical development of genetic, gonadal, and/or anatomic sex (Table 63.1). Recent nomenclature replaces the word "disorders" with "differences". The new term DSD (differences in sexual development) thus represents the equal access to human rights of "normal" people with differences and not disease.

A diagnosis of DSD is considered when the genitalia is atypical of either sex, such as the following:

A. A penis and bilaterally nonpalpable testes (cryptorchidism)

B. Unilateral cryptorchidism with hypospadias

C. Severe penoscrotal, scrotal, or perineal hypospadias, with or without microphallus, even if the testes are descended

D. Apparently female appearance with enlarged clitoris (clitoromegaly) and/or inguinal hernia(s) or palpable gonad(s)

E. Asymmetry in size, pigmentation, or rugation of labioscrotal folds

F. Discordance of external genitalia with prenatal karyotype

II. IMMEDIATE POSTNATAL CONSIDERATIONS PRIOR TO SEX ASSIGNMENT. Because internal genital anatomy, karyotype, and sex assignment 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

Table 63.1. Revised Nomenclature

Previous	Proposed
Intersex	DSD
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Virilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

DSD, Differences in sex development.
Source: From Hughes IA, Houk C, Ahmed SF, et al; for the Lawson Wilkins Pediatric Endocrine Society/European Society for Paediatric Endocrinology Consensus Group. Consensus statement on management of intersex disorders. *Arch Dis Child* 2006;91(7):554–563.

hyperplasia (CAH), which can be life-threatening within the first week of life, as well as the urgency felt by most parents in assigning a sex of rearing. Although a rapid decision about sex assignment is essential for the parents' peace of mind, care must be taken to avoid drawing premature conclusions; need to change sex assignment later could be difficult and more traumatic psychologically. Until a sex assignment is made, gender-specific names, pronouns, or other references should be avoided. Prompt consultation with a pediatric endocrinologist will facilitate the evaluation, and most causes of DSD can be identified in 2 to 4 days, 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 and then discuss with them the process of genital development, that their child's genitalia are incompletely or variably formed, 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 reconstruction.

III. NORMAL SEX DEVELOPMENT. The process of gonadal differentiation and genital development is depicted in Figure 63.1. In general, early structures will develop down the female pathway unless specific factors are present that direct development down the male pathway.

A. Genetic sex refers to the sex chromosome complement.

B. Gonadal sex. Undifferentiated gonads develop in the bilateral genital ridges 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

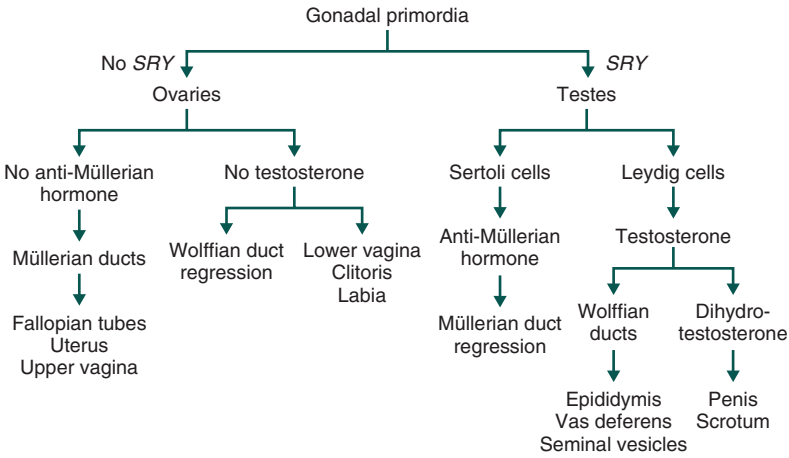

Figure 63.1. The process of gonadal, internal genital, and external genital differentiation. (From Holm IA. Ambiguous genitalia in the newborn. In: Emans SJ, Laufer M, Goldstein D, eds. *Pediatric and Adolescent Gynecology*. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:53.)

the Y chromosome, promotes the gonads to develop into testes. Several other genes can also promote testicular and/or ovarian development, including *NR5A1* (*SF1*), *NR0B1* (*DAX1*), *SOX3*, *SOX9*, *WNT4*, and *RSPO1*.

C. Anatomic sex refers to the external and internal genitalia. The testis secretes two hormones critical for male genital formation: Anti-Müllerian hormone (AMH, also called Müllerian-inhibiting substance or factor [MIS or MIF]) is produced by Sertoli cells, and testosterone is produced by Leydig cells.

1. **Internal genitalia.** AMH causes regression of the Müllerian ducts that would otherwise become the uterus, fallopian tubes, cervix, and upper vagina. Testosterone prevents the regression of the Wolffian ducts and promotes their development into the vas deferens, seminal vesicles, and epididymis. Müllerian duct regression and Wolffian duct development require high *local* concentrations of AMH and testosterone, respectively. Failure of a testis to develop on one side 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 the genital skin, converts testosterone to dihydrotestosterone (DHT). DHT is the primary hormone responsible for masculinizing the external genitalia, including the genital tubercle and labioscrotal folds, which form the penis and scrotum, respectively. In the absence of DHT, these undifferentiated structures develop into the clitoris and labia. 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*. Hence, boys born premature often have an undescended testis; examination must confirm normal descent of testis on follow-up of these babies after discharge from the neonatal ICU.

Formation of normal male internal and external genitalia under the influence of testosterone and DHT requires functional androgen receptors in the target tissues.

Time course. The timeline of fetal sexual differentiation is depicted in Figure 63.2 and Table 63.2.

1. **First trimester.** Testicular synthesis of testosterone is stimulated by activation of the luteinizing hormone (LH) receptor by human chorionic gonadotropin (hCG) produced by the placenta. The first trimester is the only period during which the labioscrotal folds are susceptible to fusion. If a 46,XX fetus is exposed to excess androgens during the first trimester, the clitoris and labioscrotal folds will virilize and may appear almost like a normal male penis and scrotum, although the latter will be empty and urethral meatus most often will not be normally located at the tip.
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 final testicular descent. High intrauterine concentrations of testosterone may influence brain development, possibly affecting later behavior, sexual orientation, and gender identity.

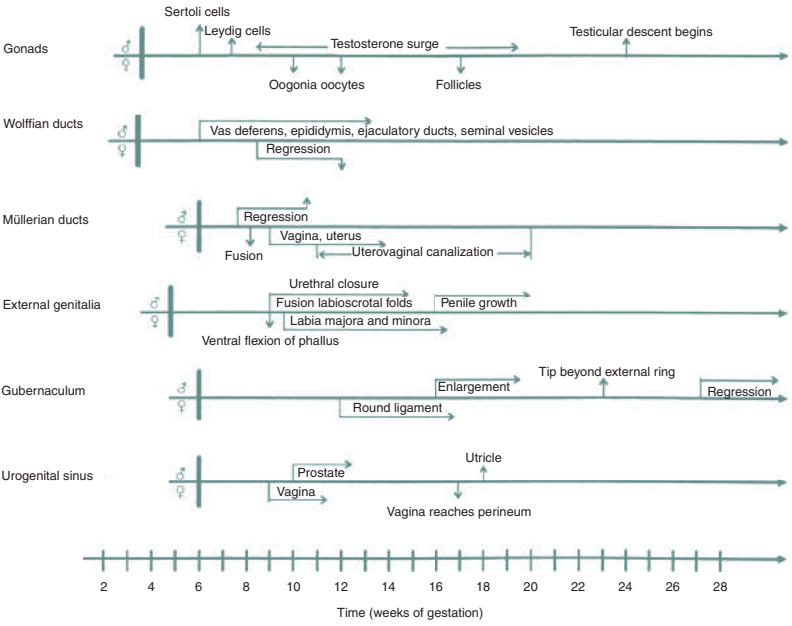

Figure 63.2. Timelines for six aspects of sex differentiation. (Adapted from White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev* 2000;21(3):245–291. Adapted from Barthold JS, Gonzalez R. Intersex states. In: Gonzalez ET, Bauer SB, eds. *Pediatric Urology Practice*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:547–578.)

Table 63.2. Timetable of 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 SUSPECTED DIFFERENCES IN 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 poorly controlled maternal CAH, a virilizing adrenal or ovarian tumor, or placental aromatase deficiency
3. **Placental insufficiency.** First-trimester synthesis of testosterone in the fetal testis is dependent on placental hCG due to its activation of the LH receptor.
4. **Prenatal findings** of genital ambiguity; sex chromosome mosaicism; a karyotype discordant with phenotypic sex; or potential DSD-associated conditions, such as oligohydramnios, renal anomalies (genitourinary malformations), or skeletal abnormalities (campomelic dysplasia)
5. **Family history** of CAH, atypical genitalia (severe degrees of hypospadias or cryptorchidism) infertility, pubertal delay, corrective genital surgery, genetic syndromes, or consanguinity. Neonatal death or unexplained death with features such as vomiting/shock/dehydration in family may suggest undiagnosed CAH.

B. Physical examination

1. **External genitalia.** The examiner should note the stretched penile length, width of the corpora, presence of chordee (abnormal downward curvature of the penis), position of the urethral orifice, presence of a vaginal opening,

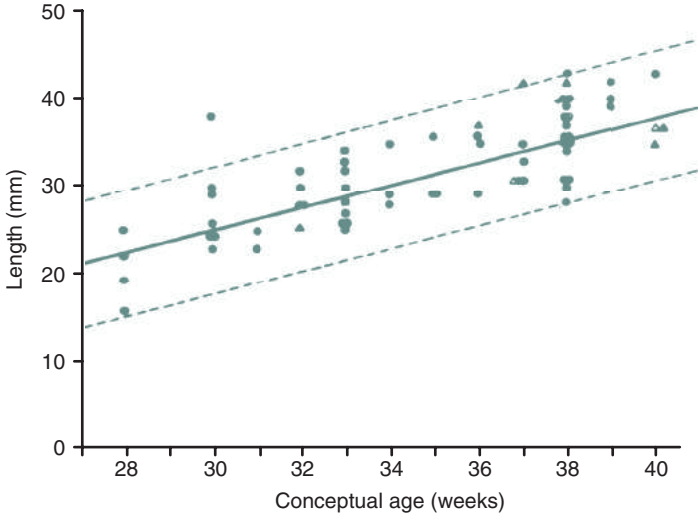

Figure 63.3. Stretched penile length of normal premature and full-term babies *(closed circles)*, showing lines of mean ± 2 standard deviations. Superimposed are data for two small-for-gestational-age infants *(open triangles)*, seven large-for-gestational-age infants *(closed triangles)*, and four twins *(closed boxes)*, all of whom are in the normal range. (From Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr* 1975;86:395.)

and pigmentation and symmetry of the scrotum or labioscrotal folds. The normal full-term male infant has a penile length of at least 2.5 cm, measured stretched from the pubic ramus to the tip of the glans (Fig. 63.3), and usually 1 cm or more in width. The normal full-term female infant 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 phallus. 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 uterus herniating into the inguinal canal. Abnormal genital development 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 46,XY infants. A few examples of other conditions associated with DSD include Smith–Lemli–Opitz, Robinow's, Antley–Bixler, and Goldenhar's syndromes; campomelic dysplasia (*SOX9* mutations); and trisomy 13.

C. Diagnostic tests

1. **Laboratory tests** are tailored to the differential diagnosis.

   a. **Chromosome analysis** on peripheral blood (karyotype is reported within 48 hours in some centers) by **fluorescent *in situ* hybridization (FISH)**. Although a standard karyotype may show 46,XX, FISH for *SRY* may reveal that it has been translocated to an X chromosome or an autosome. Any abnormal karyotype detected prenatally should be confirmed immediately after birth.

   b. **First-line testing** in addition to a karyotype (which is often available only in labs outside the hospital) should include a 17-hydroxyprogesterone, LH, and testosterone which are to be drawn after 48 to 72 hours of life. Baseline labs can also include serum electrolytes, blood urea nitrogen (BUN), and creatinine, with electrolytes followed frequently to look for evidence of salt wasting.

   c. **Other tests** such as plasma renin activity, follicle-stimulating hormone (FSH), AMH, or other adrenal precursors and hormones may be indicated in certain circumstances.

   d. **Targeted genetic testing and/or chromosomal microarray** may be indicated to look for 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 46,XX males. With the input of geneticists, testing may be appropriate in many cases of DSD. Some institutions have started to use whole-exome sequencing to aid in the diagnosis of DSD cases. Cost, insurance coverage, and incomplete knowledge of the genetics of DSD remain limiting factors with this approach.

2. **Pelvic ultrasonography**, especially when the bladder is full, can determine whether a uterus is present. Even though pelvic ultrasound demands expertise, it is a cost-effective as well as a practical first step in a case with clitoromegaly and no palpable gonads. Presence of Müllerian structures in such a baby guides to a working diagnosis of CAH and one can up the vigil for an adrenal crisis while awaiting the serum 17-OHP and serum cortisol values. Testes can often be visualized by ultrasound, but ovaries 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 testes or to confirm the presence of a uterus when ultrasonography is indeterminate.

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 abnormal connections between the urinary and genital tracts (e.g., urogenital sinus).

V. CLINICAL CLASSIFICATION OF DSD

In the year 2006, Lawson Wilkins Pediatric Endocrinology Society and the European Society of Pediatric Endocrinology proposed a classification of DSD based on karyotype analysis. It included three main categories (Table 63.3). Recently, the International Classification of Pediatric Endocrine Diagnosis (ICPED) suggested a revised and expanded classification of DSD under the broad heading of sex development and gender (Table 63.4). Although there may be varied approaches to classification, clinical approach to DSD would start with physical examination (atypical/ambiguous genitalia), palpable gonads (symmetric/asymmetric), ultrasound to look for internal genitalia (uterus/testis), lab evidence of gonadal function (AMH, response to hcg stimulation), occasionally histology of the gonad (ovary or testis), and ultimately the karyotype.

A. DSD sex chromosomes

B. DSD, XY

C. DSD, XX

Table 63.3. Clinical Classification of DSD (LWPES and ESPE 2006)

DSD, Sex Chromosomes	DSD, XY	DSD, XX
1. 45 XO (Turner) **2.** Klinefelter **3.** MGD **4.** Ovotesticular DSD	**1.** Disorders of gonadal development **a.** Complete gonadal dysgenesis **b.** Partial gonadal dysgenesis **c.** Gonadal regression **d.** Ovotesticular DSD **2.** Androgen insufficiency (androgen synthesis/action **a.** Androgen biosynthesis defect ■ 17 Alpha hydroxylase deficiency ■ POR def ■ 3 B hydroxysteroid dehydrogenase 3 deficiency ■ 5ARD* ■ StAR mutation **b.** Defect in androgen action ■ CAIS ■ PAIS **c.** LH receptor defect **d.** Disorder of AMH and AMH receptor (Persistent Mullerian duct syndrome) **3.** Other (e.g., severe hypospadias, cloacal extrophy)	**1.** Disorders of gonadal (ovarian) development **a.** Ovotesticular DSD **b.** Testicular DSD (e.g., SRY+, dup SOX9) **c.** Gonadal dysgenesis **2.** Androgen excess **a.** Fetal (e.g., 21 hydroxylase deficiency, 11 hydroxylase deficiency) **b.** Fetoplacental (aromatase deficiency, POR) **c.** Maternal (e.g., luteoma, exogenous) **3.** Other (e.g., cloacal exstrophy, vaginal atresia, MURCS, other syndromes)

*5ARD-5 Alpha reductase deficiency

Table 63.4. Disorders of Sex Development (ICPED 2016)

Disorders of Gonadal Development with Sex Chromosome Anomaly	Disorders of Gonadal Development with Sex Chromosome Anomaly	Disorders and Differences of Sex Development in the Presence of Typically Formed Gonads
Turner syndrome and variants	46, XY gonadal dysgenesis, partial or complete	46, XY deficiencies of secretion or action of Luteinizing hormone
Klinefelter syndrome and variants	46, XY ovotesticular of sex development	46, XY disorders of synthesis or action of Androgen hormone
45, X/ 46 XY mixed gonadal dysgenesis	46 XY, testicular regression with typical male genital development	46, XY disorders of anti- Mullerian hormone production or action
46, XX/ 46, XY ovotesticular disorder of sex development	46 XX, testicular disorder of sex development	46, XY disorders of genital development not otherwise classified
Other, specified form of sex chromosome anomaly with atypical gonad development	46, XX ovotesticular of sex development	46, XX disorders of androgen excess
Other, unspecified form of sex chromosome anomaly with atypical gonad development	46, XX gonadal dysgenesis or agenesis with typical female genital development	46, XX disorders of Mullerian duct development
		46, XX disorders of genital development not otherwise classified elsewhere

A. DSD, sex chromosomes

1. Turner syndrome
2. Klinefelter syndrome

   Turner and Klinefelter DSD do not present as ambiguous (atypical) genitalia in the newborn.

3. **46 X/46 XY mixed gonadal dysgenesis (MGD)**

   The hallmark of MGD is the presence of a testis on one side and either a streak gonad or a dysgenetic gonad on the other side. This disorder is most often due to a 45,X/46,XY mosaic karyotype. Often, the Y chromosome is abnormal, or Y chromosome material may be translocated to an autosome.

   On physical examination, the combination of *asymmetric external genitalia and one palpable testis (Fig. 63.4) in the labioscrotal fold is often MGD.* However, 45,X/46,XY mosaicism can result in an appearance of the external genitalia ranging from normal male to normal female. In fact, 90% of 45,X/46,XY infants diagnosed prenatally appear phenotypically male with cryptorchidism

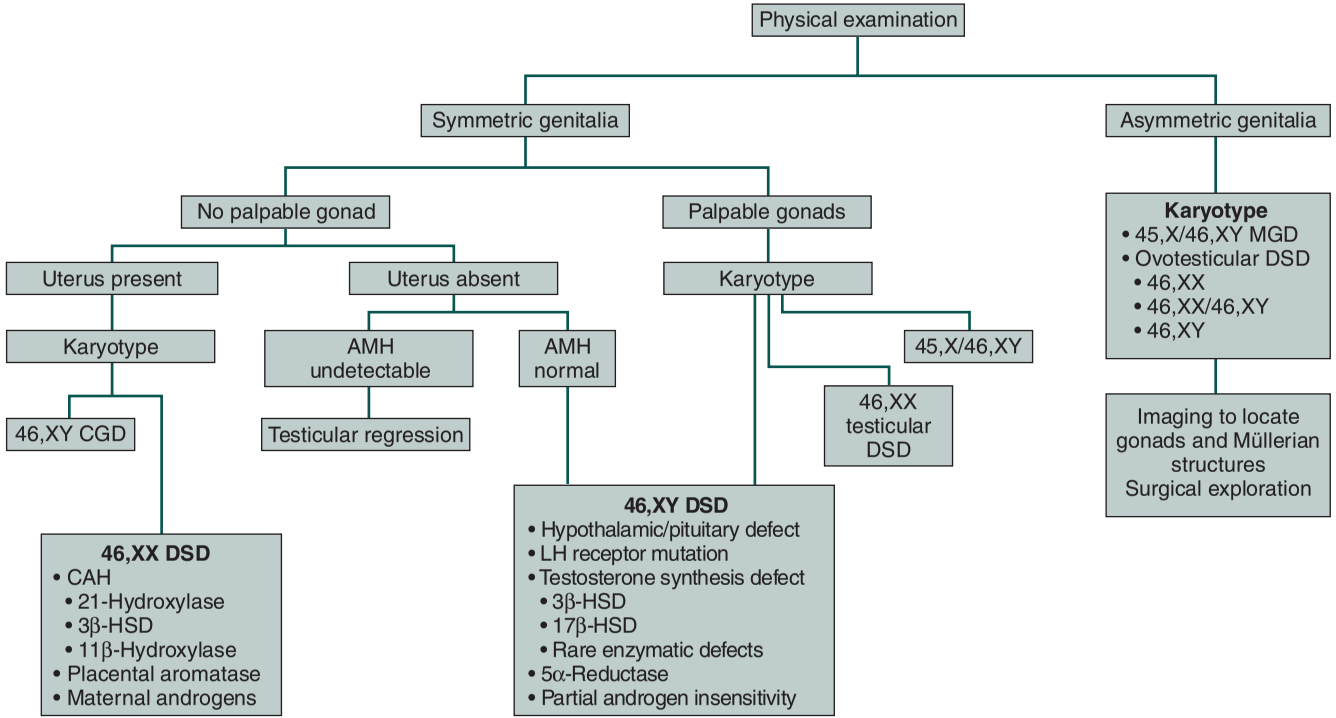

Figure 63.4. Algorithm for the evaluation of disorders of sex development (DSDs). AMH, anti-müllerian hormone; CAH, congenital adrenal hyperplasia; CGD, complete gonadal dysgenesis; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; LH, luteinizing hormone; MGD, mixed gonadal dysgenesis.

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 MGD may have features similar to those of Turner's syndrome such as webbed neck, lymphedema, short stature, renal abnormalities, and cardiac defects (e.g., coarctation of the aorta).

Management. Presence of AMH (measurable) or significant rise in serum testosterone on hCG stimulation test (Fig. 63.4) indicates the presence of testicular tissue. Streak gonads and some dysgenetic testes should be removed in infancy if the sex assignment is female. In case of male sex assignment, orchidopexy is required for fixation of the testes in the scrotum, to make it accessible for periodic clinical examination, biopsy may be recommended at the time of puberty. Grossly dysgenetic gonad may be removed earlier, 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.

4. **46, XX/46, XY Ovotesticular DSD.**

Gonads contain both testicular and ovarian tissues (histology)

The chromosomal complement in this rare condition is variable: 70% the of patients are 46,XX, <10% are 46,XY, and the remainder show mosaicism with a Y chromosome-containing cell line (most commonly 46,XX/46,XY). Physical findings. The external genitalia may appear normal or may show partial labioscrotal fusion, asymmetric labioscrotal folds, 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.

Evaluation. An hCG stimulation test that produces a rise in serum testosterone confirms the presence of Leydig cells, whereas a measurable AMH level indicates the presence of *Sertoli cells*.

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.

Management. Dysgenetic gonadal tissue that contains a Y chromosome should be assessed further by examination and/or imaging. The rate of tumors in ovotestes is lower than with gonadal dysgenesis but is still elevated from the normal 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 assignment, see section VIII.

B. DSD, XY

Evaluation of the infant with 46, XY DSD is complex, and early consultation with a pediatric endocrinologist will help direct the evaluation. Nevertheless, only 20% to 50% of children with 46, XY DSD will receive a definitive diagnosis. Even if genetic testing demonstrates Y chromosome material, the parents should not be told hastily that a male sex assignment is appropriate.

1. **46, XY gonadal dysgenesis, partial or complete**

   a. **Complete gonadal dysgenesis (CGD)** is also called Swyer's syndrome. Infants with *46, XY CGD fail to masculinize due to a failure of testicular differentiation*, 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 genital structures are female* due to inadequate production of AMH and testosterone. *The external genitalia usually appear female,* but clitoromegaly may occur if "gonadal" hilus cells secrete testosterone. *These patients are usually raised female and may not be diagnosed until they fail to initiate puberty* and exhibit high gonadotropins consistent with gonadal failure. Up to 30% of patients with 46, XY CGD may develop germ cell tumours, so their streak gonads should be removed in infancy.

   b. **Partial gonadal dysgenesis** occurs when there is partial but incomplete testicular differentiation, leading to inadequate production of testosterone and/or AMH, and in turn leading to varying degrees of external virilization and Müllerian regression. The tumour risk is also elevated in these cases, but there remains a lack of consensus regarding the degree of tumour risk and whether close monitoring is adequate if the gonad has a scrotal location and can be evaluated by physical examination and ultrasound.

   c. **46, XY Ovotesticular DSD** See section V. 4 for discussion of 46, XX Ovotesticular and testicular DSD.

2. **Defects in androgen (testosterone) synthesis or action**

   a. Defect in androgen synthesis. These individuals typically have no Müllerian structures because AMH is produced normally. Enzymatic defects in testosterone synthesis include deficiency of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD, encoded by *HSD17B3*), 3β-hydroxysteroid dehydrogenase (3β-HSD, encoded by *HSD3B2*), 17α-hydroxylase/17,20-lyase (17-hydroxylase or *CYP17*), isolated 17,20-lyase (17,20-Des), or very rarely side-chain cleavage enzyme (20,22 Des or *CYP11A1*) or steroidogenic acute regulatory protein (StAR) mutation.

   b. 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 46, XY DSD.

   c. 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).

   d. Environmental disorders. Maternal drug ingestion of antiandrogens (e.g., spironolactone) and 5α-reductase inhibitors (e.g., finasteride) can cause ambiguous genitalia. Maternal phenytoin exposure has been associated with ambiguous genitalia in rare cases.

Evaluation focuses on establishing the *presence or absence of testes* and their *ability to produce androgens*.

Presence of testes. If testes are not palpable, (Figure 63.4) their presence can be determined by imaging and/or AMH level or doing a hCG stimulation test later. Sometimes a laparoscopic evaluation of the abdomen may be required.

Imaging. USG or MRI - inguinal or intra-abdominal testes

Laboratory evaluation. If testicular tissue cannot be found by examination or imaging, levels of serum FSH, LH, testosterone, and AMH should be measured. The *testosterone and gonadotropins* rise shortly after birth (usually by 72 hours) and *are present at pubertal levels until approximately 6 months of age in boys*.

a. Elevated serum gonadotropins with *a low testosterone concentration suggest absent or non-functioning testes.*

b. Undetectable serum **AMH** is indicative of bilateral anorchia rather than undescended testes.

Laboratory evaluation is focused on determining whether the cause of under virilization is a defect in gonadal development or testosterone synthesis, metabolism, or action. Blood samples should be obtained for the measurement of electrolytes, FSH, LH, testosterone, DHT, androstenedione, 17-OHP, 17-hydroxypregnenolone, cortisol, and AMH. Serum electrolytes may reveal hyponatremia and hyperkalaemia in 3β-HSD deficiency. Measurement of 11-deoxycorticosterone and plasma renin activity may help define the type of enzyme deficiency.

*An **hCG stimulation test*** may be necessary if the above-mentioned results do not lead to a diagnosis.

Technique. The neonate is given 2,000 IU of hCG intramuscularly. Androstenedione, testosterone, and DHT concentrations are measured before the first dose and 72 hours after the final dose of hCG.

Interpretation. Inability to increase the testosterone level in response to hCG is characteristic of testicular dysgenesis, LH-receptor mutations, gestational loss of testicular tissue, 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.

*An **ACTH stimulation test*** may be necessary to define defects in earlier 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 (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.

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 PAIS. **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 PAIS.

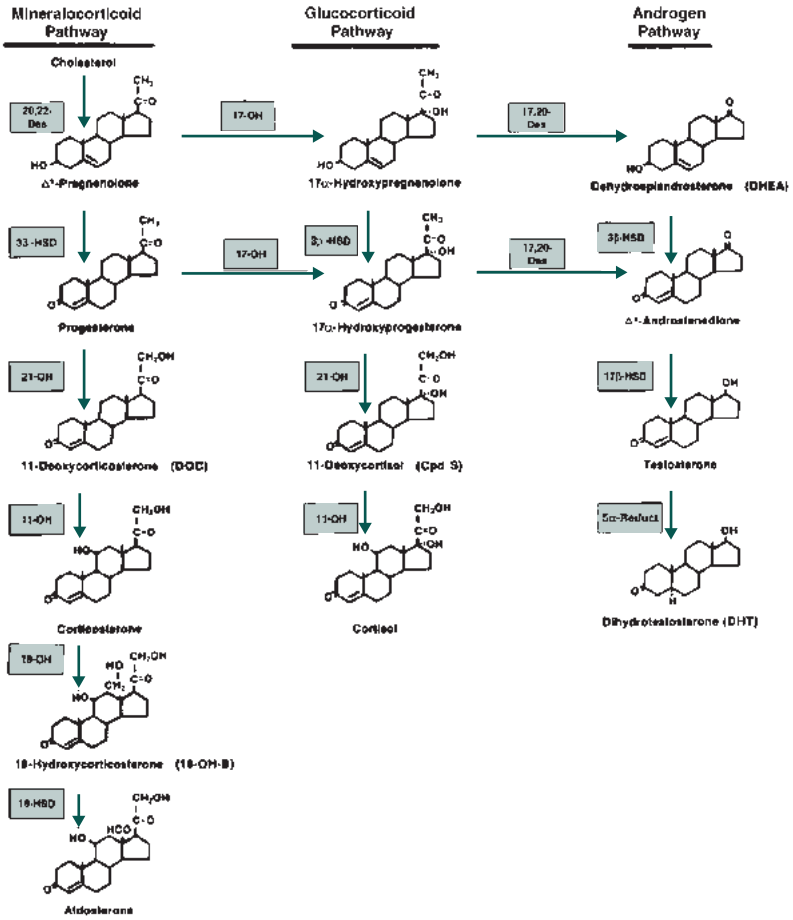

Figure 63.5. Pathways of steroid biosynthesis. (From Esoterix, Calabasas Hills, CA.)

Genetic studies of the androgen receptor will detect mutations in some but not necessarily all clinical cases of PAIS.

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 46,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.

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. It is produced in a sexually dimorphic manner. Starting at birth, AMH from Sertoli cells rises to a peak of 115 ng/mL at 6 months of age 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 in the normal or detectable range has a 100% positive predictive value for the presence of testicular tissue; the predictive value for anorchia is 94% if AMH is undetectable.

C. DSD, XX

1. **Disorders of gonadal development.** These individuals usually appear phenotypically male, but 20% have ambiguous genitalia. At puberty, they may produce insufficient testosterone and can resemble patients with Klinefelter's syndrome (small testes, azoospermia, disproportionately long limbs, gynecomastia). Cryptic mosaicism with a Y chromosome–bearing cell line or 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 have been reportedly associated with testicular or Ovotesticular DSD including *SOX3*, *WNT4*, and *RSPO1*.

2. **Androgen excess**

   a. **Excess androgens-fetal-CAH.** The most common DSD presenting in the neonatal period is a 46, XX infant with CAH presenting with varying degrees of virilization (androgen excess). This diagnosis is of utmost importance because the neonate may develop severe adrenal insufficiency and shock if proper treatment is not initiated timely. The most common form of CAH (>90%) is deficiency of 21-hydroxylase (21-hydroxylase, in Fig. 63.5) caused by mutations in *CYP21A2*. Virilization may occur in rarer forms of CAH due to deficiency of 11β-hydroxylase (11-beta hydroxylase, encoded by *CYP11B1*) or 3β-hydroxysteroid dehydrogenase (3β-HSD, encoded by *HSD3B2*). 46, XX DSD babies with CAH typically do not have testicular tissue and therefore usually have normally developed Müllerian structures and no Wolffian structures.

   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 male:female sex ratio is 1:1. Whereas females are easily detected at birth due to abnormal genital development, males have normal genitalia and may be missed on clinical examination (although hyperpigmentation of the scrotum can be a clue).

   Diagnosis. Newborn screening is important in the early detection of CAH, thus preventing life-threatening complications. In India, only a few states mandate newborn screening programs which 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.

   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.

False-negative results. Prenatal administration of steroids (e.g., betamethasone) may suppress 17-OHP levels and cause false-negative result. This is common practice, as late preterm pregnancies are treated with antenatal steroids; neonatologists must be aware of this. Newborns who have received antenatal steroids should be rescreened after 3 to 5 days.

Rapid evaluation of suspected 21-OHase deficiency is critical to avert salt-wasting crisis. 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. However, serum aldosterone may occasionally be raised due to cross interference in assay by precursor androgens. Serum electrolytes should be monitored at least every other day until salt wasting is confirmed or ruled out.

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.

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-OH progesterone levels.

Newborn screening may not detect infants with mild simple virilizing 21-OHase deficiency. Therefore, in a virilized 46,XX female 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 (Fig. 63.5).

Management. In an infant suspected of 21-OHase deficiency, treatment should be started as soon as the laboratory tests mentioned have been obtained.

Glucocorticoids. Hydrocortisone 20 mg/m^2/day, divided into dosing every 8 hours, should be given to all infants suspected of 21-OHase deficiency.

$$\text{Body surface area } (m^2) = \sqrt{\frac{\text{Length (cm)} \times \text{weight (kg)}}{3{,}600}}$$

Neonates with CAH presenting in adrenal crisis should receive stress dosage of steroids, initial bolus of 25 mg hydrocostisone, followed by 50 to 100 mg/m^2/day in six to eight hourly divided doses. Hydrocortisone dose is reduced to reach the maintenance dose once baby is clinically stable

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 the 5th and the 14th day of life but can occur as late as 1 month and may occur even in affected 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, salt loss 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, salt 1 to 2 g daily, divided into dosing every 6 hours, should be given mixed with milk in the initial days of life (each gram of salt, NaCl, contains 17 mEq of sodium).

b. Feto-placental-placental aromatase deficiency. The hallmark of this rare disorder is that both the mother and the infant are virilized due to an inability to convert androgens to estrogens.

c. Maternal hyperandrogenic conditions. Maternal CAH, virilizing tumors of the adrenal or ovary, or exposure to androgenic medications during pregnancy must be severe to overcome placental aromatase, which protects the fetus from androgens by converting them to estrogens.

VI. MICROPALLUS. 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's 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; and Prader–Willi, Robinow's, Klinefelter's, Carpenter's, Meckel–Gruber, Noonan's, de Lange's, Fanconi's, and fetal hydantoin syndromes. Treatment with testosterone enanthate or cypionate 25 to 50 mg intramuscularly given monthly for 3 months may substantially increase the penile length in these patients.

VII. 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. 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's, Cockayne's, Fanconi's, Noonan's, Klinefelter's, and fetal hydantoin syndromes.

The presence of any of the following physical findings merits evaluation for a DSD in neonates with cryptorchidism:

A. Unilateral cryptorchidism *with hypospadias*, especially proximal (e.g., perineoscrotal or penile) hypospadias

B. Unilateral cryptorchidism *with microphallus*

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 tumours in cryptorchid testes.

Persistent Müllerian duct syndrome (PMDS) in 46, XY infants is caused by defects in AMH or its receptor. Cryptorchidism is common in infants with PMDS, who otherwise have normal male genitalia but retain a uterus and fallopian tubes.

VIII. ISSUES OF SEX ASSIGNMENT. Today, most providers agree that the primary goal in sex assignment 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 of rearing itself, but there are undoubtedly other, currently unknown factors that affect the formation of gender identity. Only in cases of complete androgen insensitivity and 46,XY CGD can sex assignment (as female) be done with full confidence. Also, for CAH with 46,XX, 90% of children raised as females are happy with the assigned gender as adults. Hence, for this group of infants also, most agree with a female sex assignment. It is a well-known fact that gender change can occur at pubertal age in around half of the individuals assigned female gender in conditions such as 5α- reductase deficiency and 17α-hydroxylase deficiency. In PAIS, an incomplete type of gonadal dysgenesis and testosterone biosynthesis defects, around one-fourth of the individuals will be dysphoric to the assigned sex irrespective of which sex they are assigned to.

The 46,XY infants born with little or no penile tissue had traditionally been assigned a female sex and surgically and hormonally feminized by means of genitoplasty and gonadectomy early in life and estrogen treatment at the age of puberty. This practice is no longer routine.

It is still a controversy whether and when to perform other gonadal and/or genital surgeries, such as clitoral reduction in virilized infants being raised female or gonadectomy in infants with CAIS. Whereas some adults with DSD view their genital surgery as mutilation, many parents prefer surgery so that their child's genitalia appear more consistent with the assigned sex. The High Court in India has ruled that sex-reassigning surgeries should be considered in infants only if a multidisciplinary committee agrees upon the necessity of such a procedure, to sustain the life of the infant. It is increasingly becoming accepted that informed discussion with the family as well as the assent of the child is needed for genital surgeries in the context of gender assignment. In female patients with CAH when decided for surgery, the existing guidelines suggest vaginoplasty using urogenital mobilization, and if clitoroplasty is chosen, a neurovascular-sparing procedure should be done. 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.

Parents require a thorough explanation of their child's condition as laboratory and imaging data become available. They should participate with the interdisciplinary team in decision making during assessment of the options for medical and surgical therapy and of the prospects for gender identity, genital appearance, sexual functioning, and fertility. The 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 assignment for these infants.

Suggested Readings

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64 Surgical Emergencies in the Newborn

Steven A. Ringer and Anne R. Hansen

KEY POINTS

- Bilious emesis is malrotation until proven otherwise.
- Open lesions (e.g., myelomeningocele and abdominal wall defects) require immediate attention to infection control and fluid losses as well as arrangement for timely surgical closure.
- Patients with known diaphragmatic hernia should be intubated immediately after birth and 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 an appropriate facility.

I. POTENTIAL SURGICAL CONDITIONS PRESENTING IN THE FETUS

A. Polyhydramnios (single deepest measure fluid pocket >8 cm or and amniotic fluid index >25 cm) 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, diaphragmatic hernia (DH), maternal diabetes with consequent fetal hyperglycemia and polyuria 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. In experienced hands, this is the study of choice for the diagnosis of intestinal obstruction, abdominal wall defects, DH, as well as abnormalities leading to an inability of the fetus to swallow.

4. If intestinal obstruction is diagnosed antenatally and there is no concern for dystocia, vaginal delivery is acceptable. Pediatric surgical consultation should be obtained before delivery.

B. Oligohydramnios is associated with amniotic fluid leak, intrauterine growth restriction, postmaturity, fetal distress, and renal dysgenesis or agenesis (Potter's syndrome; see Chapter 28). If the duration of oligohydramnios is prolonged, it is important to anticipate respiratory compromise in these infants, as adequate amniotic fluid volume is generally necessary for normal pulmonary development,

particularly during the second trimester of gestation. Severity of pulmonary hypoplasia correlates with the degree and duration of oligohydramnios.

C. 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 IV.A).

D. Fetal ascites is usually associated with urinary tract anomalies (e.g., lower urinary tract obstruction due to posterior urethral valves). Other possible causes include hemolytic disease of the newborn, any severe anemia (e.g., α-thalassemia), 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). After birth, ascites may be seen in congenital nephrotic syndrome. Accurate prenatal ultrasonography is important in light of the potential for fetal surgery to minimize renal parenchymal injury by decompressing either the bladder or a hydronephrotic kidney (see Chapters 1 and 28).

E. Dystocia may result from fetal hydrocephalus, intestinal obstruction, abdominal wall defect, genitourinary anomalies, or fetal ascites (see section I.D).

F. Fetal surgery. The potential for surgical intervention during fetal life continues to develop. 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).

Advances in obstetric and anesthesia management have also contributed to the feasibility of performing *in utero* procedures. The mother must be carefully managed through what is often a long and unpredictable anesthesia course. Medications that reduce uterine irritability have been developed that maximally ensure that the uterus can be maintained without contractions 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 pain or harm to the mother as well as the impact on the family as a whole.
2. **Technical feasibility**
3. **Severity of fetal condition.** Initially, most cases dealt with conditions that were life threatening either because they caused death *in utero* or because of the inability to survive postnatal life if born unrepaired. 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 worsening hydrops due to a large teratoma).
4. **Necessary resources.** The care of the mother, fetus, and potential baby during surgery, in the immediate postoperative period and after birth, must all be available in seamless proximity to the institution where the surgery is performed.

Fetal surgery has been successfully used for the removal of an enlarging chest mass, such as an adenomatoid malformation of the lung or a

bronchopulmonary sequestration. Mass lesions, such as sacrococcygeal teratoma, when diagnosed *in utero*, have been treated with excision or by fetoscopically guided laser ablation of the feeder vessels, resulting in involution, but this type of intervention is considered only when the lesion is causing life-threatening complications, such as fetal hydrops. Progressive fetal urethral obstruction has been ameliorated by the use of shunts or fulguration of posterior urethral valves. Similar fetoscopic laser ablation of connecting vessels has been used successfully in the treatment of twin–twin transfusion syndrome (TTTS) or twin reversed arterial perfusion (TRAP).

Fetal surgical correction of meningomyelocele is a rapidly evolving area of endeavor. A multicenter randomized controlled trial comparing *in utero* surgical correction with standard management found that performing prenatal surgery may lead to better outcomes than performing postnatal surgery. 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. At 2.5-year follow-up, those treated prenatally showed improved physical development and motor function, such as unassisted walking, compared to those treated after birth. However, prenatal surgery was associated with an increased risk of complications during pregnancy including premature delivery and tearing of the uterine wall from the surgical scar. Long-term effects of this approach remain uncertain. When the diagnosis of myelomeningocele is made prenatally, *in utero* repair is an option that parents may consider.

Successful fetal procedures that we are currently performing include ***ex utero* intrapartum treatment** (EXIT) procedures for complex airway obstructions and complex congenital DH, aortic valve dilation for critical aortic stenosis, atrial septostomy, or stent placement for intact atrial septum with hypoplastic left heart syndrome, vascular photocoagulation for TTTS or TRAP syndrome, and percutaneous bladder shunt for bladder outlet obstruction. Indications for fetal intervention continue to evolve and change.

II. POSTNATAL SURGICAL DISORDERS: DIAGNOSIS BY PRESENTING SYMPTOM

A. Respiratory distress (see sections III.B and III.C; Chapters 29 to 39). Although most etiologies of respiratory distress are treated medically, some respiratory disorders do require surgical therapies.

1. Choanal atresia (see section III.C.1)
2. Laryngotracheal clefts (see section III.C.3)
3. Tracheal agenesis
4. EA with or without tracheoesophageal fistula (TEF) (see section III.A)
5. Congenital lobar emphysema
6. Cystic adenomatoid malformation of the lung, pulmonary sequestration
7. DH (see section III.B)
8. Spontaneous pneumothorax
9. Biliary tracheobronchial communication (extremely rare)

B. Scaphoid abdomen

1. DH (see section III.B)

2. EA without TEF (see section III.A)

C. Excessive mucus and salivation.

1. EA with or without TEF (see section III.A)

D. Abdominal distention can be due to ascites, pneumoperitoneum, or intestinal obstruction (mechanical or functional).

1. Pneumoperitoneum. Any perforation of the bowel may cause pneumoperitoneum (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.

2. Intestinal obstruction

a. EA with TEF (see section III.A) can present as abdominal distension. Obstruction of the proximal bowel (e.g., complete duodenal atresia) typically results in rapid distension of the left upper quadrant. Obstruction of the distal bowel causes more generalized distention, varying with the location of the 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; and 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 vomit in the newborn should be treated as a life-threatening emergency, with at least 20% of such infants requiring emergency surgical intervention after evaluation. Surgical consultation should be obtained immediately. Unless the infant is clinically unstable, a contrast study of the upper gastrointestinal (UGI) tract should be obtained as quickly as possible.

Intestinal obstruction may result from malrotation with or without midgut volvulus; duodenal, jejunal, ileal, or colonic atresias; annular pancreas; Hirschsprung's 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 II.E.2.c). In these cases,

the bile-stained vomiting will occur only one or two times and will present without abdominal distention. However, a nonsurgical condition is a diagnosis of exclusion; bilious emesis is malrotation 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 $MgSO_4$ or antenatal, prenatal, or postnatal exposure to narcotics
     - **iii.** Sepsis with ileus
     - **iv.** Central nervous system (CNS) lesion
   - **d.** Lesion above the 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. Anorectal malformations
2. Microcolon
3. Mucous plug
4. Hirschsprung's disease
5. Other causes of intestinal obstruction

G. Failure to develop transitional stools after the passage of meconium

1. Volvulus, other intestinal obstruction
2. Malrotation

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 (see section XI.G).
     - **ii.** In breastfed infants, either microscopic or macroscopic blood noted several days after birth in either emesis or stool may be due to swallowed blood during breastfeeding in the 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) and 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. Cirsoid aneurysm

I. Abdominal masses (see section VIII)

1. Genitourinary anomalies including distended bladder (see section VII and Chapter 28)

2. Hepatosplenomegaly: may be confused with other masses; requires medical evaluation

3. Tumors (see section VII)

J. Birth trauma (see Chapter 6)

1. Fractured clavicle/humerus (see Chapter 58)

2. Intracranial hemorrhage (see Chapter 54)

3. Lacerated solid organs—liver, spleen

4. Spinal cord transection with quadriplegia

III. LESIONS CAUSING RESPIRATORY DISTRESS

A. EA and TEF. At least 85% of infants with EA also have TEF. Pure EA and TEF 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 it 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. 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. 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 cardiac or 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. Approximately 20% of these babies are premature (five times the normal incidence), and another 20% are small for gestational age (eight times the normal incidence). Other anomalies may be present, including chromosomal abnormalities and the VACTERL association: **v**ertebral defects, anorectal malformations, **c**ardiac defects, **TE**F with EA, renal and radial abnormalities 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) should be placed in the proximal pouch and put to continuous suction immediately after the diagnosis is made.

b. The head of the bed should be elevated 30° to diminish reflux of gastric contents into the fistula and aspiration of oral secretions that may accumulate in the proximal esophageal pouch.

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. The endotracheal tube should be advanced to just above the carina in the hopes of obstructing 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.

d. Surgical therapy usually involves placement of a gastrostomy tube, if long-gap EA is expected. 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. Thoracoscopy versus thoracotomy (conventional open repair): offers equal incidence of postoperative leaks and strictures. Thoracoscopy, however offers less postoperative pain, earlier first feed, and shorter hospital stay inspite of longer operative time. Although oesophagostomy is discouraged for fear of damage to upper pouch, if continuous suction is going to be difficult for long durations, this may be the only option to prevent aspiration.

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 because of the TEF. These patients need 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. 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. Many approaches are there:

i. Delayed primary repair. The infant undergoes esophagostomy and gastrostomy. After months, when the infant has good nutrition and the gap may be lesser, definitive surgery is planned.

ii. Traction and elongation techniques. Intrathoracic and extrthoracic traction, thoracoscopic traction and esophageal circular, or spiral myotomy are options.

iii. Transposition. Gastric, colonic, jejunal, and gastric tube transposition have been tried to bridge the long gaps

5. Prognosis

Survival of babies with EA is nearly 100% in good centers and nearly 90% in babies with associated major anomalies. In developing countries the survival is as low as 50%. Causes for poor outcome include delay in suspicion and diagnosis with resultant aspiration pneumonia, poor facilities for transfer to advanced centers, lack of facilities for ventilation, and parenteral nutrition. Many babies reach hypothermic, dehydrated, malnourished with severe aspiration pneumonia several days after birth to surgical units.

6. Long-term follow-up

Immediately post-op, anastomostic leak and recurrence of fistula can happen.

EA babies are at risk of swallowing dysfunction and gastroesopahageal reflux disease (GERD). Esophageal stricutres are not uncommon.

B. Diaphragmatic hernia

1. Anatomy. The most common site is the left hemithorax, with the defect in the diaphragm being posterior (foramen of Bochdalek) in 70% of infants. It can

also occur on the right, with either an anterior or a posterior defect. Bilateral DH is extremely rare.

2. Incidence occurs in approximately 1 in 4,000 live births. Fifty percent of these hernias are associated with other malformations, especially cardiac, neural tube, intestinal, skeletal, and renal defects. DH has been associated with trisomies 13 and 18 and 45,XO and has been reported as part of Goldenhar's, Beckwith–Wiedemann, Pierre Robin, and Wolf–Hirschhorn syndrome (4p deletion); Pallister–Killian syndrome (tetrasomy 12p); Fryns' syndrome; Goltz–Gorlin syndrome; and congenital rubella syndrome. In rare cases, DH is familial.
3. Symptoms. Infants with large DHs 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, right-sided hernias, sac-type hernias, and substernal 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. DHs often occur after the routine 16-week prenatal ultrasonography; therefore, many of these cases are not diagnosed prenatally. The development of polyhydramnios should prompt a later fetal ultrasonography that will detect DH. Diagnosis earlier in gestation may correlate with a poorer prognosis due to the severity of the condition. The prognostic advantage of prenatal diagnosis is that it generally leads to delivery in a center equipped to optimize chances for survival. Preterm birth can add respiratory distress syndrome and other problems of prematurity and increases need for intensive care and mortality several folds. Baby must be delivered preterm only for definite maternal/fetal indications. Presence of the liver in the thorax correlates with increased severity and poorer prognosis. Lung-to-head ratio (LHR) can also be measured prenatally and in skilled hands can help predict the severity of the involvement. LHR performs well if performed between 18 to 38 weeks gestation. Severe pulmonary hypoplasia is suggested by <25% observed to expected LHR on left side and <45% on right-sided diaphragmatic hernia.
   b. Postnatal diagnosis. The diagnosis is made or confirmed by radiograph of the chest and abdomen. Because of the possibility of marked cardiothymic shift, a radiopaque marker should be placed on one side of the chest to aid interpretation of the x-ray film.
   c. Differential diagnosis. Diaphragmatic eventration, congenital cystic adenomatoid malformation (CCAM), pulmonary sequestration, bronchogenic cyst
5. Treatment
   a. Severe cases that have been diagnosed before birth may be best managed with delivery by the EXIT procedure. This requires a multidisciplinary team consisting of obstetricians, specialized anesthesiologists, surgeons, neonatologists, nurses, respiratory therapists. The fetus is partially delivered

from the mother, and initial interventions are completed including intubation and ventilation.

b. Intubation. All infants with known DH should be intubated immediately after delivery or at the time of postnatal diagnosis. Bag-and-mask ventilation is contraindicated. Immediately after intubation, a large sump nasogastric 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. Peripheral venous and arterial lines are preferable, as umbilical lines may need to be removed during surgery. However, if umbilical lines are the only practical access, these should be placed initially. Heavy sedation and paralysis should be avoided as spontaneous respiratory effort enables the use of the pressure support mode of ventilation which we have found to induce the least barotrauma.

c. Preoperative management is focused on avoiding barotrauma and minimizing pulmonary hypertension (PH). Permissive hypercapnia is the preferred respiratory approach, although the optimal mode of ventilation remains controversial, including the role for high-frequency ventilation. Targets may be preductal saturation 85% to 95%, PCo2 of 45 to 60, pH of 7.25 to 7.4 with PIP restricted to 25 if possible. Preductal arterial lines (radial) may give better measure of physiology than postductal (umbilical) artery. Avoidance of hypoxia and acidosis will aid in minimizing PH. PH is a major determinant of outcomes. iNO is the first choice, sildenafil may be tried in nonresponders. Milrinone is beneficial in PH associated with cardiac dysfunction proven on ECHO. The role of exogenous surfactant remains controversial.

6. Surgical repair is through either the abdomen or the chest, with reduction of intestine into the abdominal cavity. Minimal invasive surgery is offered at some centers. Open surgical procedures are associated with better outcomes. Need for a patch for primary closure is associated with poor prognosis.

7. Mortality and prognosis

a. Mortality from DHs is largely related to associated defects, especially pulmonary hypoplasia and CHD. Our local survival is now >90% for infants without associated CHD. Repair of the defect itself is relatively straightforward; the underlying pulmonary hypoplasia and PH are largely responsible for the overall mortality. ECMO has improved outcomes of severest cases. It must be decided early.

b. Prognosis. Factors associated with better prognosis include herniation of the bowel into the chest after the second trimester, absence of liver herniation, and absence of coexisting anomalies, especially cardiac. Early oxygen tension (PO_2) and carbon dioxide tension (PCO_2) are predictive of prognosis. In addition, the later the onset of postnatal symptoms, the higher the survival rate. Long-term follow-up of neurodevelopment, hearing, and for scoliosis in some cases is necessary.

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. Transnasal endoscopic repair is the preferred initial technique. In unilateral cases, repair can be delayed up to 2years. Drilling of atretic plate, balloon dilatation, cold instruments, and use of laser have been described in repair.

2. **Robin anomaly** (Pierre Robin syndrome) consists of a hypoplastic mandible associated with a secondary U-shaped midline cleft palate. Often, the tongue occludes the airway causing obstruction. Prone positioning and a nasopharyngeal airway (insert a 2.5 size endotracheal tube [ET], such that the 5 mark on ET is at the nostril; or just as deep that one may visualize the tip of the ET tube at the level of soft palate). The nasopharyngeal tract is bent and prone for injury by a stiff tube. So, we insert a feeding tube number 5 first and then thread the number 5 ET over it. Most babies can be discharged to home on this airway. The airway may have to be retained for 2 to 3 months. If the infant can be supported for a few days, he or she will sometimes adapt, and aggressive procedures can be avoided. In some cases, a lip–tongue adhesion or mandibular distraction can avoid the need for tracheostomy or enable earlier decannulation. A specialized feeder (Breck) facilitates PO feeding the infant, but sometimes, a gastrostomy is necessary. Severely affected babies will require tracheostomy and gastrostomy.
3. **Laryngotracheal clefts.** The length of the cleft determines the symptoms. The diagnosis is made by direct bronchoscopy under anesthesia. Very ill newborns should undergo immediate bronchoscopy without contrast studies.
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 should time permit. Prognosis is poor as tracheal reconstruction is difficult.
6. **Congenital lobar emphysema** (CLE) is associated with progressive airtrapping and hyperinflation of the affected lobe and compression atelectasis of normal lung parenchyma of adjacent lobes and mediastinal shift. The cause of ball valve obstruction is idiopathic in most cases, in some it is due to extrinsic or intrinsic obstruction. Unlike other congenital lung malformations (CLM), CLE is missed most often on antenatal scans. CLE is mostly symptomatic unlike other CLM (CPAM), progressive tachypnea may be noted, starting after a few weeks. Diagnosis may be better with CT than MRI, understanding well the radiation exposure. Left upper lobe, right middle, and upper lobe are involved most often. Open thoracotomy is preferred over thoracoscopy.
7. **Cystic pulmonary airway malformation (CPAM).** CPAM is a common antenatal diagnosis. It is characterized by multiple cysts in the lung parenchyma due to overproliferation and dilatation of the terminal bronchioles with an absence of normal alveoli. The CPAM size may be small and involute in the antenatal scans in some cases. If the CPAM appears to be big (CPAM volume ratio> 1.6), the baby should be delivered at a center with facility for emergency care at birth and pediatric surgery. Rarely, the CPAM may be huge, may cause mediastinal shift, and even hydrops fetalis; EXIT procedure may be required at birth.

Most CPAM are asymptomatic at birth. They may be prone for respiratory infections. The outcomes of electively operated babies is not better than those managed conservatively, hence, surgery is best not done in asymptomatic babies. Small less than or equal to 1 cm in size CPAM may be managed by observation alone. Type 1 CPAM (Stocker's classification) has malignant potential but the magnitude of risk is not known.

8. **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 echocardiogram may be necessary to rule out intracardiac anomalies. Bronchoscopy can be helpful if tracheal stenosis is suspected.

IV. 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 nasogastric sump catheter placed to continuous suction without delay. Any infant with a GI obstruction is at an 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's disease) or other intrinsic defects in the bowel wall

3. Paralytic ileus
   a. Induced by medications
      i. Narcotics (prenatal 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 Down's syndrome, cardiovascular anomalies, and such GI anomalies as annular pancreas, EA, malrotation of the small intestine, other small bowel atresias, and imperforate anus.
   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 decompression with nasogastric suction.
   i. Antibiotics should be started until perinatal sepsis evaluation is complete and then consider tailoring to prophylactic antibiotics until definitive repair.
   j. Definite repair for duodenal atresia is duodenoduodenostomy (preferred) or duodenojejunostomy by laparoscopic or open techniques.
2. **Jejunal and ileal atresias.** Most are 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 IV.D.3.b).
3. **Meconium ileus** is a frequent cause of meconium peritonitis. Abdominal distension at birth differentiates meconium ileus from other small bowel obstructions. 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. Blood sample or cheek brushing for DNA analysis can be used to screen for CF if newborn or antenatal screening has not been performed. If the results are negative or equivocal or if the baby weighs >2 kg and is older than 2 weeks ideally (but certainly older than 3 days), a sweat test should be performed. Sweat tests on babies who are younger or smaller risk both false-positive results due to the high NaCl content of the sweat of newborn babies and false-negative or uninterpretable results when an adequate volume of sweat cannot be obtained.

c. Decompression with continuous nasogastric 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.

d. Surgical therapy is indicated in uncomplicated meconium ileus only if not relieved with conservative management, surgery may be necessary for complicated meconium ileus.

Complications include DIOS (distal intestinal obstruction syndrome), adhesions, anastamotic ulcers, and strictures.

e. Microcolon distal to the atresia will generally dilate spontaneously with use.

4. **Imperforate anus.** Fifty percent have anomalies including those in the 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. Of note, in order to prevent urinary tract infections, prophylactic antibiotics should be considered until the fistula can be definitively repaired.

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 rectovesical 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. **Volvulus with or without malrotation of the bowel**

a. Malrotation may be associated with other GI abnormalities such as DH, annular pancreas, and bowel atresias and is always seen with omphalocele.

b. If this condition develops during fetal life, it may cause the appearance of a large midabdominal calcific shadow on x-ray examination; this results from calcification of meconium in the segment of necrotic bowel.

c. After birth, there is a sudden onset of bilious vomiting in an infant who has passed some normal stools. Malrotation, as the cause of intestinal obstruction, is a surgical emergency because intestinal viability is at stake. **Bilious emesis equals malrotation until proven otherwise.**

d. If the level of obstruction is high, there may not be much abdominal distension.

e. Signs of shock and sepsis are often present.

f. A radiograph of the abdomen will often show a dilated small bowel; although radiographs may be normal in malrotation, distinct evidence of ileus will be there once volvulus has set in.

g. If a malrotation is present, barium enema may show failure of barium to pass beyond the transverse colon or may show the cecum in an abnormal position.

h. The test of choice is an UGI series, specifically looking for an absent or abnormal position of the ligament of Treitz that confirms the diagnosis of malrotation.

6. **Meconium and mucous plug syndrome** is seen in infants who are premature or sick (see section II.F), and those with functional immaturity of the bowel with a small left colon, as seen in infants of diabetic mothers or those with Hirschsprung's disease (see section IV.D.7). CF should also be ruled out. Treatment may simply consist of a glycerin suppository, warm half-normal 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's 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 newbor. A retention film, after 24 hours , gives a better clue regarding the transition zone in newborn.

   c. Rectal biopsy is obtained to confirm the diagnosis. If suspicion is relatively low, a suction biopsy is useful, as the presence of ganglion cells in the submucosal zone rules out the diagnosis. If the index of suspicion is high, or the suction biopsy is positive, formal full-thickness rectal biopsy is the definitive method for diagnosis. Absence of ganglion cells and hypertrophic

nonmyelinated axons is diagnostic. Histochemical tests of biopsy specimens show an increase in acetylcholine.

d. Obstipation can be relieved by gentle rectal irrigations with warm saline solution. If the patient has a barium enema, gentle rectal saline washes are helpful in removing the trapped air and barium. Once the abdomen is decompressed, feedings may be offered.

e. Babies require surgical intervention when the diagnosis is made. A primary pull-through procedure is usually possible for correction, avoiding the need for a colostomy. In many institutions, colostomy is the standard, and it is always indicated when there is enterocolitis or adequate decompression cannot be achieved. Definitive repair 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. The risk of enterocolitis varies with the type of surgical procedure. Contrast enema is contraindicated when hirschprung associated enterocolitis is suspected due to high chance of perforation. Bowel rest, IV fluid resuscitation, broad spectrum antibiotics, and rectal irrigations (including metronidazole) are given. Failure of improvement with conservative management or pneumoperitoneum warrants surgical therapy.

8. Pyloric stenosis typically presents with nonbilious vomiting, classically in a firstborn boy, after the age of 2 to 3 weeks, but it 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," cannot be felt in the newborn. 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. Surgical therapy is pyloromyotomy and it is not an emergency. The child's hydration status and electrolyte levels should be stabilized prior to surgery to avoid a stormy postoperative course.

9. Annular pancreas may be nonobstructing but associated with duodenal atresia or stenosis. It presents as a high intestinal obstruction.

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.

V. OTHER GASTROINTESTINAL SURGICAL CONDITIONS

A. Omphalocele. The sac may be intact or ruptured. 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 the liver.

1. **Intact sac.** Emergency treatment includes the following:
   - **a.** Provide continuous nasogastric sump suction.
   - **b.** It is preferable to encase intestinal contents in a bowel bag (e.g., Vi-Drape Isolation Bag) as it is the least abrasive. Otherwise, cover the sac with warm saline-soaked gauze and then wrap the sac on abdomen with Kling gauze and cover with plastic wrap to support the intestinal viscera on the abdominal wall, taking great caution to ensure no kinking of the mesenteric blood supply.
   - **c.** Do not attempt to reduce the sac because this can rupture it, interfere with venous return from the sac, or cause respiratory compromise.
   - **d.** Bowel viability may be compromised with a small abdominal wall defect and an obstructed segment of the eviscerated intestine. In these circumstances, with surgical consultation, it may be necessary before transfer to enlarge the defect by incising the abdomen cephalad or caudad to relieve the strangulated viscera.
   - **e.** Keep the baby warm, including thoroughly wrapping in warm blankets to prevent heat loss.
   - **f.** Place a reliable intravenous line in an upper extremity.
   - **g.** Monitor temperature, pH, and electrolytes.
   - **h.** Start broad-spectrum antibiotics (ampicillin and gentamicin).
   - **i.** Obtain a surgical consultation; definitive surgical therapy should be delayed until the baby is stabilized. 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.** Emergency treatment is as in the preceding text for intact sac, except surgery is more emergent.
3. As up to 80% will have **associated anomalies**, physical examination should include a careful search for phenotypic features of chromosomal defects as well as CHD, genitourinary defects such as cloacal exstrophy, and craniofacial, musculoskeletal, vertebral, or limb anomalies. The Beckwith–Wiedemann syndrome includes (typically small) omphalocele, macroglossia, hemihypertrophy, and hypoglycemia.

B. Gastroschisis, by definition, contains no sac, and the intestine is eviscerated.

1. For uncomplicated gastroschisis, there is no advantage to a specific route of delivery, but a cesarean section is recommended for large lesions or those in which the liver is exposed. Preoperative management is as per omphalocele with ruptured sac (see section V.A.2).
2. Obtain immediate surgical consultation.

3. About 12% of these infants will have other GI anomalies, including volvulus, atresias, intestinal stenosis, or perforation.
4. Unlike omphalocele, gastroschisis is not commonly associated with anomalies unrelated to the GI tract.
5. There are several approaches to handle the problem including primary abdominal wall closure with (1) resection and primary anastomosis, (2) creating an ostomy, (3) and reoperation after 4 weeks to reanastomose the bowel. Alternatively, silo is applied for delayed resection of intestinal atresia and abdominal wall closure.

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. Rule out Hirschsprung's disease.

VI. RENAL DISORDERS (see Chapter 28)

A. Genitourinary abnormalities. 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 of life. 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 cause obstruction.
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. The 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 starts with medical support in the hope 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.** It ranges from an epispadias to complete extrusion of the bladder onto the abdominal wall. Most centers attempt bladder turn-in within the first 48 hours of life.
   a. Preoperative management
      i. Protect the exposed bladder mucosa by covering with a clear plastic wrap.
      ii. Transport the infant to a facility for definitive care as soon as possible.
      iii. Start antibiotics, adjust dose for the estimated renal function.
      iv. Provide adequate hydration in the setting of increased insensible losses; monitor lytes and renal function.
      v. Obtain renal ultrasonography.
   b. Intraoperative management. Modern staged repair of extrophy (MSRE) is more commonly practised than complete primary repair of extrophy

(CPRE). Surgical management of an exstrophied bladder includes turn-in of the bladder to preserve bladder function. The symphysis pubis is approximated. For males, the penis is lengthened. Iliac osteotomies are not necessary if repair is accomplished within 48 hours. No attempt is made to make the bladder continent at this initial procedure.

4. **Cloacal exstrophy** is a complex GI and genitourinary anomaly that includes vesicointestinal fissure, omphalocele, exstrophied bladder, hypoplastic colon, imperforate anus, absence of vagina in females, and microphallus in males.

   a. Preoperative management

      i. Gender assignment. It is surgically easier to create a phenotypic female, regardless of genotype. Understanding of the long-term psychological effects of this practice 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. Nasogastric suction 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 the intestine or stomach. There is lack of relevant literature whether early closure of bladder improves preservation of bladder function.

      iii. Subsequent procedures are designed to reduce the number of stomas and create genitalia, although this remains controversial. There is no consensus on timing of surgical reconstruction of uterus and vagina.

VII. 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 by the EXIT procedure (see section III.B.5.a) with the establishment of an airway before complete delivery of the baby.

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 the possible complications.

B. Neuroblastoma is the most common malignant neonatal tumor, accounting for approximately 50% of cases, although the overall incidence is rare. It is irregular, stony 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. Prenatal diagnosis by ultrasonography is associated with improved prognosis. Of note, many neuroblastomas diagnosed prenatally resolve spontaneously before birth. Nuclear imaging is an integral part in management of neuroblastoma.

C. Wilms tumor is the second most common malignant tumor in the newborn. Syndromic Wilm's tumor may be bilateral. It presents as a smooth flat mass and may be bilateral. One should palpate gently to avoid rupture. Ultrasonography is useful diagnostic test. In bilateral disease, nephron sparing procedures are preferred. Complete resection of lung and liver metastasis are associated with poor survival.

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 unknown, but estimated as high as 4% to 5% in Caucasian newborns, and most are benign. Other tumors such as lymphangiomas, hepatoblastomas, hepatomas, hamartomas, and nephromas and sarcoma botryoides may be seen in newborns, but they are extremely rare.

VIII. ABDOMINAL MASSES

A. Renal masses (see section VI and 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 VII), adrenal hemorrhage, ovarian tumor or cysts, pancreatic cyst, choledochal cyst, hydrometrocolpos, mesenteric or omental cyst, intestinal duplications, and hepatosplenomegaly.

IX. INGUINAL HERNIA.

It is found in 5% of premature infants with birth weight <1,500 g and as many as 30% of infants with 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 prematurely born infants. 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 should be 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 should be repaired as soon as 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 the infants with respiratory problems. As these infants often develop postoperative apnea, they should be monitored in the hospital for at least 24 hours after surgery.

2. **Repair after discharge.** Infants with significant pulmonary disease, such as bronchopulmonary dysplasia, are often best repaired at a later time when their respiratory status has improved. We have occasionally had well-instructed parents bring their babies 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.

X. SCROTAL SWELLING

A. Differential diagnosis

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 long-standing, 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 a 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, emergency surgical exploration and detorsion should be performed within 4 to 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 those of testicular torsion.

   c. **Prognosis.** Testicular prosthesis 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. It 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. Current guidelines recommend ligation of persistent processus vaginalis at 2 years of age.

3. **Incarcerated hernia**
4. **Trauma/scrotal hematoma.** Trauma to scrotum can happen in 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. Only pain management is needed.
6. **Spontaneous idiopathic scrotal hemorrhage.** It is most common in large-for-gestational-age (LGA) infants. distinguishable from torsion by the appearance of a small but distinct ecchymosis over the superficial inguinal ring.
7. **Tumors.** These are usually nontender, solid, and firm. Transillumination is negative.

XI. COMMON TESTS.

The common tests used in the diagnosis of surgical conditions include the following:

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's 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 diatrizoate meglumine 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 an UGI contrast study. In combination with air or contrast media, an 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 excreted in the newborn and hence IVP may be deferred if possible beyond first week of life (when GFR is very low).

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.

G. The Apt test differentiates maternal from fetal blood. A small amount of bloody material is mixed with 5 mL of water and centrifuged. One part 0.25N sodium hydroxide is added to five parts of the pink supernatant. The fluid remains pink in the presence of fetal blood but rapidly becomes brown if maternal blood is present. The test is useful only if the sample is not contaminated by pigmented material (e.g., meconium/stool).

H. Screening for CF is usually done by measuring immunoreactive trypsin from Guthrie spots. More definitive genetic testing can be performed on DNA sampling obtained from blood or cheek brush sampling. When the test result is negative but clinical suspicion remains high, a sweat test should be done. Ideally, the baby should be older than 2 weeks (certainly older than 3 days) and weigh >2 kg to avoid both false-positive results due to the relatively high chloride content of newborn infants' sweat and false-negative or uninterpretable results if <100 mg of sweat can be collected. It may be necessary to repeat the test when the infant is 3 to 4 weeks old if an adequate volume of sweat cannot be collected.

XII. PREOPERATIVE MANAGEMENT BY PRESENTING SYMPTOM

A. Vomiting without distention

1. The mechanics of feeding the baby should be observed. Rapid feeding, intake of excessive volume, and lack of burping are all causes of nonbilious vomiting without distension.

2. Functional and mechanical causes must be ruled out. Often, a history, physical examination, and observation of feedings are sufficient. An abdominal x-ray and ultrasound may be useful.

3. If the baby's general condition is good, milk feeding should be tried again. If vomiting recurs and there is a family history of milk allergy, blood in the stool, or elevated percentage of eosinophils on the complete blood count (CBC), consider a trial of non–cow's milk-based formula (e.g., elemental).

B. Nonbilious vomiting with distension. An overall assessment of the well-versus-sick appearance of the baby as well as the degree of the abdominal distension is critical in determining the evaluation and management of nonbilious vomiting and distension. In general, there should be a low threshold to assess for mechanical and functional obstruction, starting with history, physical examination, abdominal radiographs, ± contrast studies depending on the clinical presentation. If no source of obstruction is identified, many babies with nonbilious vomiting and mild distention respond to a combination of glycerin suppositories, half-strength

saline enemas (5 mL/kg body weight), and rectal stimulation with a soft rubber catheter. Limited feedings, stimulation to the rectum, and care for the general condition of the baby will solve most of these problems.

C. Bilious vomiting and abdominal distension

1. Immediately arrange for appropriate diagnostic evaluation (generally UGI series) to rule out malrotation with midgut volvulus.
2. **Enteral feedings should be discontinued.** Continuous gastric decompression with a sump catheter is mandatory if intestinal obstruction is suspected. All infants with presumed intestinal obstruction should be transported with a nasogastric suction catheter in place, attached to a catheter-tip syringe for continuous aspiration of gastric contents. Failure to decompress the stomach could lead to gastric rupture, aspiration, or respiratory compromise secondary to excessive diaphragmatic convexity into the thorax. This is especially important in infants who are to be transported by air because loss of cabin pressure would create a high-risk setting for the rupture of an inadequately drained viscous.
3. Shock, dehydration, and electrolyte imbalance should be prevented or treated if present (see Chapters 23 and 40).
4. Broad-spectrum antibiotics (ampicillin and gentamicin) should be initiated if there is suspicion of volvulus or any question about bowel integrity. Clindamycin should be added, or ampicillin and gentamicin should be substituted with piperacillin and tazobactam (Zosyn) if perforation is high risk or documented.
5. Studies that should be performed include the following:
   a. Monitoring of oxygen saturation, blood pressure, and urine output
   b. Blood tests as follows:
      i. CBC with differential and blood culture
      ii. Electrolytes
      iii. Blood gases and pH
      iv. Clotting studies (e.g., prothrombin time, partial thromboplastin time)
   c. Contrast study (start with UGI) to rule out malrotation

D. Masses. The following steps may be taken to determine the etiology of abdominal masses:

1. CBC with differential
2. Determination of the level of catecholamines and their metabolites
3. Urinalysis
4. X-ray examination of the chest and abdomen with the infant supine and upright
5. Abdominal ultrasonography
6. Contrast-enhanced CT
7. MRI
8. Angiography, venous and arterial
9. Surgical consultation

XIII. GENERAL INTRAOPERATIVE MANAGEMENT

A. Monitoring devices

1. Temperature probe
2. Electrocardiogram (ECG)
3. Pulse oximetry responds rapidly to changes in the patient condition but is subject to artifacts.
4. Transcutaneous PO_2 (see Chapter 30) is helpful if pulse oximetry is unavailable but can be inaccurate in the setting of anesthetic agents that dilate the skin vessels.
5. Arterial cannula to monitor blood gases and pressure

B. Well-functioning intravenous line. Babies with omphalocele or gastroschisis should have the intravenous 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 the exposed parts of the baby, especially the head (with a hat).

D. Fluid replacement

1. Replace loss of >15% of the total blood volume with warmed packed red blood cells.
2. Replace ascites loss with normal saline, estimated volume lost must be replaced to maintain perfusion and blood pressure.
3. The neonate loses approximately 5 mL of fluid per kilogram for each hour that the intestine is exposed. This should generally be replaced by Ringer lactate.

E. Anesthetic management of the neonate is reviewed in Chapter 70.

F. Postoperative pain management is discussed in Chapter 70.

G. 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

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KEY POINTS

- Epidermal barrier function of skin is not mature at birth, it takes 2 to 4 weeks following exposure to extrauterine environment.
- In preterm babies, the stratum corneum has very few layers, cohesion between dermis and epidermis is decreased, and skin has lesser collagen.
- In labor room, preterm babies must be wrapped in polythene wraps/bags to decrease heat loss; in NICU they must be nursed in humidifed incubators to reduce evaporative loss of heat.
- Standard pediatric tools for assessment of intravenous site extravasation should be used.
- High risk medications include dopamine, phenytoin, parenteral nutrition, high concentration dextose, blood, and caffeine.
- Check IV site every 10 minutes when high risk medication is administered.
- In case of extravasation, stop infusion, remove catheter, and elevate limb.
- Saline flushes, hyaluronidase, or phentolamine may be used in specific situations.
- Most skin lesions are benign in newborn, few may point to underlying serious diseases or metabolic conditions. .

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 maintain electrolyte balance. Other functions include tactile sensation and protection against noxious stimuli. 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 will describe 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 infants have 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 the dermis, less collagen, and a marked increase in transepidermal water loss.

III. SKIN CARE PRACTICES.

Routine assessment and avoidance of harmful exposures combined with early identification and 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) 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. Daily inspection and assessment of sites of intravenous catheters, and use of standard extravasation tools will reduce skin injury (Table 65.1).

1. All babies admitted to NICU must be assessed for risk factors for skin injury, common ones are
   - **a.** Prematurity
   - **b.** Use of monitoring equipment
   - **c.** Adhesives used to secure central and peripheral access lines, and endotracheal tubes
   - **d.** Edema
   - **e.** Immobility secondary to extracorporeal membrane oxygenation (ECMO), muscle relaxant, and high-frequency ventilation, which can cause pressure necrosis
   - **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 be higher than 41°C/105°F.

B. Bathing

1. Initial bath should be delayed until 2 to 4 hours after admission until temperature has been stabilized, this will reduce the risk of hypothermia. Provide

Table 65.1. Pediatric Peripheral Intravenous Infiltration Assessment Tool

Grade	Characteristics
0	No symptoms Flushes with ease
1	Localised swelling Flushes with difficulty Pain at site
2	Slight swelling at site (upto one-fourth of the limb above or below the site) Pain Redness
3	Moderate swelling (one-fourth to half limb above or below the site) Skin cool to touch below the site Blanching Poor pulses
4	Severe swelling (more than half the extremity) Infiltration of high-risk medications or blood (any amount) Skin break down, necrosis, blistering Capillary refill more than 4 seconds Absent pulse

Adapted from Pediatric Peripherally inserted intravenous (PIV) extravasation scale. Simona R. A pediatric peripheral intravenous infiltration assessment tool. J Infus Nurs Off Publ Infus Nurses Soc. 2012 Aug;35(4):243–8.

a controlled environment using warming lights and warm blankets. Bathing is often deferred for the first 24 hours in infants <36 weeks' gestation.

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 sterile water is sufficient for premature infants during the first few weeks of life.

C. Adhesives

1. Minimize the use of adhesives and tape.
2. Use nonadhesive products in conjunction with transparent dressings and double-backed tape to secure IV catheters.
3. Avoid the use of adhesive bonding agents that can be absorbed easily through the skin.
4. Pectin barriers should be applied to the 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 warm sterile water to remove adhesives from the skin to prevent epidermal stripping.
6. Adhesive removers contain hydrocarbon derivatives or petroleum distillates that can result in toxicity in the preterm and term infants. They are best avoided.

D. Cord care

1. Clean the umbilical cord area with mild soap and water during the first bath. Keep clean and dry. Wipe gently with water if the area becomes soiled with stool or urine.
2. Routine application of alcohol is not recommended and may delay cord separation.
3. The routine use of antibiotic ointments and creams is not recommended.
4. Assess for signs of swelling or redness at the base of the 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% depending 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 isolette temperature as necessary to maintain euthermia.
4. Strict equipment cleaning protocols must be in place during humidification (i.e., changing out isolette, humidification chamber, linen changes, etc.).

F. Circumcision care

1. Maintain dressing with petroleum gauze for the first 24 hours.
2. After dressing is removed, clean the site with water and dry gently for the first few days.

G. Disinfectants. Alcohol or chlorhexidine is the primary disinfectant 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 <2 months of age. There are no data to support use in the premature infant, but it is widely used in NICUs across the country. Povidone–iodine is no longer used due to the side effect of altering thyroid function in premature infants due to their permeable skin and increased risk of systemic absorption.

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 the 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 necrosis
4. IV extravasation
5. Prolonged contact with moisture or chemicals
6. Skin excoriation

B. Three phases of wound healing

1. **Inflammatory phase** begins with hemostasis and leads to inflammation. This phase removes necrotic tissue, debris, and bacteria from the wound.
2. **Proliferative phase** is characterized by collagen production, increase in wound strength, creation of new capillaries, and epithelialization.
3. **Remodeling phase** 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 gestational 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**
   Assess the wound for location, color, depth, size, odor, and exudates along with characterizing tissue type covering the wound base and description of the surrounding skin in order to provide consistent, objective documentation.
2. **Wound cleansing**
   - **a.** Avoid the use of antiseptics in open wounds. Sterile normal saline (NS) is the preferred cleanser to remove debris and devitalized tissue, using gentle friction or irrigation. Moistening the wound every 4 to 6 hours until the wound surface is clear facilitates the healing process.
   - **b.** A full-thickness wound is not sterile and does not require sterile saline, and so forth, to clean (tap water with baby shampoo is often preferred).
   - **c.** Clinical signs of infection (erythema, induration, and/or 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 be

considered only 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.

4. Quality improvement.
High risk medications include **Dopamine, parenteral nutrition, > 12 .5% dextrose, phenytoin, Acyclovir, and caffeine!.**

Nurse must check the catheter site every 10 minutes, when high risk medication is administered. Stop infusion, remove catheter, elevate limb in case of extravasation. For phenytoin and parenteral nutrition hyaluronidase flush was used. Phentolamine was used for vasopressor extravasation. The extravasation rate before and after the intervention (evidence based practice guideline education) was 14.04 and 2.90 per 1,000 peripheral intravenous catheters days, respectively. The extravasation from a central line rate of the control and intervention groups postintervention was 4.94 and 0 per 1,000 central venous catheter days, respectively.

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. Pharmacologic intervention should be administered as soon as possible but no later than 12 to 24 hours from the time of injury if applicable.

2. Convincing evidence that antidotes improve outcomes for extravasation injuries does not exist. Although health care providers and patients feel better "doing something" when an iatrogenic injury occurs, often the best management is "active nonintervention." The added volume of an antidote administered to an injured area theoretically may worsen the injury from pressure necrosis. In addition, by the time the extravasation is appreciated, the antidote is ordered, the drug arrives at the bedside, and a health care provider has injected it, the effects of the extravasation have worn off. For example, vasoconstriction from epinephrine lasts 60 minutes, and its effects are likely resolved by the time an antidote has been administered. Although the plastic surgery service at our institution does not advocate for the use of antidotes, the two most commonly used are briefly described in the following text.

a. Saline flush-out techniques (with or without prior hyaluronidase) is most commonly practiced. Hyaluronidase has been used in an effort to facilitate subcutaneous diffusion of an extravasate (i.e., parenteral nutrition). Administer as a solution diluted to 1 mL in NS. Refer to hospital formulary for concentration and dilution guidelines. Inject 0.2 mL subcutaneously in five separate sites around the leading edge of the infiltrate using a 25G or 27G needle. Change the needle after each skin entry. Some feel flush-out is too invasive in neonates and recommend puncture points and hydrocolloid dressings.

b. Phentolamine has been used to treat injury caused by extravasation of vasoconstrictive agents such as dopamine, epinephrine, or dobutamine. Use a 0.5 to 1 mg/mL solution of phentolamine diluted in NS. Consult hospital formulary for dosage. Inject 0.2 mL subcutaneously in five separate sites around the leading edge of the infiltrate using a 25G or 27G needle. Change the needle after each skin entry.

3. Consult with plastic surgeon 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 usually occur on the trunk but also frequently appear on the extremities and face. It occurs in up to 70% of term newborns, and occurs rarely in premature infants.

2. Unknown etiology

3. Vesicle contents when smeared and stained with Wright stain will show a predominance of eosinophils.

4. No treatment necessary

B. Incontinence-associated dermatitis

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, and 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. Air the area (keep open and allow to dry, before applying the next diaper), keeping the diaper area clean with warm water, and applying barrier products if needed. Vaseline can be used preventatively to intact skin. If signs of incontinence-associated dermatitis (IAD) are present (redness, excoriation, bleeding), start treatment with barrier products. Barrier creams benefit both in prevention and cure but do not provide a substitute for frequent diaper changes. Cleanse the skin with water or pH-balanced cleanser and soft cloths. Reassess the ointment regimen every 48 hours; if there is no improvement, consider alternate regimens. Start with application of thin creams to provide a the skin barrier, and if skin is not responding, move to thick pastes. If candidal rash is present, use an antifungal ointment or powder first and then apply the barrier cream.

Climbazole or miconazole are the preferred antifungals. Combination with zinc oxide improves results. It is critical to avoid occlusion and maceration of skin. Consider astringent and oatmeal baths to dry out and soothe the irritated skin. Dab or gently wipe off excess stool and reapply the barrier cream with each diaper change. Super-absorbent diapers reduce moisture at skin level and reduce diaper dermatitis. Neither the use of wipes nor water increases diaper dermatitis prevalence. Remove all barrier products at least once daily to assess the skin.

3. Use of powder is not recommended due to the risk of inhalation.

C. Milia

1. Multiple pearly white or pale yellow papules or cysts mainly found on the nose, chin, and forehead in term infants
2. Consist of epidermal cysts up to 1 mm in diameter that develop in connection with the pilosebaceous follicle
   Disappear 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

E. Infection

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

F. Infantile seborrhoeic dermatitis (ISD)

Typical presentation - plaques and patches covered by greasy yellow scales on scalp (cradle cap) and face, usually after 2 to 3 weeks of life. Cause can be hormonal fluctuations and malassezia infection. Management is mostly conservative, babies outgrow in months. May use petrolatum or frequent shampoo (containing tar/urea) and brush the scales. In severe cases, low potency steroids (hydrocortisone 1% or ketoconazole 2%) may be used.

VII. VASCULAR ABNORMALITIES. Vascular anomalies occur in up to 40% of newborns.

A. Infantile hemangiomas. Although popularly called "birth marks," they are usually not present at birth and develop later. They 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 required only in the rare instance when the hemangioma interferes with vital functions or if there is accidental bleeding. There is mounting evidence that NDRG1 (a hypoxia-inducible protein) and FOXOs (which are tumor suppressor proteins) play a role in the pathogenesis of infantile hemangiomas; NDRG1 positively regulates hemangioma proliferation. FOXO1 dysregulation plays an important role. Management option for problematic lesions in infancy is oral propranolol. Topical timolol, intralesional triamcinolone, and oral prednisolone are used less often. 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, and some, usually larger ones, may leave a deformity requiring intervention in childhood, generally for cosmetic purposes.

B. Fading capillary stains. They are 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. Generally, they appear more prominent soon after bath or when the baby is warm, which may worry the parents.

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 subsequent 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. They are benign pigmented lesions found in 70% to 90% of black, Hispanic, and Asian infants. The lesions may be small or large or grayish blue or bluish black in color. They are caused by the increased presence of melanocytes, and are most commonly found in the lumbosacral region.

B. Café au lait spots. They are flat, brown, round, or oval lesions with smooth edges occurring in 10% of normal infants. They are usually of little or no significance, but they may indicate neurofibromatosis if they are larger than 4 to 6 cm in size or if >6 spots are present.

C. Albinism. It is 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). It is an 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's syndrome, is a feature of this disorder.

E. Junctional nevi. They are brown or black, flat or slightly raised lesions present at birth occurring at the junction of the dermis and the epidermis. They are benign lesions requiring no treatment.

F. Compound nevi. They are larger than junctional nevi, involving the dermis and epidermis. Removal is recommended to decrease possibility of later progression to malignant melanoma.

G. Giant hairy nevi. Present at birth, they may involve 20% to 30% of the body surface, with other pigmentary abnormalities frequently present. Brown to black and leathery in appearance, also known as bathing trunk nevi, they have a large amount of hair and may include central nervous system involvement. Surgical removal is indicated for cosmetic reasons and because of the fact that they can progress to malignant melanoma.

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. If the bottom of the dimple can be seen, it is unlikely to have the tethering of the cord. If the dimple is deep enough or sinus is suspected, the child should be on surveillance for change in gait—asymmetry or tip-toeing until 2 years of age. MRI spine may be required, in case of suspicion. If confirmed, releasing the tethered cord is recommended if gait problems are progressive.

3. Some of the babies may show a small tuft of hair or a lipoma at the lower back—indicative of occult spina bifida occulta or tethered cord. If there is an obvious break in the skin on the lower back, one would suspect meningomyelocele or meningocele. Although ultrasound spine is noninvasive and has reasonable sensitivity, MRI spine would be confirmatory.

4. 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.

5. A preauricular sinus is the most common and may be unilateral or bilateral. It appears in the most anterior upper portion of the tragus of the external ear. It rarely causes problems in the newborn period but may require later excision due to infection. It may have a higher incidence of hearing difficulties and renal anomalies. Higher occurrence in families indicates possible autosomal dominant inheritance.

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. Several of the more common developmental and hereditary disorders are mentioned in the following text.

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, bullous ichthyosis, and others.

B. Vesicobullous eruptions

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.

XI. PRETERM SKIN CARE

Plastic wraps at birth reduce the incidence of hypothermia.

Semipermeable and transparent adhesive dressings improve skin quality.

Tub bathing causes less body temperature variability than sponge bathing and can be performed as infrequently as once every 4 days.

Topical emollients, particularly sunflower seed oil, appear to reduce the incidence of skin infections and even sepsis in premature neonates; the decrease in infection was observed in Bangladesh, Egypt and other LMIC. In some studies in high-income countries, Candida and Cougulase negative *Staphylococcal* infections seem to increase.

For preterm infants with catheters, povidone-iodine and chlorhexidine are comparably effective at preventing catheter colonization.

Oral thrush is common in preterm babies. Nystatin is the preferred therapy, miconazole or clotrimazole are also effective.

XII. NEONATAL SKIN EMERGENCIES

Neonatal and infantile erythroderma. Erythroderma is a generalized and persistent erythema of the skin involving at least 90% of the body surface. It may be the presenting feature of a wide range of acquired and inherited diseases, including infections, inflammatory skin diseases, ichthyosis, and congenital immunodeficiencies. Diagnostic work up must be planned if newborns have failure to thrive or serious infectious, neurologic, or metabolic complications.

Serious systemic illness with skin manifestations. Skin manifestations may be the first clue to serious infections such as herpes simplex virus, syphilis, varicella, cytomegalovirus, fungal infections, and *staphylococcal* scalded skin syndrome.

Purpura fulminans, sclerema neonatorum, neonatal lupus, and blueberry muffin rash may point to serious underlying disorders

Collodion baby. On first days of life, collodion babies may be nursed in humidified incubators, this prevents hypernatremic dehydration.

XIII. METABOLIC SKIN DISORDERS. Common ones include Acrodermatitis enteropathica (AE), biotin deficiency, pyridoxine deficiency. Cause of AE is zinc deficiency; characterized by triad of diarrhea, acral dermatitis and alopecia. Secondary

AE (preterm, parenteral nutrition) is commoner - zinc dose for secondary AE is 0.5 to 1 mg/kg/day. The inherited AE is uncommon, but requires life long zinc at 3 mg/kg/day.

Biotin deficiency presents as periorificial, perianal seborrheic-like dermatitis (scaly, erythematous dermatitis around body orifices), cheilitis, angular stomatitis, glossitis, and alopecia. The rash mimics zinc deficiency. Treat with 1 to 10 mg oral biotin per day.

Pyridoxine deficiency may happen after deficient diet or medications like INH. Seborrheic eruption on scalp, trunk, buttock, and perineal area. Dietary replacement typically requires dosages of 1 to 2 mg/day.

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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 (20% to 30%) and malformations (70% to 80%).
- Hemangiomas mostly resolve without treatment, whereas vascular malformations continue to cause significant morbidity despite treatment.

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). The International Society for the Study of Vascular Anomalies (ISSVA) has recently (2018) released an expanded classification. 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 minimal 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. Infantile hemangioma. IH is the most common tumor of infancy, affecting 4% to 5% of infants. Risk factors for IH include prematurity, multiple gestations, preeclampsia, placenta previa, invasive antenatal procedures, advanced maternal age, assisted reproductive techniques, and female sex. 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. It grows faster than the child during the first 5 months of age (proliferating phase). The majority of IH are small, harmless lesions that can be monitored under the watchful eye of a pediatrician. After 12 months, the tumor begins to regress (involuting phase). Involution ceases in most of the children by age 4 years (involuted

Table 66.1. Classification of Vascular Anomalies

Tumors	Malformations		
	Slow Flow	**Fast Flow**	**Overgrowth Syndromes**
Infantile hemangioma	Capillary malformation	Arteriovenous malformation	CLOVES
Congenital hemangioma	Lymphatic malformation		Klippel–Trenaunay
Kaposiform hemangioendothelioma	Venous malformation		Parkes Weber
Pyogenic granuloma			Sturge–Weber

CLOVES: congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis.

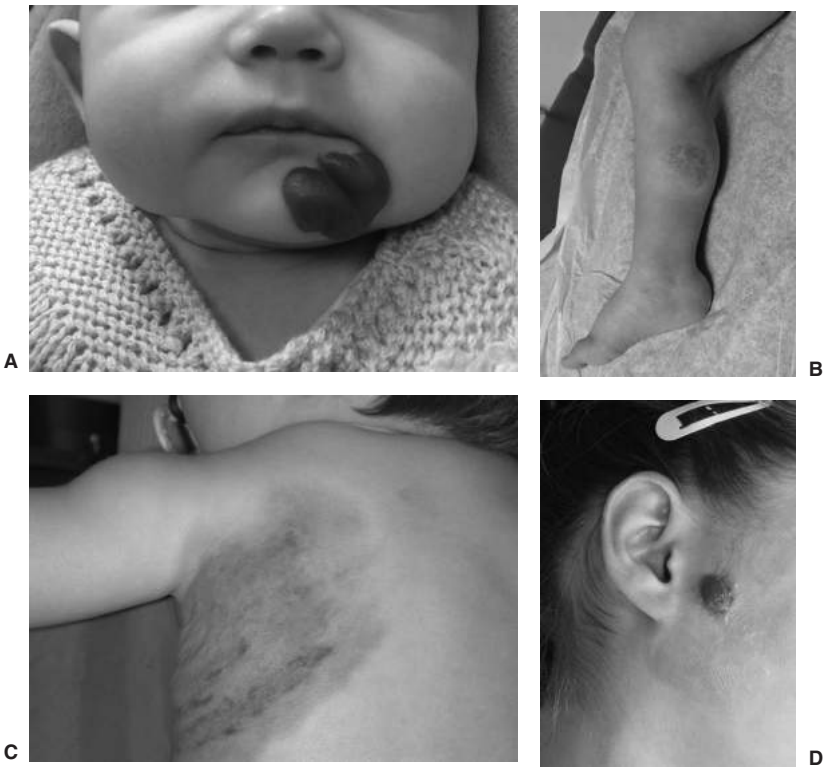

Figure 66.1. Examples of the four major types of vascular tumors. **A:** Infantile hemangioma. **B:** Congenital hemangioma. **C:** Kaposiform hemangioendothelioma. **D:** Pyogenic granuloma.

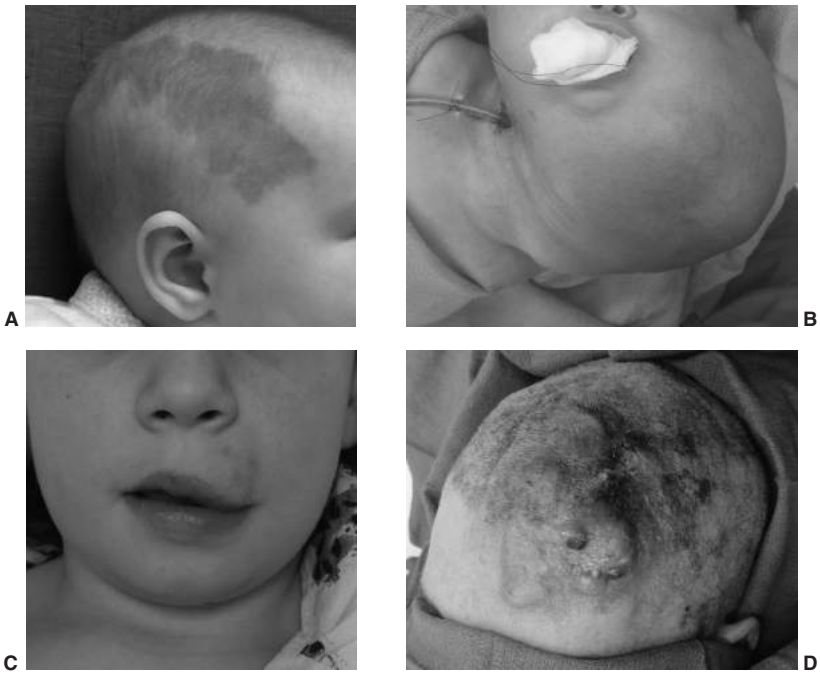

Figure 66.2. Examples of the four major types of vascular malformations. **A:** Capillary malformation. **B:** Lymphatic malformation. **C:** Venous malformation. **D:** Arteriovenous malformation.

phase). After involution, one-half of the children will have a residual deformity. Most IHs are simply observed. To protect against ulceration, IH 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 will heal with local wound care within 2 to 3 weeks.

IH may need treatment if they risk the function (periorbital, perioral), cause disfigurement, have a disturbing ulceration, or, rarely, risk the life (beard area associated with upper airway obstruction). Some are rarely associated with syndromes and may need to be investigated. 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 (~16%).

A diffuse hemangioma replacing hepatic parenchyma and parotid IH necessitates thyroid-stimulating hormone (TSH) monitoring. 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.

Treatment options. Treatment options for IH include:

1. **Topical pharmacotherapy.** Topical corticosteroid is relatively ineffective, especially if IH involves the deep dermis and subcutis. Although lightening may occur, if there is deep component, it will not be affected. Adverse effects include hypopigmentation, cutaneous atrophy, and even adrenal suppression. Topical timolol may be effective for superficial lesions but will not affect hemangiomas with a subcutaneous component.
2. **Intralesional corticosteroid.** Problematic IHs that are well localized (tip of the nose, lip) and <3 cm in diameter 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.** Systemic steroid therapy has almost completely been replaced by propranolol, which has similar efficacy and lesser side effects. Steroid use will be limited to conditions in which propranolol is contraindicated—bronchial asthma and compromised cardiovascular health.
4. **Propranolol.** Dosing is typically 1 to 3 mg/kg/day in three divided doses, given till there is response (duration 6 to 12 months) and then gradually tapered every 4 weeks. Approximately 90% of tumors will stop growing or regress. Risks (<3%) include bronchospasm, bradycardia, hypotension, hypoglycemia, seizures, and hyperkalemia. Preterm infants and those <3 months of age are more likely to have adverse events. Patients usually have cardiology consultation; electrocardiogram; echocardiogram; glucose/electrolyte measurements; and frequent blood pressure, heart rate, and respiratory examinations. Inpatient initiation of treatment is used for premature or infants <3 months of age. Potential contraindications include asthma, glucose abnormalities, heart disease, hypotension, bradycardia, and PHACES (posterior fossa abnormalities, hemangioma, arterial lesions, cardiac abnormalities eye problems, sternal notch or dimple) association.
5. **Laser therapy.** Pulsed dye laser generally is not indicated for a proliferating IH; it is typically used for ulcerated IH. The laser affects only 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.
6. **Resection.** Resection of IH typically is not recommended during the early growth phase. The tumor is highly vascular, and there is a risk for 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 improve 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.

B. 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; it remains unchanged with persistent fast flow.

RICH usually does not require resection in infancy because it regresses so quickly. Rarely, surgical removal may be necessary to control hemorrhage from ulceration or high-output congestive heart failure caused by progressive flow through the tumor. After involution, RICH may leave behind atrophic skin and subcutaneous tissue. NICH is rarely problematic in infancy and is observed until the diagnosis is clear; resection may be indicated to improve the appearance of the area.

C. Kaposiform hemangioendothelioma. KHE is an extremely rare vascular neoplasm that does not metastasize. It is present at birth in 50% of patients. 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. Vincristine is first-line therapy; the response rate is 90%. KHE does not respond as well to second-line drugs, interferon (50%), or corticosteroid (10%). Recently, patients have been treated with sirolimus as first-line therapy with good efficacy. 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 normalizes.

D. Pyogenic granuloma. PG is a solitary, red papule that grows rapidly on a stalk. It is small, with an average diameter of 6.5 mm; the mean age of onset is 6.7 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 the cheek (29%), oral cavity (14%), scalp (11%), forehead (10%), eyelid (9%), or lips (9%).

PGs require intervention to control likely ulceration and bleeding. Numerous methods have been described: curettage, shave excision, laser therapy, and excision. Because the lesion extends into the reticular dermis, it may be out of the reach of the pulsed dye laser, cautery, or shave excision. Consequently, these modalities have a recurrence rate of approximately 50%. Full-thickness excision is the definitive treatment.

III. VASCULAR MALFORMATIONS

A. Capillary malformation. Capillary malformations (CM) include the 1. nevus simplex (stork bite, angel kiss) and 2. cutaneous and/or mucosal CM (portwine stain). The cutaneous CM further include (a) nonsyndromic CM, (b) CM with CNS and/or ocular anomalies (Sturge Weber syndrome) (c) CM with bone and or soft tissue overgrowth, (d) diffuse CM with overgrowth (there are other CMs, details are listed in ISSVA classification for vascular anomalies, 2018). The lesion

is obvious at birth, and the pink-purple skin discoloration can cause psychosocial distress. Over time, cutaneous CM darkens and the soft tissue and bone may enlarge underneath the stain. Nevus simplex, 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; no treatment is necessary because it lightens over the first 2 years of life.

The mainstay of treatment for portwine stain is 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. 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 ≥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 are not purely macrocystic or microcystic; they 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. Sclerosant most commonly used is bleomycin. 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 are managed by resection which is typically subtotal. Sirolimus recently has shown efficacy for very problematic microcystic lymphatic malformations.

C. Venous malformation. Lesions are blue, soft, and compressible. Hard calcified phleboliths may be palpable. Lesions 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 phlebectatic 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 lesions causing a visible 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. Sclerosant most commonly used is sodium tetradecyl sulfate. Resection of a venous malformation should be considered for small lesions that can be completely removed or for persistent symptoms after completion of sclerotherapy.

D. Arteriovenous malformation. Arteriovenous malformation has an absent capillary bed which causes shunting of blood directly from the arterial to the 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. Handheld Doppler examination shows fast flow. MRI is usually 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. It is generally not curative, and most arteriovenous malformations will reexpand following treatment.

Resection of an arteriovenous malformation, when feasible, has a lower recurrence rate when compared to 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 24 to 72 hours after embolization, before recanalization restores blood flow to the lesion.

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67 Retinopathy of Prematurity

Kristen T. Leeman and Deborah K. VanderVeen

KEY POINTS

- Screening for retinopathy of prematurity (ROP) and timely treatment can prevent blindness.
- First screening by an ophthalmologist must be initiated before 30 days of life.
- The preferred treatment for ROP is laser photoablation.
- Incidence of ROP differs across populations; ROP screening is recommended in premature infants weighing ≤2,000 g and/or ≤34 weeks' gestation at birth (Indian population data).
- The risk for ROP increases with decreasing gestational age.
- Other risk factors include prolonged or labile oxygen exposure and increased illness severity.
- Preterm babies are at a higher risk of refractive errors (myopia) and must have periodic examination, starting at 6 to 9 months and continuing through till 7 years of age.

GENERAL PRINCIPLES

I. DEFINITION.

Retinopathy of prematurity (ROP) is a potentially blinding disease; timely screening of preterm babies and treatment can prevent severe visual handicap. Inability to provide and guide families of a preterm baby for eye examination within 30 days of life and subsequently as indicated has become a reason for severe visual handicaps and several medicolegal conflicts.

ROP is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age. Approximately 65% of infants with a birth weight <1,250 g and 80% of those with a birth weight <1,000 g will develop some degree of 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. The retinal vessels, which arise from 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. 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, however, the disease process is mild and regresses spontaneously.

C. Risk factors. ROP has been consistently associated with low gestational age, low birth weight, and prolonged oxygen exposure. Small for gestation age (SGA) was associated with ROP, severe ROP, and treated ROP. In the subgroup of <29 weeks, the associated was stronger. SGA must also be included in the risk factors for screening for ROP. Slow postnatal weight gain is highly predictive of ROP. The G-ROP (postnatal growth and ROP) model seems to be highly predictive of ROP and selection of babies for screening and follow up. 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. Breast milk is protective. Early use of erythropoiesis stimulating agents (before 8 days age) is associated with ROP. Omega-3 fatty acids and prevention of hyperglycemia may have protective role.

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***. In the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, for infants <1,250 g, the median postnatal ages at the onset of stage 1 ROP, prethreshold disease, and threshold disease were 34, 36, and 37 weeks, respectively.

B. The current American Academy of Pediatrics (AAP) recommendation is to screen all infants with a birth weight <1,500 g or gestational age <30 weeks. Infants who are born after 30 weeks' gestational age may be considered for screening if they had significant cardiorespiratory instability. In India, China, and other Asian countries, however, "heavier" and "more mature" infants are at risk of ROP, even severe disease. Screening criteria, therefore, are different compared to in Western nations. In India, for example, the national guidelines suggest that all infants born ≤34 weeks of gestational age should undergo screening. In those infants whose gestational age is not known or unsure, a birth weight of ≤2,000 g is used as a cutoff.

The first screening is performed before discharge from the neonatal intensive care unit (NICU), but surely before 30 days of life. For infants born weighing <1,200 g and <30 weeks gestational age, the first screening is recommended between 2 and 3 weeks of life, for aggressive posterior ROP (APROP). The screening must be performed in the NICU for admitted infants. Discharged infants may be screened in the NICU or the ophthalmologist's office with adequate monitoring and resuscitation facilities.

C. Dilatation for ROP screening. There are multiple protocols for dilatation for ROP screening; the lowest dose (least side effects) that seems to be effective is single application of one drop of phenyehrine 1% and cyclopentolate (0.2%). The UK recommendation for mydriasis for ROP is one drop each of phenylephrine 2.5% and cylopentolate 0.5% at 5 minutes interval for 2 to 3 applications, 1 hour prior to examination (UK recommendation). To reduce pain, nonpharmacologic (containment and nonnutritive sucking) measures of pain relief and local anesthetics are recommended. If indentation is not required, nonpharmacologic measures with oral sucrose work well.

D. Diagnosis. ROP is diagnosed by retinal examination with indirect ophthalmoscopy; this should be performed by an ophthalmologist with expertise in ROP screening. Wide-field digital imaging and tele-screening is also recommended. The latter must be performed by a skilled ophthalmologist or by nonphysicians who must be accredited for acquiring images and must be aligned to an ophthalmologist skilled in interpreting ROP from retinal images. The decision after each screening session will be one of the following: (i) no further screening required if the retinal vessels are mature or the ROP has regressed, (ii) requires follow-up, and (iii) requires urgent treatment. The frequency of follow-up would depend on the stage of ROP, zone of disease, or level of immaturity. In general, zone 1 disease will require closer follow-up than zone 2 or 3 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 (see 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.

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) _____

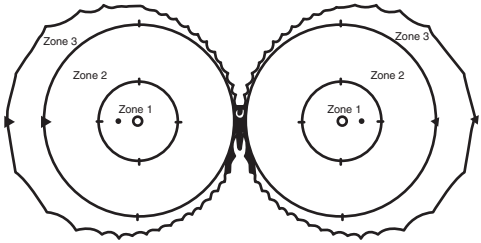
Ophthalmologist _____ MD
(PRINT NAME)

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. (*Source*: Boston Children's Hospital, Ophthalmology Department.)

c. Stage 3. The ridge has extraretinal fibrovascular proliferation. 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 the disease and is reported as clock hours in the appropriate zone.

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 (APROP)** is a rapidly progressing, severe form of ROP characterized by its posterior location (usually zone 1, but can be zone 2 posterior) and an ill-defined nature of retinopathy without a classical ridge. It is characterized by ischemic loops, capillary nonperfusion, and flat intraretinal network neovascularization. Untreated, it will rapidly progress to retinal detachment.

2. **Hybrid ROP** is the presence of ridge tissue, characteristic of staged ROP, along with the flat neovascular syncytium which is characteristic of APROP.

3. **Type 1 ROP** is now used to denote a disease that must be treated and includes stages 1, 2, or 3 in zone 1 with plus disease, stage 3 in zone 1 without plus disease, and stage 2 or 3 in zone 2 with plus disease. Type 2 ROP is used to denote zone 1, stage 1 or 2 without plus disease and zone 2, stage 3 without plus disease. The older term threshold ROP is not used anymore.

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 for treatment of eyes with type 1 ROP.

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.

VI. PROGNOSIS

A. Short-term prognosis. Most infants with stage 1 or 2 ROP will experience spontaneous regression. About 77% of eyes with type 2 ROP regress without treatment, but only 32% of eyes with type 1 ROP regress spontaneously. In the ETROP trial, treatment for type 1 ROP (compared to conventional timing at threshold) 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 that more work to prevent the development of ROP is

needed. Risk factors that determine outcomes following ROP requiring treatment include posterior location (zone 1 or posterior zone 2), APROP, presence of ROP on the first properly timed examination, increasing severity of stage, circumferential involvement, presence of vitreous hemorrhage, presence of plus disease, and rapid progression of the disease.

B. Long-term prognosis

- Preterm infants with spontaneously regressed ROP can also have vision impairment and refractive errors. Infants with significant ROP have an increased risk of myopia, anisometropia, astigmatism, strabismus, amblyopia, late retinal detachment, and glaucoma. Subclinical retinal findings detected by newer imaging tools such as optical coherence tomography and optical coherence tomography angiography (OCTA) may also influence long-term outcomes. **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. Stage 5 has a very poor prognosis overall even if surgery is performed.
- Prematurity itself is a risk factor, independent of ROP, for cortical vision impairment and vision processing disorders. 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. The recommendation for long-term follow-up starts at 6 months of the corrected age or earlier and must extend annually for 7 years of age.

VII. PREVENTION.

Lower or more tightly regulated oxygen saturation limits early in the neonatal course may reduce the severity of ROP. The recommended target oxygen SpO_2 for preterm babies is 90% to 95%. Some of the other strategies include antenatal steroids, attention to postnatal nutrition and weight gain, judicious use of blood products, and use of oxygen blenders to titrate the delivery. Few observational studies have shown the benefits of exclusive human breast milk feeding in reducing the incidence of ROP in very low-birth-weight babies. Breast milk is known to have antioxidant factors that can reduce the oxidative stress in preterm neonates and hence play a role in decreasing the incidence of ROP. Currently, no proven methods are available to completely stop ROP.

A recent review article from India showed a shocking number of advanced-stage ROP and 89% of these infants had never been screened. Some of the underlying causes include lack of trained personnel for screening, lack of implementation of screening protocols, need for improvement in oxygen use, infections, and transfusion practices. High incidence of ROP especially from small peripheral hospitals underlines the potential for primary prevention. In India, there are more than 800 special newborn care units (SNCUs) and with improving survival of preterm infants' blindness from ROP is increasing.

The knowledge and skills of healthcare providers about optimal management of preterm neonates need to be enhanced for primary prevention of ROP (not just improve screening of ROP). Given the large geographical area and many healthcare

providers, a hybrid mode of online knowledge dissemination and in-person skill training can lead to rapid coverage. The know-do gap can be reduced by infrastructure enhancement (e.g., provision of compressed air, air-oxygen blenders, and pulse oximeters) in newborn care units, point-of-care quality improvement projects, and supportive supervision.

Low coverage of screening by indirect ophthalmoscopy can be addressed by locally relevant approaches like hub-and-spoke screening using wide-field retinal cameras and training of newborn care providers (nurses and doctors of NICU) in conducting the screening using indirect ophthalmoscope or low-cost retinal cameras.

Innovative methods to circumvent the lack of trained personnel is the use of wide-field camera. The images of retina can be captured by a trained nurse, doctor, or an ophthalmic assistant and shared with the retina expert. Such an innovative method was started in the state of Karnataka, India. In a quality initiative, an increase in ROP screening rate from 10.7% to 87.3% was noted by organizing a structured follow-up date, place, educating parents, and training nurses.

VIII. TREATMENT

A. Laser therapy. Laser photoablation therapy for ROP is the preferred treatment. Laser treatment is delivered through an indirect ophthalmoscope and is applied to the avascular retina anterior to the ridge of extraretinal fibrovascular proliferation for 360°. The spots must be contiguous or near-contiguous for best results. Diode laser has been popular for treatment, but has been replaced largely by 532-nm Nd:YAG (green) laser which causes less pain and collateral damage due to its lower wavelength. *Treatment must be performed within 48 hours of diagnosis.* Laser photoablation may be performed with orally administered sweet agents (24% sucrose or 25% dextrose) with topical anesthesia and multisensory stimulation. General anesthesia is also used in certain cases. Sick infants can also be treated through the incubator wall if required. The development of cataracts, glaucoma, or anterior segment ischemia following laser surgery or cryotherapy has been reported.

B. Anti-VEGF therapy. Pharmacotherapy with intravitreal injection of VEGF inhibitor is a modality of treatment often used in cases of posterior zone 1 or APROP, as salvage treatment after laser therapy or in conjunction with vitreoretinal surgery. A Cochrane review shows decreased refractory errors (high myopia). However, concerns remain about systemic absorption which may result in reduced VEGF and vascularization of other organ systems. The ocular safety profile is reasonably good, although endophthalmitis is a rare but potentially devastating complication. Recurrences after injections are commoner in type 2 ROP. Late recurrences, even months after injection, make the follow-up challenging. Some benefits of intravitreal injection include potentially less stress for the infant (because the procedure time is short and requires only topical anesthesia), less skill (laser treatment is a highly skilled procedure), less destruction of the retina (because laser is an ablative procedure), and possibly lower risk of myopia (disease-adjusted risk is currently unknown).

C. 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 is useful for more peripheral detachments with selective indications. Repeat operations for redetachment 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 return only to low visual acuity, children find any amount of vision useful. Untreated stage 5 ROP in most cases leads to no effective vision (not even light perception).

IX. RECENT ADVANCES. Prophylactic oral propranolol may prevent progression to severe ROP requiring laser or anti-VEGF. Prophylactic oral propranolol appeared to be effective in preventing severe ROP in premature infants ≤32 weeks gestational age. The relative risk (RR) of severe ROP in the primary (before established) and secondary prophylaxis (threshold stages) groups were 0.65, NNT = 7) and 0.48 (NNT = 6) in RCTs, respectively. RR of severe ROP in one observational study was 0.21 with a NNT of 3 (confidence intervals have been omitted).

Innovations in imaging including ultra-wide-field retinal photography and handheld spectral domain optical coherence tomography (SD-OCT) with and without angiography have provided a new tool for evaluating foveal growth, vascularization, and disease, and correlating with structural and functional outcomes. Innovations in portable, wide-field, digital cameras have made tele-screening of ROP affordable and effective especially in countries like India. Computer software equipped with artificial intelligence tools are being developed to automatically detect, grade, and classify the disease which are helping in triaging screening programs.

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68 Hearing Loss in Neonatal Intensive Care Unit Graduates

Jane E. Stewart, Jennifer Bentley, and Aimee Knorr

KEY POINTS

- Hearing loss incidence is 1 to 3 per 1,000 live births in healthy neonates and 20 to 40 per 1,000 births in high-risk babies, a 10-fold increase.
- 1–3–6: screen before 1 month, diagnose before 3 months, start rehabilitation/treatment before 6 months; centers that have an established early hearing impairment detection and intervention (EHDI) must target the 1–2–3 month standard.
- Even mild and unilateral hearing losses can cause significant communication problems.
- Children with risk factors for hearing impairment should be evaluated and followed up by an audiologist.
- Some children have a genetic predisposition to hearing loss, following exposure to aminoglycoside antibiotics.
- The earlier the habilitation starts, the better the child's chance of achieving age-appropriate language and communication skills.

I. DEFINITION. Neonatal intensive care unit (NICU) graduates have an increased risk of developing hearing loss. When undetected, hearing loss can delay language, communication, and cognitive development. Hearing loss falls into four major categories:

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 a rare type of hearing loss 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. The etiology of this disorder is not well understood; however, babies who have a history of extreme prematurity, hypoxia, severe hyperbilirubinemia, and immune disorders are at an 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, inner ear, and neurosensory pathways; the hearing loss is due to abnormal auditory processing at level of central nervous system (cortex).

II. INCIDENCE.

The overall incidence of severe congenital hearing loss is 1 to 3 per 1,000 live births. However, 20 to 40 per 1,000 infants surviving neonatal intensive care have some degree of sensorineural hearing loss.

III. ETIOLOGY

A. Genetic. Approximately 50% of cases of congenital hearing loss is thought to be of genetic origin (30% syndromic and 70% nonsyndromic). Of the nonsyndromic, 75% to 85% of cases are autosomal recessive, 15% to 24% autosomal dominant, and 1% to 2% X-linked. The most common genetic cause of nonsyndromic autosomal recessive hearing loss is a mutation in the **connexin 26 (Cx26) gene**, located on chromosome 13q11–12 (at least 90 deletions have been associated with hearing loss). The carrier rate for a Cx26 mutation is 3%, and it accounts for approximately 20% to 30% of all cases of congenital hearing loss. Deletion of the mitochondrial gene 12SrRNA, A1555G, is associated with a predisposition to hearing loss after exposure to aminoglycoside antibiotics. Approximately 30% of infants with hearing loss have other associated medical problems that are part of a syndrome. More than 400 syndromes are known to include hearing loss (e.g., Robin sequence, Usher's and Waardenburg's syndromes, neurofibromatosis type 2, branchio-oto-renal syndrome, trisomy 21). To see a full review of the genetics of hearing, please refer the hereditaryhearingloss.org website.

B. Nongenetic. In approximately 25% of cases of childhood hearing loss, a nongenetic cause is identified. Hearing loss is 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 newborn intensive care or a special care nursery are often exposed to these factors.

Cytomegalovirus (CMV) congenital infection is the most common cause of nonhereditary sensorineural hearing loss. Approximately 1% of all infants are born with CMV infection in the USA. 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 hearing loss. Although most (90%) infants born with CMV infection have no clinical signs of infection, hearing loss still develops in some (10% to15%) of these infants, and it is often progressive. In a recent prospective study of 150 confirmed cases of congenital CMV, 12% of infants had hearing loss and 6% required amplification. Although treatment protocols vary from 6 weeks to 12 months, data indicate that treatment with the antiviral agent valganciclovir given orally for 6 months after birth is associated with an improved long-term hearing function as well as improved neurodevelopmental outcomes at 2 years of life (when compared to shorter courses of antiviral therapy). Prompt diagnosis of congenital CMV is essential to determine whether the infant is a possible candidate for treatment; ideally, treatment should

be initiated within 1 month after birth. Screening-all babies who fail their newborn hearing screen for CMV (urine and saliva samples) has been implemented by some hospitals to facilitate making this diagnosis. Educating women on strategies to avoid CMV exposure during pregnancy is equally important.

C. Risk factors. The Joint Committee on Infant Hearing (JCIH) listed the following risk factors associated with permanent congenital, progressive, or delayed-onset hearing loss in their 2019 Position Statement:

	Risk factors for early childhood hearing loss: Guidelines for infants who pass the newborn hearing screen		
	Risk factors classification	**Recommended diagnostic follow-Up**	**Monitoring frequency**
	Perinatal		
1	Family history* of early, progressive, or delayed-onset permanent childhood hearing loss	By 9 months	Based on etiology of family hearing loss and caregiver concern
2	Neonatal inensive care of more than 5 days	By 9 months	As per concerns of ongoing surveillance of hearing skills and speech milestones
3	Hyperbilirubinemia with exchange transfusion regardless of length of stay	By 9 months	
4	Aminoglycoside administration for more than 5 days†	By 9 months	
5	Asphyxia or hypoxic ischemic encephalopathy	By 9 months	
6	Extracorporeal membrane oxygenation (ECMO)*	No later than 3 months after occurrence	Every 12 months to school age or at shorter intervals based on concerns of parent or provider
7	*In utero* infetions, such as herpes, rubella, syphilis, and toxoplasmosis	By 9 months	As per concerns of ongoing surveillance
	In utero infetion with cytomegalovirus (CMV)*	No later than 3 months after occurrence	Every 12 months to age 3 or at shorter intervals based on parent/provider concerns
	Mother + Zika and infant with *no* laboratory evidence and no clinical findings	Standard	As par AAP (2017) schedule
	Mother + Zika and infant with laboratory evidence of Zika + clinical findings	AABR by 1 month	AABR by 4–6 months or VRA by 9 months

(continued)

	Mother + Zika and infant with laboratory evidence of Zika × clinical findings	AABR by 1 month	AABR by 4–6 months Monitor as per AAP (2017) periodicity shedule
8	Certain birth conditions or findings: ■ Craniofacial malformations including microtia/atresia, ear dysplasia, orofacial clefting, white forelock, and microphthalmia ■ Congenital microcephaly, congenital or acquired hydrocephalus ■ Temporal bone abnormalities	By 9 months	As per concerns of ongoing surveillance of hearing skills and speech milestones
9	Over 400 syndromes have been identified with atypical hearing thresholds.‡ For more information, visit the hereditary hearing loss website (Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage. https://hereditaryhearingloss.org)	By 9 months	Every 12 months to school age or at shorter intervals based on concerns of parent or provider
	Perinatal or postnatal		
10	Culture-positive infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis or encephalitis	No later than 3 months after accurrence	Every 12 months to school age or at shorter intervals based on concerns of parent or provider
11	Events associated with hearing loss: ■ Significant head trauma, especially basal skull/temporal bone fractures ■ Chemotherapy	No later than 3 months after accurrence	According to findings and/or continued concerns
12	Caregiver concern§ regarding hearing, speech, language, developmental delay, and/or developmental regression	Immediate referral	According to findings and/or continued concerns

AABR, automated audiotory brainstem response. AAP, American academy of pediatrics; ABR, audiotory brainstem response; VRA, visual reinforcement audiometry.
*Infants at increased risk of delayed onset or progressive hearing loss.
†Infants with toxic levels or with a known genetic susceptibility remain at risk.
‡Syndromes (hereditaryhearingloss.org website).
§Parental/caregiver concern should always prompt further evaluation.

D. Universal newborn hearing screen. Universal newborn hearing screening is recommended to detect hearing loss 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 USA prior to 1 month of age has increased from 46.5% in 1999 to 97.2% in 2013.

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 cutoff for an abnormal screen, this necessitates further testing.

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' postnatal 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 hearing loss including auditory dyssynchrony.

B. EOAEs. This records 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 sensorineural hearing loss including auditory dyssynchrony. EOAE is often combined with automated ABR in a two-step screening system. For high-risk babies (NICU babies), ABR is mandatory and the two-step approach should not be used to select babies.

V. FOLLOW-UP TESTING.

Follow-up testing of infants who fail their newborn screen is critical. Despite the high success in screening of newborns (97%), currently, 32% of infants who fail their initial screen are lost to follow-up. Family issues associated with poor follow-up include age of the 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 hearing screening and follow-up services.

Infants who fail the screen (OAE), must have a repeat OAE test within 2 weeks, those who fail again should have a diagnostic ABR performed by a pediatric audiology specialist within 3 months age. The diagnostic testing format should include measures to rule out or identify auditory dyssynchrony, or 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. Behavior assessment of hearing is the gold standard for hearing assessment. Visual reinforcement audiometry (VRA) is used for infants 6 to 24 months of age and conditioned play audiometry for children older than 24 months.

Table 68.1. Degree and Severity of Hearing Loss

Degree of Hearing Loss	Hearing Loss Range (dB HL)
Normal	–10 to 15
Slight	16–25
Mild	26–40
Moderate	41–55
Moderately severe	56–70
Severe	71–90
Profound	>91

Source: Clark JG. Uses and abuses of hearing loss classification. *ASHA.* 1981;23:493–500.

A. Definitions of the degree and severity of hearing loss are listed in Table 68.1.

B. Infants who have risk factors for progressive or delayed-onset sensorineural and/or conductive hearing loss require continued surveillance, even if the initial newborn screening results are normal.

C. Infants with mild or unilateral hearing loss should also be monitored closely with repeat audiology evaluations and provided with early intervention services because they are at an 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 normal hearing and language development.

VI. MEDICAL EVALUATION/ETIOLOGIC EVALUATION

A. An infant diagnosed with true hearing loss should have the following additional evaluations: genetic, CMV, ophthalmology, ECG, and metabolic screen including urine analysis and imaging. Complete evaluation should be performed by an otolaryngologist or otologist who has experience with infants. Genetic evaluation and counseling should be provided for all infants with true hearing loss. Infants with bilateral hearing loss have a much higher incidence of genetic causes.

B. Examination should be performed by a pediatric ophthalmologist to detect eye abnormalities that may be associated with hearing loss.

C. Developmental pediatrics, neurology, cardiology, and nephrology referral should be made as indicated.

D. Imaging with computed tomography (CT) or magnetic resonance imaging (MRI) should be done if clinically indicated.

VII. HABILITATION/TREATMENT. Infants with true hearing loss, regardless of degree of loss or laterality, should be referred for early intervention services to enhance the child's acquisition of developmentally appropriate language skills. This should

include therapy from speech and language pathologists, audiologists, and special educators. For infants who are appropriate candidates for personal amplification systems (hearing aid, bone-anchored hearing aid [BAHA]), if parents consent, the child should be fitted as soon as possible. Children with severe to profound bilateral hearing loss may be candidates for cochlear implants by the end of the first year of age. Another option currently in clinical trials for children with profound hearing loss who have exhausted all other alternatives is the auditory brainstem implant.

Preterm infants (<30 weeks) may have a change in their hearing threshold. In a prospective study, 50% of babies detected to have hearing impairment were normal at 6-month evaluation.

Families who do not choose personal amplification systems may use American Sign Language (ASL) or Signing Exact English (SEE) for their child's primary language. Because it may take up to 1 year for an infant to be eligible for implants, many families opt to incorporate both oral and manual languages into their child's repertoire. 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 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.

Early intervention resources and information for parents to make decisions regarding communication choices should be provided as promptly as possible.

VIII. PROGNOSIS. The prognosis depends largely on the extent of hearing loss, the time of diagnosis and treatment, 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. The earlier the 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 and the accompanying intensive multidisciplinary team therapy are also very promising. Initiation of early intervention services before 3 months of age has been associated with improved cognitive developmental outcomes at 3 years. Family involvement is also critical to success. Early identification, together with early intervention and an actively involved family, results in higher-level language outcomes at age 5 years.

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69 Common Neonatal Procedures

Steven A. Ringer

KEY POINTS

- The benefit of a procedure must be balanced against the impact on the patient stability and the risk of complications.
- Procedures are often painful or uncomfortable, and care should be taken to ensure adequate environmental and medical support to minimize these effects.
- All procedures, no matter how invasive, should be done with strict attention to safety and infection control, with clear and complete documentation.

I. INTRODUCTION.

Invasive procedures are a necessary but potentially risk-laden part of newborn intensive care. To provide maximum benefit, these techniques must be performed in a manner that both accomplishes the task at hand and maintains the patient's general well-being.

II. GENERAL PRINCIPLES

A. Consideration of noninvasive alternatives and selection of most suitable devices.

For each procedure, all alternatives should be considered and risk–benefit ratios evaluated. Considerable deliberation is required before a decision for an invasive procedure is taken. Many procedures involve the placement of indwelling devices made of silicone, polyurethane, polyethylene, or polyvinyl chloride (PVC). Each material has its own advantages and disadvantages. Polyurethane has good pressure tolerance and therefore does not rupture easily. Silicone and PVC devices cause less risk of vessel perforation. PVC devices may require addition of plasticizers (di(2-ethylhexyl)-phthalate [DEHP]), which may be toxic with long-term exposure. DEHP-free devices should be used on neonates.

B. Infection control.

For any procedure, care should be taken to ensure antisepsis. The aseptic nontouch technique (ANTT) relies on the protection of "key sites" and "key parts," which if contaminated result in a high risk of infection. The optimal agent to use for an infant is not clear; chlorhexidine and alcohol are common choices. Chemical burns have been described with alcohol as well as chlorhexidine. Aqueous-based (alcohol-free) chlorhexidine solutions have been used with good efficacy. The best concentration of chlorhexidine is yet to be established, but as low as 0.1% has been tried in extreme preterm neonates. Care should be taken to use the smallest possible quantity on minimal surface area followed by

removal of antiseptics that have seeped below the infant's body. Iodine solution may be avoided in extremely preterm infants as thyroid disturbances have been described. Octenidine is being used in some units. Concentrations up to 0.05% have been considered safe.

C. Monitoring and homeostasis. Monitoring for physiologic stability of the patient is a priority during and after any procedure. Ideally, the operator should delegate another care provider to be responsible for the ongoing monitoring and management of the patient during a procedure. Assessment of cardiorespiratory and thermoregulatory stability should be ongoing throughout the procedure. This monitoring can most effectively be standardized through the use of a procedure checklist so that the monitoring caregiver can ensure that each step is appropriately completed and documented by sign off on the part of all providers at the conclusion of the procedure.

D. Pain control. It is well established that the neonate is sensitive to pain and also that pain assessment and control are often under-recognized in the intensive care unit. Use of appropriate nonpharmacologic and pharmacologic methods is recommended based on the assessed pain (standard pain scales) and the anticipated pain associated with the type of procedure. Focus should be on striking a balance between good pain relief and avoidance of adverse effects from the drugs used. Minimizing the number of painful procedures, developmental care, skin-to-skin contact, breastfeeding/non-nutritive sucking, facilitated tucking, swaddling, positioning, and massaging are used in combinations to reduce the use of pharmacologic agents. Oral sucrose (e.g., 24% solution, 0.2 to 0.4 mL/kg) is effective in reducing pain of minor procedures. Either morphine or fentanyl is commonly administered before beginning moderately painful procedures and postoperatively (whenever there is tissue injury).

E. Informing the family. Other than during true emergencies, informed consent from the parents is essential. Indications, utility, expected results, and possible complications (including therapy for each complication) of each procedure should be discussed. In addition, alternative procedures, when available, are also discussed.

F. Precautions. The operator should use universal precautions, including wearing gloves, impermeable gowns, barriers, and eye protection, to prevent exposure to blood and bodily fluids that may be contaminated with infectious agents.

G. Time-out and checklist. Before beginning any procedure, the entire team should take a "time-out" or "safety pause" to ascertain that the correct procedure is being performed on the correct patient and, if appropriate, on the correct side (e.g., thoracostomy tube). 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 before performing the procedure on patients. This training should include a discussion of indications, possible complications and their treatment, alternatives, 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 skills. Experienced operators should be available at all times to

provide further guidance and needed assistance. "Credentialing and privileging" staff for procedures may be an objective method of ensuring safety.

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. Notes are usually written after all procedures, including unsuccessful attempts. We document the date and time, indications, performance of the time-out, monitoring, premedication for pain control, the techniques used, difficulties encountered, complications (if any), and results of any laboratory tests performed.

III. BLOOD DRAWING.

The preparations for drawing blood depend on the studies that are required.

A. **Capillary blood** is drawn when a small volume of blood suffices for analysis for point-of-care testing (POCT). It is not preferred when there is an injury, infection, or anomaly at the site.

1. **Applicable blood studies** include hematocrit, blood glucose (using glucometers or other POCT methods), bilirubin levels, electrolyte determinations, lactate, and blood gas studies.

2. **Techniques**

   a. The extremity to be used may be warmed to increase peripheral blood flow.

   b. **The skin should be cleaned carefully** with an antiseptic (alcohol) and allowed to dry before puncture. Povidone–iodine may interfere with some analytes. Alcohol is avoided, if glucose estimation is planned.

   c. **Capillary punctures of the foot should be performed on the lateral side of the sole of the heel**, avoiding previous sites if possible.

   d. **Spring-loaded lancets minimize pain** while ensuring a puncture adequate for obtaining blood. The blood should flow freely, with minimal or no squeezing. This will ensure the most accurate determination of laboratory values.

B. **Venous blood** for blood chemistry studies, blood cultures, and other laboratory studies can be obtained from a peripheral vein of adequate caliber to enable access and withdrawal of blood. In neonates anticipated to need peripheral intravenous access, it would be prudent to preserve prominent veins for these instead of "using" them for sampling alone.

C. **Arterial blood** may be needed for blood gases, for some metabolic studies, and when the volume of blood needed would be difficult to obtain from a peripheral vein and no indwelling catheter is available. Arterial cannulation carries the risk of vasospasm, thrombosis, or thromboembolism. **Arterial punctures** usually involve the radial, dorsalis pedis, posterior tibial, or ulnar artery. Radial artery punctures are most easily done using a 25G to 23G butterfly needle, and transillumination often aids in locating the vessel. Although the utility has been contested, it would be prudent to perform an Allen test to ensure collateral perfusion. The radial artery is identified and entered with the bevel of the needle facing up and at a 15° angle against the direction of flow. If blood is not obtained

immediately during insertion, the needle may be advanced until the artery is transfixed and then slowly withdrawn until blood flow occurs.

D. Catheter blood samples

1. **Umbilical artery or radial artery catheters** are often used for repetitive blood samples, especially for blood gas studies.
2. **Techniques**
   - **a.** A needleless system for blood sampling from arterial catheters should be used. Specific techniques for use vary with the product, and the manufacturer's guidelines should be followed.
   - **b.** For blood gas studies, a preheparinized syringe, or a standard 1-mL syringe rinsed with least possible volume of heparin, is used to withdraw the sample. The rate of sample withdrawal should be limited to 1.5 mL/minute to avoid altering downstream arterial perfusion.
   - **c.** 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.

IV. INTRAVENOUS THERAPY.

The insertion and management of intravenous catheters require great care. As in older infants, hand veins are used most often, but veins in the foot, ankle, and scalp can be used. Transillumination of an extremity can help identify a vein, and newer devices that enhance the detection of veins may be even more useful.

V. BLADDER CATHETERIZATION

A. A sterile technique is crucial. Careful cleaning with an antiseptic such as alcohol or an iodine solution over the prepubic region is essential.

B. Technique. The urethral meatus is identified, and a small gauge (3 to 5 F) silicone catheter is gently advanced into the bladder, with care taken to keep the distal end of the catheter sterile until the urine sample is collected. Resistance to insertion should be minimal. If obstruction is sensed, it is usually best to abort the procedure and consult urology as indicated.

VI. LUMBAR PUNCTURE

A. Technique

1. The infant should be placed in the lateral decubitus position with the hips flexed or in the sitting (upright) position. Interspinous distance has been found to be maximum in the sitting position with the legs flexed. 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. Traditionally, chlorhexidine used to be avoided for antisepsis prior to lumbar puncture (LP), but 0.5% solution with alcohol has been deemed safe.

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, as 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. It 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 1.0 mL.

B. 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.

1. **Tube 1.** Glucose and protein determinations should be obtained.

2. **Tube 2.** Cell count and differential should be determined from the unspun fluid.

3. **Tube 3.** Culture and sensitivity studies should be obtained.

4. **Tube 4.** The cells in this tube also should be counted if the fluid is bloody. The fluid can be sent for other tests (such as polymerase chain reaction [PCR] amplification for herpes simplex virus [HSV], multiplex PCR, metabolic studies).

C. Information obtainable

1. CSF culture is the gold standard for the diagnosis of meningitis. However, most neonates receive antibiotics prior to LP, greatly decreasing the yield from culture. Hence, clinicians most often need to rely on cell counts and biochemistry reports to rule in or rule out meningitis.

2. **White blood cell (WBC) count.** The normal number of WBCs per cubic millimeter in newborns is a matter of great controversy, and different practitioners accept different cutoffs for cells as normal, and accept as normal if some polymorphonuclear cells are noted. Studies have reported that glucose levels and cell counts (contrary to common belief) do not decrease with increasing gestational age or postnatal age. Standard practice of using upper bound of 21 cells/mm^3 results in only 79% sensitivity. Data obtained from infants in a neonatal intensive care unit (NICU) have shown that the upper limit (95th percentile) of CSF WBC count is 12 cells/μL in preterm infants and 14 cells/μL in term infants. Another study reports an upper bound of 16 cells/mm^3 in neonates without meningitis. If there is contamination of the CSF sample with RBCs, there is no reliable method to "correct" the WBC. Because of the overlap between normal infants and those with meningitis, the presence of polymorphonuclear leukocytes in CSF deserves careful attention.

3. There are more reports on lower bounds of absolute values of glucose (40 mg/dL without meningitis) in CSF than on the traditionally used ratios of CSF and blood glucose concentrations. If the blood glucose level is high or low, there is a 4- to 6-hour equilibration period with the CSF glucose.

The normal level of CSF protein in newborns may vary over a wide range. CSF protein levels are higher in preterm infants (upper limit 209 mg/dL) than in term infants (159 mg/dL), and this declines with increasing postnatal age. Authors have reported upper bound of 172 mg/dL in those without meningitis. The level of CSF protein in the premature infant appears to be related to the degree of prematurity.

No single parameter can be used to rule out or rule in meningitis. Three percent of neonates with culture-positive meningitis had 0 cells/mm^3. Using cutoffs of CSF WBC 25 cells/mm^3, CSF protein 170 mg/dL, and CSF glucose 24 mg/dL would identify only 26% of preterm infants with bacterial meningitis. Presence of >25 WBC cells/mm^3, a glucose of <10 mg/dL, and >250 mg/dL of CSF protein has been found to have a 164-fold increase in the odds of having a positive CSF culture. These parameters have a high positive likelihood ratio but a sensitivity of only 18%. Meningitis may occur in the absence of positive blood cultures (see Chapter 49).

VII. INTUBATION

A. Endotracheal intubation. In most cases, an infant can be adequately ventilated by bag and mask, so that endotracheal intubation can be performed as a controlled procedure.

1. **Tube size and length.** The correct tube size (see Chapter 4) and insertion depth can be estimated from the infant's weight as well as by several other methods based on weight and gestational age. For insertion depth of oral ETTs, the most common rule is weight (kg) + 6 cm. There are two other methods for estimating ETT insertion depth as recommended by *Textbook of Neonatal Resuscitation* (7th edition).

   Nasotragal length has been validated in term as well as preterm babies (nasotragus distance + 1 cm at the level of the upper lip). Another method suggested is based on the gestational age, presented in the form of a table (proposed by Kembley et al.). 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. Studies have shown that point-of-care ultrasound (POC-USS) can be used for rapid confirmation of ETT tip location. But because of need for specialized skills, lack of widespread availability, and difficulties to correctly identify anatomical landmarks, USS is not yet commonly used for confirming ETT in newborns.

2. **Route.** Contradictory data exist over whether oral or nasal endotracheal intubation is preferred. Oral ETTs can cause a palatal groove, and nasal ETTs can cause asymmetry of the nares. In most circumstances, local experience should guide this selection with two exceptions. First, oral intubation should be performed in all emergent situations because it is generally easier and quicker than nasal intubation. Second, oral intubation is preferable when significant coagulopathy or thrombocytopenia exists. Benefits attributed to nasal intubation are less tube displacement and less incidence of ventilator-associated pneumonias because of better oral hygiene. A functioning ETT should not be electively changed simply to provide an alternate route.

3. Technique

a. Adequate preparation is mandatory, with all essential equipment such as O_2 source, suction, appropriate-sized bag and masks, ETTs, laryngoscope, and fixing tapes.

b. Clear assignment of roles to all participants will decrease confusion.

c. **The patient should be adequately ventilated using bag and mask or T-piece resuscitator** to ensure that the patient has normal oxygen saturations (appropriate for gestational age) before laryngoscopy. Laryngoscopy and intubation of an active, unmedicated patient is more uncomfortable for the patient and more difficult for the operator, and the risk of complications may be increased. The American Academy of Pediatrics (AAP) recommends the use of premedications for all elective intubations in newborn. An ideal combination and/or sequence of premedications has not been established. The AAP has recommended the use of a combination of vagolytic, analgesic, and neuromuscular blocker for premedication. Evidence-based guidelines from Italy suggest the use of atropine (0.01 to 0.02 mg/kg) + fentanyl (2 µg/kg) + succinylcholine (2 mg/kg) or rocuronium (0.5 to 1 mg/kg). Muscle relaxant is avoided in nonvigorous babies and ELBW babies. Succinylcholine is contraindicated in babies with hyperkalemia, muscle disorders, and family h/o malignant hyperthermia. Use of sedatives such as benzodiazepines alone without analgesics should be avoided.

d. Throughout the intubation procedure, observation of the patient and continuous monitoring of the heart rate and saturations by pulse oximetry are mandatory. If bradycardia is observed, especially if accompanied by hypoxia, the procedure should be stopped and the baby ventilated with bag and mask.

e. **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.

f. The **laryngoscope** is held between the thumb and the first finger of the left hand, with the second and third fingers holding the baby's chin and stabilizing the head.

g. The **laryngoscope blade** is passed into the right side of the mouth and then to the midline, sweeping the tongue up and 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° relative to the bed. The blade should then be lifted while maintaining the same angle, with care being taken not to rock or lever the laryngoscope blade. Visualization of the vocal cords may be improved by providing cricoid pressure by 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.

h. The **ETT** is held with the right hand and inserted between the vocal cords to the appropriate estimated depth. Do not introduce the ETT if vocal cords are closed. Wait until the vocal cord is open; if necessary, give bag and mask ventilation and try again. During nasotracheal intubation, the tube can be guided by small Magill-type forceps or by moving the baby's head

slightly. If a finger of the operator or an assistant is used to gently press down over the trachea, the tube can be felt passing through.

i. 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.

j. The **tube position** is best assessed by *a rapid improvement in heart rate*. It is further checked by auscultation of the chest to ensure equal aeration of both lungs and observation of chest movement with positive-pressure inflation. The tube will usually "steam up" if it is correctly placed in the trachea, and the baby should show improved oxygenation, but an end-tidal CO_2 monitor is recommended to confirm the intratracheal position of the tube. If air entry is poor over the left side of the chest, the tube should be pulled back until it becomes equal to the right side.

4. Once correct position is ascertained, the tube should be held against the palate (nose in case of nasal intubation) with one finger, until it can be taped securely in place; the position of the tube should be confirmed by radiograph, if the baby has been intubated for the first time. The tip of the tube should be in mid-trachea adjacent to T1 or T2. In case of reintubation, the ideal depth of insertion of ETT is known from x-ray of the first intubation.

5. Increasingly, video laryngoscopes are being used for intubation of neonates. These devices offer the possibility of concurrent observation of tube placement by another observer and easier or more reliable tube insertion. Among the available devices, each has its particular limitations in terms of size or design.

6. Commonly observed errors during intubation

a. Focus is placed on the procedure and not on the patient.

b. The baby's neck is hyperextended. This displaces the cords anteriorly and obscures visualization or makes the passing of the ETT difficult.

c. Excessive pressure is placed on the infant's upper gum by the laryngoscope blade. This occurs when the tip of the laryngoscope blade is tilted or rocked upward instead of traction being exerted parallel to the baby.

d. The tube is inserted too far and the position not assessed, resulting in intubation of the right mainstem bronchus.

7. Cuffed or uncuffed ETT. The use of uncuffed ETTs remains the standard practice in NICUs. Recently, cuffed ETTs are being used for short term during anesthesia. The smallest recommended cuffed ETT size is 3 mm, and is recommended for babies weighing >3 kg. For the use of cuffed ETTs for long-term ventilation in NICUs, efficiency of ventilation and longer outcomes are poorly studied.

8. Laryngeal mask airway (LMA). Occasionally, it is not possible for a team to successfully insert an ETT despite multiple attempts, or babies may have congenital anomalies involving the mouth, lip, palate, tongue, or neck, e.g., Pierre Robin sequence. In such cases, a LMA can be a lifesaving alternative to provide rescue ventilation until a more stable airway can be established. The

size 1 laryngeal mask is appropriate and *Textbook of Neonatal Resuscitation* recommends use of size 1 LMA for babies weighing 1.5 to 5 kg, although there are reports of its successful use in preterm babies weighing less than 1.5 kg.

The laryngeal mask may be especially useful during the initial resuscitation after birth, more so when a person skilled in intubation is not readily available. Current versions are not however designed to be used for tracheal suctioning or instillation of surfactant.

VIII. THORACENTESIS AND CHEST TUBE PLACEMENT. (See Chapter 38)

Tension pneumothorax presenting as tachycardia, hypoperfusion, worsening of respiratory status will require emergency thoracocentesis, followed by a chest tube placement. (see chapter 38)

IX. VASCULAR CATHETERIZATION. (See Figs. 69.1 and 69.2 for diagrams of the newborn venous and arterial systems.)

A. Types of catheters

1. **Umbilical artery catheters (UACs)** are used when frequent blood sampling is necessary for (i) sampling for arterial blood gases, and hematological and biochemical tests; (ii) continuous invasive BP monitoring; and (iii) exchange transfusion.

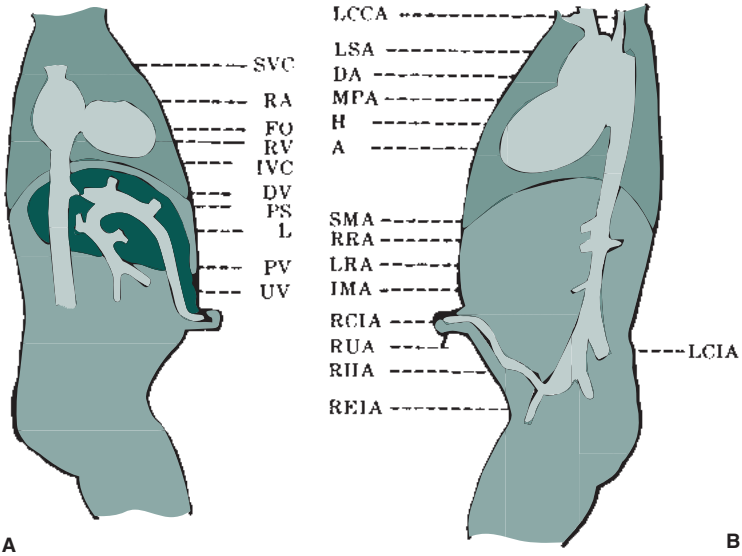

Figure 69.1. **A:** Diagram of the newborn umbilical venous system. SVC, superior vena cava; DV, ductus venosus; FO, foramen ovale; IVC, inferior vena cava; L, liver; PS, portal sinus; PV, portal vein; RA, right atrium; RV, right ventricle; UV, umbilical vein. **B:** Diagram of the newborn arterial system, including the umbilical artery. A, aorta; DA, ductus arteriosus; H, heart; IMA, inferior mesenteric artery; LCCA, left common carotid artery; LCIA, left common iliac artery; LRA, left renal artery; LSA, left subclavian artery; MPA, main pulmonary artery; RCIA, right common iliac artery; REIA, right external iliac artery; RHA, right hypogastric artery; RRA, right renal artery; RUA, right umbilical artery; SMA, superior mesenteric artery; (From Kitterman JA, Phibbs RH, Tooley WH. Catheterization of umbilical vessels in newborn infants. *Pediatr Clin North Am* 1970;17:898.)

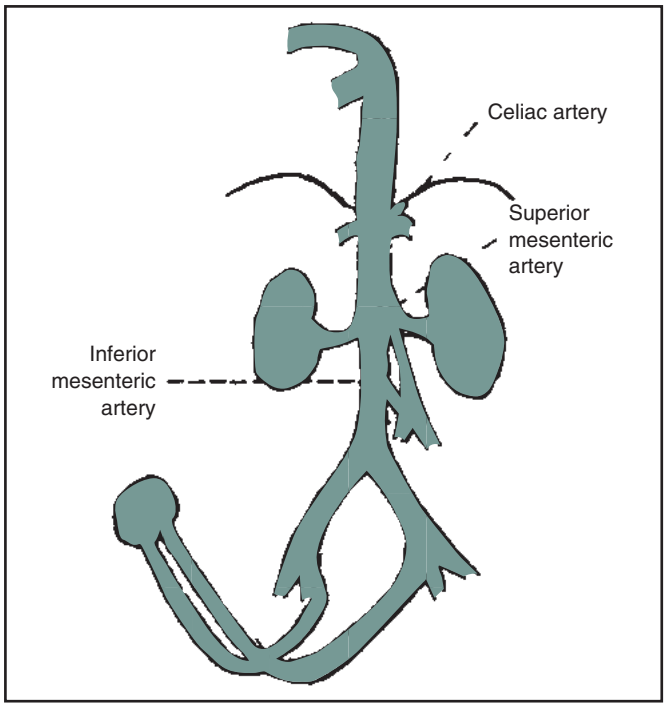

Figure 69.2. Localization of umbilical artery catheters. The cross-hatched areas represent sites in which complications are least likely. Either site may be used for placement of the catheter tip.

2. **Peripheral artery catheters** are used when frequent blood gas monitoring is still required and a UAC is contraindicated, cannot be placed, or is removed because of complications. They require that motion of the infant's arm be kept restricted.
3. **Umbilical vein catheters (UVCs)** (when passed through the ductus venous and near the right atrium) are used for monitoring of central venous pressure and infusion of fluids. Low UVCs can be used for exchange transfusion and as emergency vascular access for infusion of fluid, blood, or medications until alternate access can be obtained.
4. **Central venous catheters** used largely for prolonged parenteral nutrition or antibiotics, or for pressor administration and occasionally to monitor central venous pressure, can be placed percutaneously through the saphenous, subclavian, basilic, or external jugular vein.

B. Umbilical artery catheterization

1. In general, only seriously ill infants should have a UAC placed. If only a few blood gas measurements are anticipated, peripheral arterial punctures should be performed together with noninvasive oxygen monitoring, and a peripheral intravenous route should be used for fluids and medications.

2. **Technique**

a. Accurate placement of UAC during initial insertion is important as malposition increases catheter-related complications and subsequent repositioning exposes the baby to unnecessary handling, increased radiation exposure, and increased risk of infections.

b. Many formulas have been derived to predict accurate measurement of UACs: (i) Dunn's formula—nomogram using shoulder umbilical length which is the distance between the top of the shoulder at the lateral end of the clavicle and a point vertically below at the level of the center of the umbilicus with added umbilical stump length; (ii) Wright's formula for length of UAC insertion, in centimeters, for babies <32 weeks/<1.5 kg—(4 × birth weight [kg]) + 7; and (iii) Shukla's formula for babies >32 weeks/>1.5 kg—(3 × weight) + 9.

c. There is no consensus regarding the best method for accurate catheter positioning.

d. If Dunn's technique is used, before preparing the cord and skin, make external measurements to determine how far the catheter will be inserted (see Figs. 69.2 to 69.4). For a "high" UAC, the distance is usually (umbilicus-to-shoulder) plus the length of the stump. In a high setting, the catheter tip is placed between the 8th and 10th thoracic vertebrae; in a low setting, the tip is between the 3rd and 4th lumbar vertebrae. High-placed UACs are associated with a reduced risk of vascular complications compared to low-placed UACs.

3. Positioning of the catheter tip. A Cochrane review states that high-placed UACs are associated with a reduced incidence of clinical vascular complications without an increase in any adverse sequelae and that high catheters should be used exclusively.

a. Prepare the cord and surrounding skin carefully with an antiseptic solution as discussed. Umbilical (twill) tape should be placed as a simple tie around the base of the cord itself. In unusual circumstances, it is necessary to place the tape on the umbilical skin itself. If this is done, 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 with a scalpel to a length of 1.0 to 1.5 cm.

b. The cord stump is suspended with forceps. The cord is stabilized with a forceps or hemostat, and the two arteries are identified. The open tip of an 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 for approximately 1 minute, to dilate the vessel. This pause may be the most critical step for ensuring successful insertion of the catheter.

c. The forceps is withdrawn, and a sterile saline–filled 3.5F or 5F single-lumen umbilical vessel catheter with an end hole is threaded into the artery. The smaller catheter is generally used for infants weighing <1,500 g. 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 following problems with umbilical artery

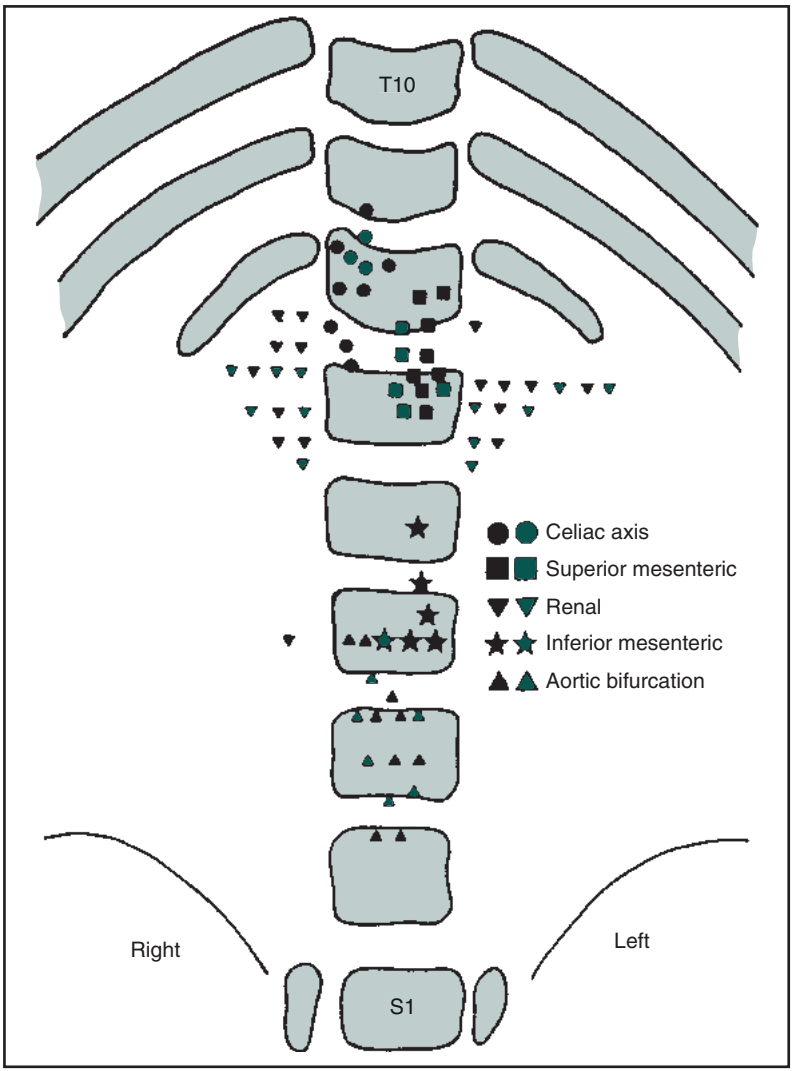

Figure 69.3. Distribution of the major aortic branches found in 15 infants by aortography as correlated with the vertebral bodies. Filled symbols represent infants with cardiac or renal anomalies (or both); open symbols represent those without either disorder. Major landmarks appear at the following vertebral levels: diaphragm, T12 interspace; celiac artery, T12; superior mesenteric artery, L1 interspace; renal artery, L1; inferior mesenteric artery, L3; aortic bifurcation, L4. (From Phelps DL, Lachman RS, Leake RD, et al. The radiologic localization of the major aortic tributaries in the newborn infant. *J Pediatr* 1972;81:336–339.)

catheterization may occur. If too much resistance is felt during insertion, the procedure should be aborted.

i. The catheter may pass into the lower aorta but then loop caudad into the contralateral iliac artery or out one of the arteries to the buttocks.

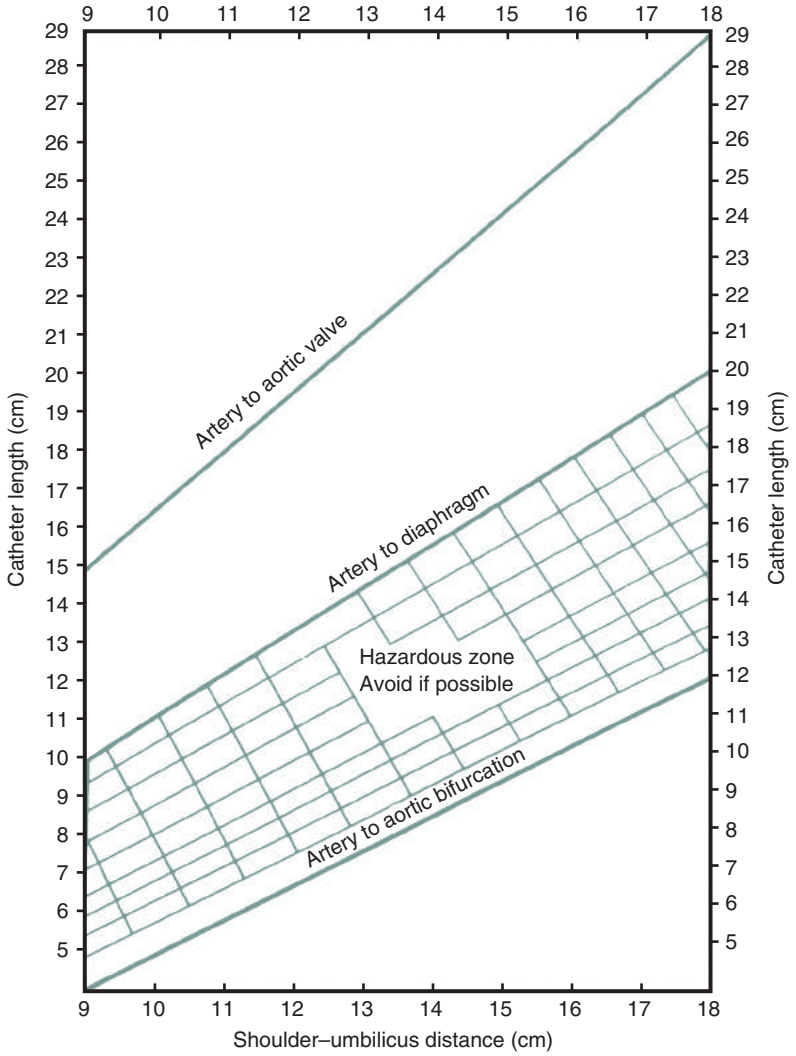

Figure 69.4. Distance from shoulder to umbilicus measured from above the lateral end of the clavicle to the umbilicus, as compared with the length of umbilical artery catheter needed to reach the designated level. (From Dunn PM. Localization of the umbilical catheter by post-mortem measurement. *Arch Dis Child* 1969;41:69.)

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 F) is placed in a large baby. Sometimes, using a larger, stiffer catheter (5 F) will allow the catheter to advance up the aorta. Alternatively, retracting the catheter into the umbilical artery, rotating it, and readvancing it into the aorta may result in aortic placement. If this fails, the catheter should be removed, and placement

attempted through the other umbilical artery. Sometimes, the catheter goes up the aorta and then loops back on itself. This also happens more frequently when a small catheter is used in a large baby. 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 or the catheter removed.

ii. There is persistent cyanosis, blanching, or poor distal extremity perfusion. This may be improved by warming the contralateral leg, but if there is no improvement, the catheter should be removed.

iii. Hematuria is also an indication for catheter removal.

d. After the catheter is placed, the appropriate distance and placement should be confirmed by radiographic examination.

The catheter should be fixed in place with a purse-string suture using silk thread and a tape bridge added for further stability.

4. Catheter removal

a. 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. Complications are noted.

b. Method of catheter removal. Heparin infusion should be stopped half an hour before 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. This usually prevents profuse bleeding. Old sutures should be removed. If bleeding should occur despite this method, pressure should be held at the stump of the umbilical artery until the bleeding ceases. This may take several minutes.

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. Careful systematic approach in assessing the baby is important to ensure early detection of 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. A ribbon of topical nitroglycerine 2% ointment at a dose of 4 mm/kg may be a useful initial

therapy for the reversal of tissue ischemia. Methemoglobin levels should be monitored and kept below 1% when topical nitroglycerine is used.

b. Thrombi. We perform Doppler ultrasonographic examination of the aorta and renal vessels in infants in whom we are concerned about vascular complications. If thrombi are observed, the catheter is removed.

If there are small thrombi without symptoms or with increased blood pressure alone, after catheter removal, we follow resolution of the thrombi by ultrasonographic examination and treat hypertension if necessary (see Chapter 28). If there are signs of emboli or loss of pulses (and no intracranial hemorrhage is present), we consider heparinization, maintaining the partial thromboplastin time (PTT) at double the control value. Published data to guide practice are limited. If there is a large clot with impairment of perfusion, we consider the use of fibrinolytic agents (see Chapter 44). Surgical treatment of thrombosis is not generally effective.

c. Use of heparin for anticoagulation to prevent clotting. Whether the use of heparin in the infusate decreases the incidence of thrombotic complications is not known. We use dilute heparin 0.5 unit/mL of infusate. Heparin preparations containing benzyl alcohol should not be used in neonates. There is increasing evidence that heparin infusion may not be necessary, and has no benefit on the life of UAC.

d. Indwelling time. 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.

i. Carefully label UAC to prevent inadvertent administration of wrong IV solutions or medications.

ii. Keep the legs uncovered for early detection of signs of vasospasm/thrombosis.

6. Infection and use of antibiotics. Strict infection control practices should be adopted during insertion and care to prevent infection. We do not use prophylactic antibiotics for the placement of UACs. In infants with indwelling UACs, after appropriate cultures have been obtained, treat with antibiotics based on regional microbiology data, whenever infection is suspected.

C. Umbilical vein catheterization (see Figs. 69.1 and 69.5)

1. Indications. In critically ill and extremely premature infants, we use high-lying UVC to infuse vasopressors and as the primary route of venous access in the first several days after birth.

We use low-lying umbilical vein catheterization for exchange transfusions and emergency vascular access; in the latter case, the venous catheter may be used as a peripheral intravenous catheter until peripheral or central venous access can be obtained.

2. Technique

a. The site is prepared as for umbilical artery catheterization after determining the appropriate length of catheter to be inserted (see Fig. 69.5).

b. Several formulas for insertion length of UVC are available; there is no consensus on which is the accurate formula to be used.

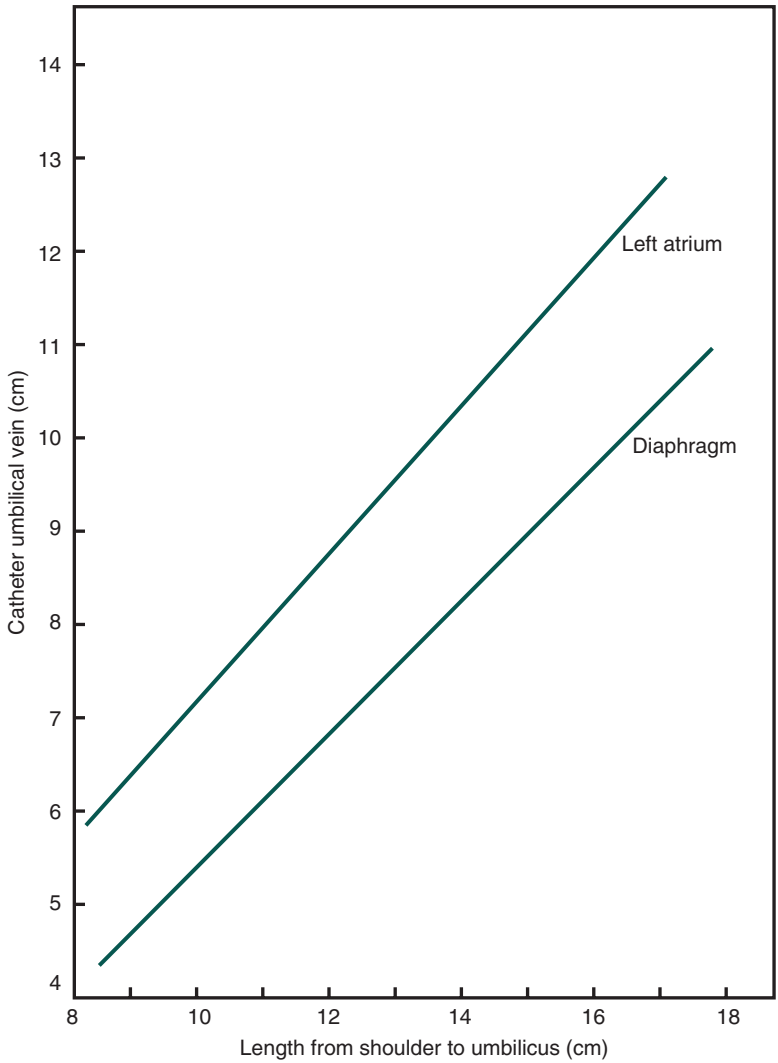

Figure 69.5. Catheter length for umbilical vein catheterization. The catheter tip should be placed between the diaphragm and the left atrium. (From Dunn PM. Localization of the umbilical catheter by post-mortem measurements. *Arch Dis Child* 1966;41:69.)

c. The most commonly used is the modified Shukla's formula (3 × weight [kg] + 9)/2. The other formulas used are as follows:

i. Gomella's formula: Measurement of distance from the umbilicus to the xiphisternum and adding 1 cm

ii. Vali's formula: Measurement from the umbilicus to the mid-xiphoid-to-bed distance on the lateral aspect of the abdomen

iii. Dunn's nomogram (Fig. 69.5)

d. Procedure. Any clots seen at the opening of the umbilical vein are removed with a forceps, and the umbilical vein is gently dilated.

i. The catheter (3.5 or 5 F) is prepared by filling the lumen with normal saline, through an attached syringe. It should never be left open to the atmosphere because negative intrathoracic pressure could cause an air embolism.

ii. The catheter 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 or for an exchange transfusion, it should be advanced only as far as is necessary to establish good blood flow (usually 2 to 5 cm). 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 USS. If USS is not available, an anteroposterior/lateral thoracoabdominal x-ray is taken to confirm the catheter tip between T9 and T10 vertebrae.

e. Only isotonic solutions should be infused until the position of the catheter is verified. If the catheter tip is in the inferior vena cava, hypertonic solutions may be infused.

f. If no other access is available, catheters may be left in place for up to 10 days, after which the risk of infections or other complications is excessive. In very low-birth-weight infants, our practice is to change access to a peripherally placed central venous catheter by 10 days whenever possible.

D. Multiple-lumen catheters for umbilical venous catheterization

1. Indications. 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 intravenous 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.

2. Technique

a. Multiple-lumen catheters are inserted according to the same procedure as single-lumen catheters described earlier. The increased pliability of many of the multiple-lumen catheters makes inadvertent passage into the hepatic veins more likely.

b. Usage. Where possible, infusions that should not be interrupted (e.g., vasopressors) are placed in the proximal lumen to allow measurement of central venous pressure from the distal port.

E. Percutaneous radial artery catheterization.

Placement of an indwelling radial artery catheter is a useful alternative to umbilical artery catheterization to monitor blood gas levels and blood pressure. The indications include if the umbilical artery cannot be cannulated or arterial access is needed after removal of UAC.

1. **Advantages**
   a. Preductal PaO_2 (if the right radial artery is used)
   b. Avoidance of thrombosis of major vessels, which is sometimes associated with umbilical vessel catheterization
2. **Risks** are usually small if the procedure is performed carefully but include arterial occlusion and subsequent impaired tissue perfusion, inadvertent injection of a solution that is potentially injurious to the artery, infection, or air embolus.
3. **Equipment** required includes a 22G or 24G intravenous cannula with stylet, a T-connector, heparinized saline flushing solution (0.5 to 1.0 unit/mL of heparin solution), and an infusion pump.
4. **Method of catheterization**
   a. As noted, it is controversial whether or not the Allen test should be considered standard of care, especially regarding the interpretation of an abnormal test. We continue to recommend that the adequacy of the ulnar collateral flow to the hand must be assessed before catheterizing the radial artery. The radial and ulnar arteries should be simultaneously compressed, and the ulnar artery should then be released. The degree of flushing of the blanched hand should be noted. If the entire hand becomes flushed while the radial artery is occluded, the ulnar circulation is adequate.
   b. The hand may be secured on an arm board with the wrist extended, leaving all fingertips exposed, to observe color changes.
   c. The wrist is prepared with an antiseptic such as alcohol and chlorhexidine solution. The site of maximum arterial pulsation is palpated.
   d. The intravenous cannula is inserted through the skin at an angle <30° to horizontal and is slowly advanced into the artery. Transillumination may help delineate the vessel and its course. If the artery is entered as the catheter is advanced, the stylet is removed and the catheter is advanced in the artery. If there is no blood return, the artery may be transfixed. The stylet is then removed, and the catheter is slowly withdrawn until blood flow occurs, and then it is advanced into the vessel.
5. **Caution.** Only heparinized saline solution (0.45% to 0.9%) is infused into the catheter. The minimum infusion rate is 0.8 mL/hour; the maximum is 2 mL/hour.

F. Percutaneous central venous catheterization is useful for long-term venous access for intravenous fluids, particularly parenteral nutrition.

1. The central venous catheter is inserted into a peripheral vein and advanced into the central circulation. This is the primary method of central venous access. We recommend establishing a specialized team of nurses and/or physicians who are responsible for placing these lines.
   a. **The materials** required include sterile towels, a splittable introducer needle, iris forceps, a 10-mL syringe, and normal saline for flushing. The size of the catheter is as follows: 1-F catheter for babies weighing less than 1 kg and 2-F catheter for more than 1 kg.

b. **Measurement.** For upper extremity insertion, measure from the insertion site (preferably the basilic vein) along the course of the vein to the right of the sternal border to the third intercostal space. For lower extremity insertion, measure from the insertion site (long saphenous vein) along the course of the vein, through the right of the umbilicus up to the xiphoid.

c. **Technique.** An appropriate vein of entry is selected. This may be a basilic, greater saphenous, or external jugular vein. The cephalic vein should be avoided because central placement is more difficult. The site is prepared with an antiseptic solution and the introducer needle is inserted into the vein until blood flows freely. The catheter is inserted through the needle with forceps and is slowly advanced to the predetermined distance for central venous positioning. The introducer needle is removed, the extra catheter length is coiled on the skin near the insertion site, and the site is covered with transparent surgical covering. The catheter tip is positioned at the junction of the vena cava and the right atrium, as confirmed by radiography/USS. 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 position the infant with his or her arms oriented as during usual care so that the tip position is not altered (raising the arm can cause the tip to shift).

d. **Complications** include hemorrhage during insertion, infection, and thrombosis of the catheter, but these are unusual. 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 is 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 syringe.

2. **Subclavian vein catheterization** may occasionally be useful in infants weighing >1,200 g, although in general, a surgically placed central venous catheter is preferred when other access cannot be established. Operators should receive specific training in this procedure before performing it.

X. ABDOMINAL PARACENTESIS FOR REMOVAL OF ASCITIC FLUID

A. Indications

1. Therapeutic indications include respiratory distress resulting from abdominal distension (e.g., hydropic infants, infants with urinary ascites) for which removal of ascitic fluid will ameliorate respiratory symptoms. In addition, interference with urine production or lower extremity perfusion resulting from increased intra-abdominal pressure may be improved by paracentesis.
2. Diagnostic indications include the evaluation of suspected peritonitis.

B. Technique

1. The **equipment** needed includes an 18G to 22G intravenous catheter, three-way stopcock, and a 10- to 50-mL syringe.

2. The lower abdomen is prepared with antiseptic solution, and the area is draped. It is best to ensure that the bladder is empty. A local anesthetic such as 1% lidocaine (Xylocaine) is infiltrated into the subcutaneous tissues when possible. A syringe is attached to the catheter. ***USS guidance is ideal***, especially in situations in which the volume of the intraperitoneal fluid is minimal enough that there is concern that the fluid may be difficult to locate or that an abdominal viscus could accidentally be punctured during the procedure. The catheter is 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. 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 effects. The catheter is removed and the site bandaged.

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.

XI. PERICARDIOCENTESIS

A. Indications

1. If a pericardial effusion is suspected based on physical examination (muffled heart sounds, sinus tachycardia, narrow pulse pressure, and signs of diminished cardiac output) or 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.
2. In most cases, even significant effusions produce little or no symptoms or signs. Diagnosis may be suspected based on physical examination, vital signs, and radiographic findings and should be confirmed by ultrasonographic examination before drainage is attempted if time permits.

B. Technique

1. The patient should be prepared and the area cleaned with antiseptic solution according to the 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 done using a 22G or 24G intravenous catheter. The catheter is inserted just below the xiphoid process and just to the left of midline (to avoid puncturing the right atrium) and angled toward the left shoulder. It is advanced forward until the pericardial sac is entered, while monitoring for arrhythmias that can signal needle advancement into the myocardium. The introducer trochar can then be removed, and a syringe and connecting tube is attached, and the fluid is aspirated as the catheter is advanced. Once no further fluid can be aspirated, the catheter is removed and the entry site covered with occlusive gauze and transparent dressing.

C. Potential complications

Cardiac puncture, pneumopericardium, pneumothorax, or transient dysrhythmias may occur. Ultrasonographic guidance may lower the risk of these complications.

Suggested Readings

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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 in hospitalized neonates is under-recognized and under-treated.
- Preterm and term newborn babies experience pain, the pain pathways develop very early in gestation.
- Unmanaged pain has significant physiologic consequences, also long-term pain responses may be modified.
- Pain assessment tools must include behavioral responses; use of physiologic changes alone may underestimate pain, especially in sick/preterm babies.
- Nonpharmacologic measures including swaddling, kangaroo care, nonnutritive suck, sucrose, and breast milk are useful in minor pain like heel lance, intramuscular injections, and venepuncture.
- Topical anesthesia is effective for venepuncture, cannulation, and lumbar puncture.
- The choice of measure for pain relief should be customized for anticipated severity and duration of pain.
- Moderate to severe pain may require opioid analgesia.
- 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.
- 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.
- Alleviating pain is the most important goal. Therefore, treatment with analgesics is recommended over sedation without analgesia.
- Premedication is recommended for all nonurgent intubations. It includes an opioid, benzodiazepine, and a muscle-relaxant.
- Routine continuous opioid infusions for mechanically ventilated newborns is not recommended because of concern about short-term adverse effects.
- for ROP screening - combination of topical agents, sucrose, and nonphramacologic methods is recommended.
- Paracetamol reduces need for opioid use in postoperative management.
- Sedatives decrease agitation and are helpful as adjuncts with opioid (decrease dose needed); they do not reduce pain and should not be used alone.
- Sedatives are not recommended in preterms.
- Epidural analgesia may be useful in extreme preterm with BPD.

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 the later part of 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, 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. Effect of Pain and Stress on 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 corrected age of 18 months. 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' gestation*. Subsequent analyses suggested that 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 are 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 that 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. PRINCIPLES OF PREVENTION AND MANAGEMENT OF NEONATAL PAIN AND STRESS

A. Neuroanatomic components and neuroendocrine systems of the neonate are sufficiently developed to allow transmission of painful stimuli.

B. Exposure to prolonged or severe pain may increase neonatal morbidity.

C. Infants who have experienced pain during the neonatal period may respond differently to subsequent painful events.

D. Severity of pain and effects of analgesia can be assessed in the neonate using validated instruments.

E. Newborn infants usually are not easily comforted when analgesia is needed.

F. A lack of behavioral responses (including crying and movement) does not necessarily indicate the absence of pain.

G. The pain intensity differs between procedures, the pain management plan should be customized to the expected severity and duration 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 comfort or 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, heart rate acceleration, blood pressure increase, and a rise in 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 is not consistently evident. Even among infants with an intact response to pain, a painful stimulus that persists for hours or days exhausts the 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. Among the behavioral components the withdrawal reflex and changes in facial expression are the most strongly associated with nociception-specific brain activity. These associations may be influenced by the gestational age and change over time. Physiological signs, such heart rate and oxygen saturation, have little to no association with this type of response. By 25 to 26 weeks, the facial expression is the same as 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 undertreatment or overtreatment, the proficiency of individual caregivers using the chosen pain scale should be reassessed periodically to maintain reliability in assessing pain.
2. Selecting the most appropriate tool for evaluating neonatal pain is essential to its 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 he or she is evaluating and treating pain. A pain scoring tool with appropriate age range, acceptable psychometric properties, clinical utility, and feasibility may reduce bias even though none is perfect. Many tools exist, and a few of the more common ones are shown in Table 70.1.
3. Documentation of pain is essential. In general, pain scores that are documented along with vital signs can be monitored most easily for trends and subtle patterns so that pain, unrelieved pain, or opioid tolerance can be identified early.

B. Critically ill infants. Pain responses are influenced by the birth gestation, age, and behavioral state of the infant. Most pain scales that have been tested used

Table 70.1. Summary of Neonatal Pain Assessment Tools

Pain Assessment Tool	Gestational Age/Post-conceptional Age	Physiologic Components	Behavioral Components	Type of Pain	Adjusts for Prematurity	Scale Metric
PIPP (Premature Infant Pain Profile)*	28–40 weeks	Heart rate, oxygen saturation	Alertness, brow bulge, eye squeeze, nasolabial furrow	Procedural and Postoperative	Yes	0–21
CRIES (Cries, Requires Oxygen, Increased Viral Signs, Expression, Sleeplessness)†	32–56 weeks	Blood pressure, heart rate, oxygen saturation	Cry, expression, sleeplessness	Postoperative	No	0–10
NIPS (Neonatal Infant Pain Scale)‡	28–38 weeks	Breathing pattern	Facial expression, cry, arms, legs, alertness	Procedural	No	0–7
COMFORT (and COMFORTneo)§,¶	0–3 years (COMFORTneo: 24–42 weeks)	Respiratory response, blood pressure, heart rate	Alertness, agitation, physical movements, muscle tone, facial tension	Postoperative (COMFORTneo: prolonged)	No	8–40
NFCS (Neonatal Facial Coding System)**	25 weeks to term	None	Brow bulge, eye squeeze, nasolabial furrow, open lips, stretched mouth (vertical and horizontal), lip purse, taut tongue, chin quiver	Procedural	No	0–10
N-PASS (Neonatal Pain, Agitation, and Sedation Scale)††	0–100 days	Heart rate, respiratory rate, blood pressure, oxygen saturation	Crying/irritability, behavior state, facial expression, extremities/tone	Acute and prolonged pain Also assesses sedation	Yes	Pain: 0–10 Sedation –10 to 0

(continued)

Table 70.1. Summary of Neonatal Pain Assessment Tools *(continued)*

Pain Assessment Tool	Gestational Age/Post-conceptional Age	Physiologic Components	Behavioral Components	Type of Pain	Adjusts for Prematurity	Scale Metric
EDIN (Échelle de la Douleur Inconfort Noveau-Né—Neonatal Pain and Discomfort Scale)[‡‡]	25–36 weeks	None	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	Prolonged	No	0–15
BPSN (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	Procedural	No	0–27
EVANDOL (Evaluation enfant douleur)	0–7 years		Vocal or verbal expression, facial expression movements Postures Interaction with the environment	Acute pain and procedural pain	No	0–15

Source: Reprinted with permission from Maxwell LG, Malavolta CP, Fraga MV. Assessment of pain in the neonate. *Clin Perinatol* 2013;40:457–469.

*Stevens B, Johnston C, Petryshen P, et al. Premature infant pain profile: development and initial validation. *Clin J Pain* 1996;12:13–22.

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**Grunau RV, Craig KD. Facial activity as a measure of neonatal pain expression. *Adv Pain Res Ther* 1990;15:147–155.

††Hummel P, Puchalski M, Creech SD, et al. Clinical reliability and validity of the N-PASS: Neonatal Pain, Agitation and Sedation Scale with prolonged pain. *J Perinatol* 2008;28:55–60.

‡‡Debillon T, Zupan V, Ravault N, et al. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F36–F41.

§§Cignacco E, Mueller R, Hamers JP, et al. Pain assessment in the neonate using the Bernese Pain Scale for Neonates. *Early Hum Dev* 2004;78:125–131.

acute pain for the stimulus (heel stick), and very few tools that measure acute 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 that may be present when an infant is severely ill or extremely premature. A lack of response does not mean that an infant is not in pain. The caregiver must base treatment decisions on other data such as the 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 pain response similar to that of 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, less 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 the assessment of prolonged pain in preterm infants is the EDIN (Échelle Douleur Inconfort Nouveau-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). In such situations, evaluation of serum or even salivary cortisol may be of some use, but more studies are required in this area.

IV. MANAGEMENT: PAIN PREVENTION AND TREATMENT. A summary of painful skin-breaking procedures (Table 70.2) illustrates some options available for the management of pain.

Attention to the intensity and duration (Table 70.3) of diagnostic, therapeutic, or surgical procedures commonly performed in the neonatal intensive care unit (NICU) is fundamental to the development of appropriate strategies. This should include consideration of the history, clinical status, and PMA of the patient.

IV.A. NONPHARMACOLOGIC MEASURES OF PAIN MANAGEMENT. Caregivers often underuse nonpharmacologic measures for pain relief. When used appropriately, these approaches to pain relief have been shown to be effective and can also be used as an adjunct to pharmacologic treatment of pain. Among preterm infants, facilitated tucking, oral sucrose, and kangaroo care significantly mitigates pain response associated with acutely painful procedures.

1. **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.

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 and less resampling than heel stick
Arterial puncture	Nonpharmacologic measures, use topical and subcutaneous local anesthetics	More painful than venepuncture
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	Venepuncture 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
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 μg/kg)	—

(continued)

Table 70.2. Summary of Procedures and Recommendations for Pain Relief *(continued)*

Skin-Breaking Procedures*,†	Proposed Interventions	Comments
Arterial or venous cutdown	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, IV fentanyl (1–2 μg/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 μg/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 μg/kg, muscle relaxant as needed	—
Tracheal intubation (e.g., for mechanical ventilation)	Give fentanyl (1 μg/kg) or morphine (10–30 μg/kg), with midazolam (50–100 μg/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 μg/kg) if a chest tube is present	Avoid areas of injured or inflamed skin, areas with indwelling drains or catheters
Removal of IV catheter	Solvent swab, consider 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	—

Source: Reprinted with permission from Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924.

*Nonpharmacologic measures include pacifier, oral sucrose, swaddling, and skin-to-skin contact with the mother.

†The frequency of procedures can be reduced without sacrificing the quality of neonatal intensive care.

Table 70.3. Type of Pain Experience in Relation to Procedures

	Routine Procedures	Acute Pain of Short Duration	Acute Pain of Long Duration	Chronic Pain	Intubation, Noninvasive and Invasive Mechanical Ventilation
Examples	Position change, diaper change, weighing, abdominal girth, vitals recording such as temperature and BP	Heel prick, venepuncture, arterial puncture, intramuscular, subcutaneous injections, bladder catheterization, nasogastric tube insertion, ROP, chest physiotherapy	Umbilical catheter insertion, tracheal suction, lumbar punctures, chest tube insertion, central line insertion and circumcision	Postoperative pain, congenital skin disorders such as epidermolysis bullosa	Delivery room intubation where IV line may not be present Short intubation such as RDS, pneumothorax, prolonged ventilation, INSURE, CPAP and noninvasive ventilation, nonemergency, or elective intubations
Pain relief measures	Nonpharmacologic measures such as sucrose, breast milk, skin-to-skin contact, facilitated tucking	EMLA, oral sucrose For ROP, as mentioned earlier, fentanyl boluses or topical eye drops along with nonpharmacologic measures which have a synergistic effect	Intravenous fentanyl, if term neonate and agitated, can consider midazolam to calm the neonate provided other causes of agitation and pain are excluded. Avoid taking sutures on the skin while umbilical vessel catheterizations	Paracetamol and morphine or fentanyl Fentanyl is reported to be better for postoperative congenital diaphragmatic hernia and other congenital lung malformations with PPHN, since fentanyl has vascular stabilizing properties	■ For delivery room intubations, intranasal midazolam has been reported to be useful, but ensure to keep the bag and mask ready in case of failure of intubation in first attempt ■ For noninvasive ventilation and CPAP, nonpharmacologic approach along with boluses of morphine or fentanyl at minimum doses should be considered ■ On mechanical ventilation, routine sedation is not preferred. Midazolam should be given only for agitated term neonates (after excluding other causes for agitation) or in neonates with PPHN (for calming effect).

(continued)

Table 70.3. Type of Pain Experience in Relation to Procedures *(continued)*

	Routine Procedures	Acute Pain of Short Duration	Acute Pain of Long Duration	Chronic Pain	Intubation, Noninvasive and Invasive Mechanical Ventilation
					Preterm neonates may not require midazolam infusions. Fentanyl or morphine boluses can suffice for analgesia in both preterm and term neonates. Dexmedetomidine is an upcoming drug being used in many neonatal centers, during mechanical ventilation ■ INSURE: Atropine plus succinylcholine or remifentanil. Atropine plus propofol is another alternative

Remember to continue nonpharmacologic measures such as swaddling, containment, and facilitated tucking wherever they are possible along with pharmacologic measures as this provides a synergistic effect. EMLA, lidocaine–prilocaine; ROP, retinopathy of prematurity.

2. **Skin-to-skin (STS) holding** or kangaroo care. Enzymes and hormones that are released during STS elevate the pain threshold resulting in better tolerance of painful procedures and a decreased crying response in minor procedures such as blood sampling in postnatal wards. For both STS and facilitated tucking, the analgesic effect remains only as long as an infant is held.

3. **Sweet-tasting solutions** (sucrose or glucose) given orally 2 minutes before and/or just prior to a painful procedure decrease the pain response in infants as old as 12 months of age (Fig. 70.1). For repetitive painful procedures, taste-mediated analgesia is more effective than environmental modification alone. Sucrose is effective for reducing procedural pain from single events such as heel lance, venepuncture, and intramuscular injection in both preterm and term infants.

   For procedures that last longer than 5 minutes, repeated dosing should be considered. Optimal dosing of sweet-tasting solutions has not been established. Long-term outcomes from repeated dosing of sweet solutions in early infancy and in preterm infants are not known. Effects of repeated dosing of sweet solutions to sick or preterm babies in not known. Sweet-tasting solutions must be given on the tongue where taste buds for sweet taste are concentrated. They are not effective if given by nasogastric tube.

   They are even more effective when combined with other nonpharmacologic strategies such as nonnutritive sucking (e.g., gloved or nongloved but clean finger or pacifier).

4. **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. An additional advantage of this approach is that mothers have an active role in alleviating their infants' pain. Breast milk alone as an analgesic may be as effective as 24% sucrose in minor procedures such as heel lance or venepuncture.

5. **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.

6. **Therapeutic touch**/massage/right positioning of infant are associated with better tolerance to pain associated with minor procedures.

7. **Environmental Modification**
   An infant's eyes should be shielded from procedural lights. 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. Music therapy has been associated with better pain tolerance.

IV.B. PHARMACOLOGIC MANAGEMENT OF PROCEDURE-RELATED PAIN

A. Analgesia for minimally invasive procedures

Topical anesthetics (TAs) such as lidocaine–prilocaine (EMLA) are safe and effective for procedures such as venipuncture, venous cannulation, and lumbar puncture but are ineffective for heel-stick blood draws. 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

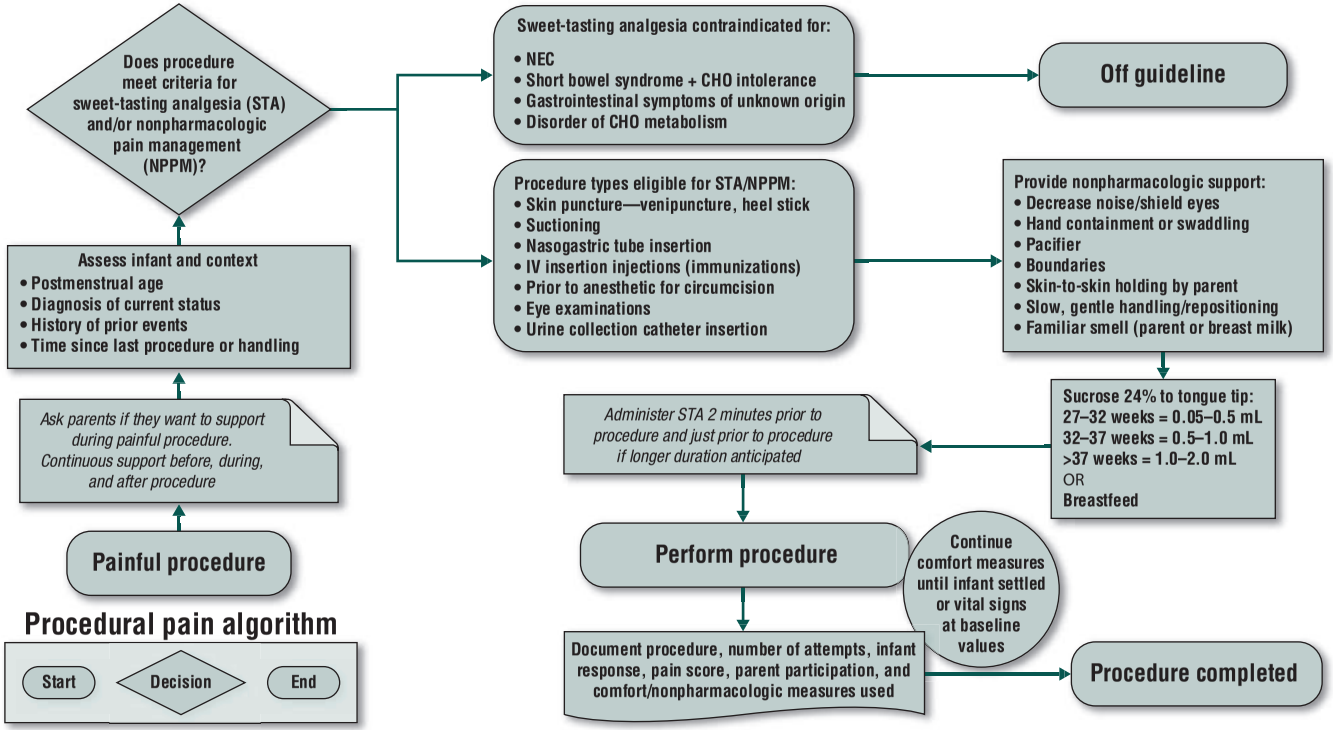

Figure 70.1. Procedural pain algorithm for minor procedures. CHO, carbohydrates; NEC, necrotizing enterocolitis.

agents (i.e., sulfas, acetaminophen, phenobarbital). New TAs (e.g., 4% tetracaine and 4% liposomal lidocaine) are faster acting but not as effective as EMLA.

B. Analgesia for invasive procedures

General principles

- The choice of measure for pain relief should be customized for anticipated severity and duration of pain (Table. 70.3).
- 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.
- Opioids and sedatives (e.g., benzodiazepines) are often used in treating critically ill newborns undergoing invasive or very painful diagnostic or therapeutic procedures.
- 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.
- Alleviating pain is the most important goal. Therefore, treatment with analgesics is recommended over sedation without analgesia.
- 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.

1. Intubation

Premedication is recommended for all nonurgent intubations. It includes an opioid, benzodiazepine, and a muscle-relaxant.

Fentanyl. Fentanyl must be infused slowly (no faster than 1 μg/kg/minute) to avoid complications of chest wall rigidity. As an alternative to fentanyl, remifentanil may be used. 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. 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 in the dose 2 mg/kg) for intubation, airway control and the ability to perform effective bag-and-mask ventilation must be assured.

2. Mechanical ventilation

AAP 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. 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.

3. Chest drains

Analgesia for chest drain insertion includes:

General nonpharmacologic measures, systemic analgesia with a rapidly acting opiate such as fentanyl.

Infiltration of the skin site with a local anesthetic may be used before incision, unless there is life-threatening instability.

Indwelling chest drains.

General nonpharmacologic measures, acetaminophen, and opioids is individualized based on the infant's pain assessment.

Chestdrain removal.

General nonpharmacologic measures (especially positioning/swaddling); may use short-acting, rapid-onset systemic analgesia.

4. **Circumcision.** Preprocedure, a combination of sucrose analgesia, acetaminophen, and dorsal penile block or ring block (with a maximum 0.5% lidocaine dose of 0.5 mL/kg) is recommended. Developmental positioning of the upper extremities using a blanket and restraining only the lower limbs may decrease the stress of medical immobilization. Following the procedure, an infant may benefit from acetaminophen 10 mg/kg every 6 hours for 24 hours (total dose should not exceed 40 mg/kg).

5. **Ophthalmology procedures.** A combination of TA eye drops (0.5% proparacaine) 30 seconds prior to examination combined with oral 24% sucrose or 25% dextrose in the dose of 0.5 mL/kg just before the insertion of eye speculum should be used for prevention of pain during screening for ROP (GRADE recommendation strong based on moderate evidence).

   Either nonnutritive sucking using a sterile single-use pacifier or provision of the mother's smell by nearby placement of a clean cloth soaked in her breast milk may be combined with TA and sucrose/dextrose to enhance pain relief during the screening procedure. When using a pacifier, the health care provider must explain the specific indication of its use and counsel the family against using a pacifier after discharge from the hospital.

   To minimize discomfort, it may be thoughtful to decrease lighting or shield the infant's eyes from light for 4 to 6 hours following dilatation for eye examinations.

6. **Analgesia during therapeutic hypothermia for HIE.** Hypothermia treatment represents a physiologic stress, even during rewarming. As per the survey data from different NICUs, most centers used fentanyl, followed rarely by midazolam or morphine.

7. **Pain relief and analgesia during vaccinations.** A number of interventions have been postulated to reduce pain during vaccinations in infants**. S**ucrose and dextrose solutions (varying from 10% to 50%) have been used 2 minutes before vaccination in infants up to 12 months of age (grade A, Level 1 evidence). Expressed breast milk (EBM) and breastfeeding have also been shown by few to be beneficial in pain due to vaccination. Also, breastfeeding during the procedure has not been reported to be associated with adverse events such as gagging or spitting. There is insufficient evidence to recommend for or against any of the skin cooling techniques such as ice packs and cold compresses. Paracetamol has been commonly used after painful vaccinations (especially DPT), however, there are concerns about it affecting the immunogenicity of the pertussis. Sequencing of vaccination in case of multiple inoculation is also said to reduce pain if a less painful vaccine is given before the more painful vaccine (e.g., pneumococcal or hepatitis B being given before DPT

vaccine). Using distraction techniques and other nonpharmacologic measures help to decrease anxiety.

8. **Postoperative analgesia.** Tissue injury, which occurs during all forms of surgery, elicits profound pain responses. Thus, minimizing the endocrine and metabolic responses to surgery by decreasing pain has been shown to significantly improve outcomes after neonatal surgery**.** Health care facilities providing surgery for neonates should establish a protocol for pain management in collaboration with anesthesia, surgery, neonatology, nursing, and pharmacy.

   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:

   - Severity of the procedure (invasiveness, anesthesia time, and amount of tissue manipulation)
   - Airway management postoperatively (expected extended intubation, short-term intubation, or not intubated)
   - Desired level of sedation postoperatively

   The goal of postoperative pain management is preventive analgesia rather than trying to "catch up" after the 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.

   a. Opioids

   Opioids (Table. 70.4) are the mainstay for postoperative analgesia after moderate/major surgery, if regional anesthesia is not feasible. During the immediate postoperative period, opioids are most effective when scheduled at regular intervals or continuously. As needed (PRN) dosing can lead to a delay in treatment, a missed dose, or fluctuating drug levels that do not provide adequate pain relief.

   Morphine and fentanyl provide a similar degree of analgesia. Morphine has a greater sedative effect and less risk of chest wall rigidity. Tolerance on long use is less common. Morphine is associated with a greater risk of hypotension. Fentanyl has a faster onset, and shorter duration of action. Effect on gastrointestinal (GI) motility, hemodynamics, and urinary retention are less common.

   Elimination of opioids may be influenced by enterohepatic recirculation and elevated plasma concentrations; therefore, monitoring for side effects should be maintained for several hours after opioids are discontinued.

   Reversal of opioid

   Naloxone is used as an emergency medication, mostly for reversal of respiratory depression. Except in emergency, Naloxone should be used in slowly escalating doses, in increments of 0.05 mg/kg until the side effects are reversed.

   Chest wall and laryngeal rigidity must be managed with airway management equipment and a neuromuscular blocker agent if unable to ventilate, these are not immediately reversed by naloxone administration.

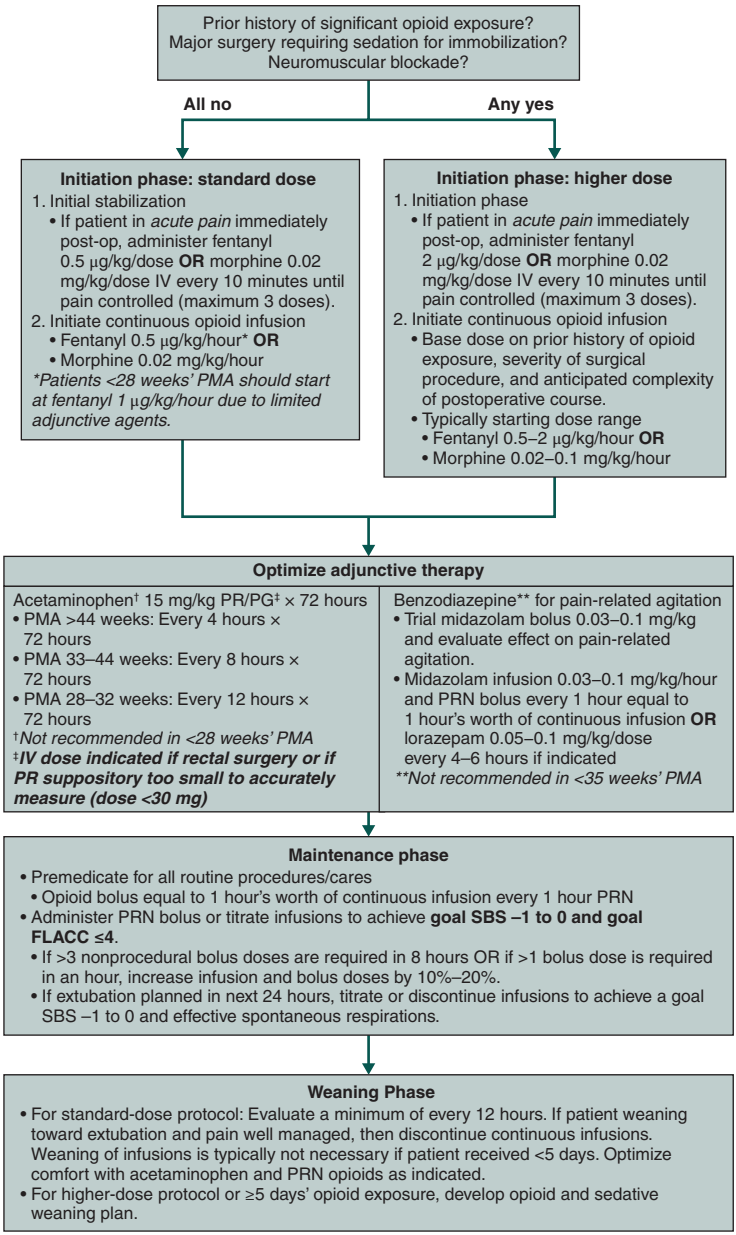

Figure 70.2. Postoperative pain management algorithm for moderate/major surgery. FLACC, Faces, Legs, Activity, Cry, Consolability Scale; IV, intravenous; post-op, postoperation; PG, per gastric; PMA, postmenstrual age; PR, per rectum; PRN, as needed; SBS, State Behavioral Scale.

Table 70.4. 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 with permission from Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924.

Opioid tolerance. Prolonged opioid administration may lead to tolerance; pain recurs, sleep is disrupted, and an infant may exhibit a high-pitched cry or tremors during handling. Infants are not able to interact with their parent or caregiver. In this case, there is a need to increase the dose, typically in increments of 10% to 20%, to relieve symptoms.

Opioid and sedative weaning. Prolonged use of opioids can result in iatrogenic physical dependence.

Neonates exposed to continuous or higher doses of opioids for >5 days are at an 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. Opioids are weaned slowly with a goal to avoid unsafe symptoms of withdrawal (Chapter 12).

Opioids are weaned by a percentage of the original dose the patient is on, typically 10% decrease. For example, a patient receiving morphine 0.2 mg/kg/hour would wean by 10% or 0.02 mg/kg at each wean. The weaning frequency is every 8 to 12 hours for moderate lengths of exposure and every 24 to 48 hours for longer lengths of exposure. Weaning is individualized by using a withdrawal assessment tool such as the Finnegan Neonatal Abstinence Scoring. Nonpharmacologic comfort methods have been used to support infants undergoing withdrawal. In general, feeding should be encouraged. Withdrawal assessment is continued until opioids have been discontinued for a minimum of 72 hours and there is no evidence of withdrawal symptoms.

b. Acetaminophen

Acetaminophen is often used as an adjunct to regional anesthetics and opioids for postoperative pain management. The administration of acetaminophen for procedural pain management has not been established as effective.

Acetaminophen decreases cumulative opioid exposure in postoperative neonates. It can be administered immediately after surgery as an adjunct when indicated. Acetaminophen is not recommended if PMA <28 weeks due to inadequate pharmacokinetic data. It should be used with caution in patients with hepatic impairment. Rectal administration route is avoided in patients following anorectal procedure, enteral route may be used if there is adequate GI motility. Intravenous acetaminophen is used when both rectal and enteral routes are not optimal.

In the postoperative period after PDA ligation, opioids have to be used with caution as they are associated with a risk of both hypertension and hypotension. Acetaminophen remains the preferred drug to be used in such cases.

c. Sedative as adjunct

Benzodiazepines and other sedatives are often given in conjunction with pain medication. (Table 70.5)

- **Manage agitation.** Sedatives do not provide analgesia but may be given to manage agitation, example during mechanical ventilation.
- **Combine with opioids.** Sedatives postoperatively can be administered in combination with analgesia to reduce opioid requirements and

Table 70.5. Benzodiazepines

Drug	Advantages	Disadvantages
	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 with permission from Hall RW, Anand KJ. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924.

associated adverse effects. Sedatives and opioids with sedative properties (fentanyl, magnesium sulfate) 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.

- **Caution in preterm infants.** In babies <35 weeks' PMA there is a potential for neurotoxicity including the induction of myoclonic jerking movements. 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. Studies on the use of midazolam infusions in preterm neonates have shown conflicting results on neurologic outcomes. Due to these results, the use of midazolam infusions in preterm neonates cannot currently be recommended.

- **Dexmedetomidine**

The *sedative and anxiolytic* effects in adults have been found to be beneficial—easy arousal *without respiratory depression*, less frequent hypertension and tachycardia, and shorter duration of mechanical ventilation. Although off-label use in neonatal care units is becoming increasingly common, its effectiveness and safety profile as a sedative and analgesic in neonates has not been systematically reviewed.

d. Epidural analgesia

Epidural analgesia is the administration of analgesics and local anesthetic agents into the epidural space (as a single, intermittent bolus, or continuous infusion).

Advantage of epidural anesthesia is 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 repair.

A dedicated team should manage the continuous infusion and any bolus requirements until the epidural is discontinued. Monitoring include cardiorespiratory monitoring, sensory responses, pain assessment, and urine output. Potential complications include accidental injection of local anesthetic agents into the intravascular system, venous air embolism, local or systemic infection, and meningitis.

V. CONCLUSION. Anticipatory planning before painful, invasive procedures optimizes pain management.

Research on the safety and efficacy of measures for pain management is an ongoing process.

A summary of the pharmacologic agents commonly used are listed in Table 70.6

Table 70.6 Commonly Used Measures for Pain Management in Neonates

Name of the Drug	Dose and Route
Oral sucrose	24% solution (0.2 mL/kg), 2 minutes before procedure
Atropine	0.01–0.02 mg/kg
Fentanyl	2 µg/kg, 5 minutes before procedure, infusion 1–3 µg/kg/minute
Succinylcholine	2 mg/kg
Rocuronium	0.5–1 mg/kg
Midazolam	0.1 mg/kg
Propofol	1–2.5 mg/kg
Ketamine	1–2 mg/kg
Remifentanil	2 µg/kg, 0.25 µg/kg/minute
Intranasal midazolam	0.2 mg/kg, 2 doses
Morphine	Loading dose 25–50 µg/kg over 1 hour followed by maintenance at <10 µg/kg/hour
Dexmedetomidine	0.05–1.0 µg/kg/hour
Intravenous paracetamol	24–30 weeks: 20–30 mg/kg/day 31–36 weeks: 35–50 mg/kg/day 37–42 weeks: 50–60 mg/kg/day 1–3 months postnatal: 60–75 mg/kg/day

Suggested Readings

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