FETAL AND NEONATAL MEDICINE

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CHAPTER 58

Assessment of the Mother, Fetus, and Newborn

ASSESSMENT OF THE MOTHER

Pregnancies associated with perinatal morbidity or mortality are considered high risk. Identification of high-risk pregnancies is essential to the care of the infant because they may result in intrauterine fetal death, intrauterine growth restriction (IUGR), congenital anomalies, excessive fetal growth, birth asphyxia and trauma, prematurity (birth at <38 weeks) or postmaturity (birth at ≥42 weeks), neonatal disease, or long-term risks of cerebral palsy, intellectual disability, and chronic sequelae of neonatal intensive care. Ten percent to 20% of women may be high risk at some time during their pregnancy. Although some obstetric complications are first seen during labor and delivery and cannot be predicted, more than 50% of perinatal mortality and morbidity results from problems identified before delivery as high risk. After a high-risk pregnancy is identified, measures can be instituted to prevent complications, provide intensive fetal surveillance, and initiate appropriate treatments of the mother and fetus.

A history of previous premature birth, intrauterine fetal death, multiple gestation, IUGR, congenital malformation, explained or unexplained neonatal death (e.g., group B streptococcal sepsis), birth trauma, preeclampsia, gestational diabetes, grand multipara status (five or more pregnancies), or cesarean section is associated with additional risk in subsequent pregnancies.

Pregnancy complications that increase the risk of a poor outcome can be secondary to maternal or fetal causes or both. Complications include placenta previa; abruptio placentae; preeclampsia; diabetes; oligohydramnios or polyhydramnios; multiple gestation; blood group sensitization; abnormal levels of unconjugated estriols, chorionic gonadotropin, or alpha-fetoprotein; abnormal fetal ultrasound; hydrops fetalis; maternal trauma or surgery; abnormal fetal presentation (breech); exposure to prescribed or illicit drugs; prolonged labor; cephalopelvic disproportion; prolapsed cord; fetal distress; prolonged or premature rupture of membranes; short cervical length (<25 mm) and the presence of fetal fibronectin in cervical secretions at less than 35 weeks' gestation (a predictor of preterm labor); cervical infections and vaginosis; and congenital infections, including rubella, cytomegalovirus, herpes simplex, human immunodeficiency virus (HIV), toxoplasmosis, syphilis, and gonorrhea.

Maternal medical complications associated with increased risk of maternal and fetal morbidity and mortality include diabetes, chronic hypertension, congenital heart disease (especially with right-to-left shunting and Eisenmenger complex), glomerulonephritis, collagen vascular disease (especially systemic lupus erythematosus with or without antiphospholipid antibodies), lung disease (cystic fibrosis), severe anemia (sickle cell anemia), hyperthyroidism, myasthenia gravis, idiopathic thrombocytopenic purpura, inborn errors of metabolism (maternal phenylketonuria), and malignancy.

Obstetric complications often are associated with increased fetal or neonatal risk. Vaginal bleeding in the first trimester or early second trimester may be caused by a threatened or actual spontaneous abortion and is associated with increased risk of congenital malformations or chromosomal disorders. Painless vaginal bleeding that is not associated with labor and occurs in the late second or (more likely) third trimester often is the result of **placenta previa**. Bleeding develops when the placental mass overlies the internal cervical os; this may produce maternal hemorrhagic shock, necessitating transfusions. Bleeding also may result in premature delivery. Painful vaginal bleeding is often the result of retroplacental hemorrhage or **placental abruption**. Associated findings may be advanced maternal age and parity, maternal chronic hypertension, maternal cocaine use, preterm rupture of membranes, polyhydramnios, twin gestation, and preeclampsia. Fetal asphyxia ensues as the retroplacental hematoma causes placental separation that interferes with fetal oxygenation. Both types of bleeding are associated with fetal blood loss. Neonatal anemia may be more common with placenta previa.

Abnormalities in the volume of amniotic fluid, resulting in oligohydramnios or polyhydramnios, are associated with increased fetal and neonatal risk. **Oligohydramnios** (amniotic ultrasound fluid index ≤2 cm) is associated with IUGR and major congenital anomalies, particularly of the fetal kidneys, and with chromosomal syndromes. Bilateral renal agenesis results in diminished production of amniotic fluid and a specific deformation syndrome **(Potter syndrome)**, which includes clubfeet, characteristic compressed facies, low-set ears, scaphoid abdomen, and diminished chest wall size accompanied by pulmonary hypoplasia and, often, pneumothorax. Uterine compression in the absence of amniotic fluid retards lung growth, and patients with this condition die of respiratory failure rather than renal insufficiency. Twin-to-twin transfusion syndrome (donor) and complications from amniotic fluid leakage also are associated

with oligohydramnios. Oligohydramnios increases the risk of fetal distress during labor (meconium-stained fluid and variable decelerations); the risk may be reduced by saline amnioinfusion during labor.

Polyhydramnios may be acute and associated with premature labor, maternal discomfort, and respiratory compromise. More often, polyhydramnios is chronic and is associated with diabetes, immune or nonimmune hydrops fetalis, multiple gestation, trisomy 18 or 21, and major congenital anomalies. Anencephaly, hydrocephaly, and meningomyelocele are associated with reduced fetal swallowing of amniotic fluid. Esophageal and duodenal atresia as well as cleft palate interfere with swallowing and gastrointestinal fluid dynamics. Additional causes of polyhydramnios include Werdnig-Hoffmann and Beckwith-Wiedemann syndromes, conjoined twins, chylothorax, cystic adenomatoid lung malformation, diaphragmatic hernia, gastroschisis, sacral teratoma, placental chorioangioma, and myotonic dystrophy. **Hydrops fetalis** may be a result of Rh or other blood group incompatibilities and anemia caused by intrauterine hemolysis of fetal erythrocytes by maternal IgG-sensitized antibodies crossing the placenta. Hydrops is characterized by fetal edema, ascites, hypoalbuminemia, and congestive heart failure. Causes of **nonimmune hydrops** include fetal arrhythmias (supraventricular tachycardia, congenital heart block), fetal anemia (bone marrow suppression, nonimmune hemolysis, or twin-to-twin transfusion), severe congenital malformation, intrauterine infections, congenital neuroblastoma, inborn errors of metabolism (storage diseases), fetal hepatitis, nephrotic syndrome, and pulmonary lymphangiectasia. Twin-to-twin transfusion syndrome (recipient) also may be associated with polyhydramnios. Polyhydramnios is often the result of unknown causes. If severe, polyhydramnios may be managed with bed rest, indomethacin, or serial amniocenteses.

Premature rupture of the membranes, which occurs in the absence of labor, and **prolonged rupture of the membranes** (>24 hours) are associated with an increased risk of maternal or fetal infection (chorioamnionitis) and preterm birth. In the immediate newborn period, group B streptococcus and *Escherichia coli* are the two most common pathogens associated with sepsis. *Listeria monocytogenes* is a less common cause. *Mycoplasma hominis, Ureaplasma urealyticum*, *Chlamydia trachomatis*, and anaerobic bacteria of the vaginal flora also have been implicated in infection of the amniotic fluid. Infection with community-acquired methicillin-resistant *Staphylococcus aureus* must be considered for infants with skin infections or with known exposures. The risk of serious fetal infection increases as the duration between rupture and labor (latent period) increases, especially if the period is greater than 24 hours. Intrapartum antibiotic therapy decreases the risk of neonatal sepsis.

Multiple gestations are associated with increased risk resulting from polyhydramnios, premature birth, IUGR, abnormal presentation (breech), congenital anomalies (intestinal atresia, porencephaly, and single umbilical artery), intrauterine fetal demise, birth asphyxia, and twin-to-twin transfusion syndrome. **Twin-to-twin transfusion syndrome** is associated with a high mortality and is seen only in monozygotic twins who share a common placenta and have an arteriovenous connection between their circulations. The fetus on the arterial side of the shunt serves as the blood donor, resulting in fetal anemia, growth retardation, and oligohydramnios for this fetus. The recipient, or venous-side twin, is larger or discordant in size, is plethoric and polycythemic, and may show polyhydramnios. Weight differences of 20% and hemoglobin differences of 5 g/dL suggest the diagnosis. Ultrasonography in the second trimester reveals discordant amniotic fluid volume with oliguria/oligohydramnios and hypervolemia/polyuria/polyhydramnios with a distended bladder, with or without hydrops and heart failure. Treatment includes attempts to ablate the arteriovenous connection (using a laser). The birth order of twins also affects morbidity by increasing the risk of the second-born twin for breech position, birth asphyxia, birth trauma, and respiratory distress syndrome.

Overall, twinning is observed in 1 of 80 pregnancies; 80% of all twin gestations are dizygotic twins. The diagnosis of the type of twins can be determined by placentation, sex, fetal membrane structure, and, if necessary, tissue and blood group typing or DNA analysis.

Toxemia of pregnancy, or **preeclampsia/eclampsia**, is a disorder of unknown but probably vascular etiology that may lead to maternal hypertension, uteroplacental insufficiency, IUGR, intrauterine asphyxia, maternal seizures, and maternal death. Toxemia is more common in nulliparous women and in women with twin gestation, chronic hypertension, obesity, renal disease, positive family history of toxemia, or diabetes mellitus. A subcategory of preeclampsia, the *HELLP* syndrome (**h**emolysis, **e**levated **l**iver enzyme levels, **l**ow **p**latelets), is more severe and is often associated with a fetal inborn error of fatty acid oxidation (long-chain hydroxyacyl–coenzyme A dehydrogenase of the trifunctional protein complex).

FETUS AND NEWBORN

The late fetal–early neonatal period has the highest mortality rate of any age interval. **Perinatal mortality** refers to fetal deaths occurring from the 20th week of gestation until the 28th day after birth and is expressed as number of deaths per 1,000 live births. Intrauterine fetal death accounts for 40-50% of the perinatal mortality rate. Such infants, defined as **stillborn**, are born without a heart rate and are apneic, limp, pale, and cyanotic. Many stillborn infants exhibit evidence of maceration; pale, peeling skin; corneal opacification; and soft cranial contents.

Mortality rates around the time of birth are expressed as number of deaths per 1,000 live births. The **neonatal mortality rate** includes all infants dying during the period from after birth to the first 28 days of life. Modern neonatal intensive care allows many newborns with life-threatening diseases to survive the neonatal period, only to die of their original diseases or of complications of therapy after 28 days of life. This delayed mortality and mortality caused by acquired illnesses occur during the **postneonatal period**, which begins after 28 days of life and extends to the end of the first year of life.

The **infant mortality rate** encompasses the neonatal and the postneonatal periods. In the United States, it declined to 5.8:1,000 in 2015. The rate for African American infants was approximately 11.0:1,000. The most common causes of perinatal and neonatal death are listed in Table 58.1. Overall, congenital anomalies and diseases of the premature infant are the most significant causes of neonatal mortality.

Low birth weight (LBW) infants, defined as infants having birth weights of less than 2,500 g, represent a disproportionately large component of the neonatal and infant mortality rates. Although LBW infants make up only about 6-7% of all births, they account for more than 70% of neonatal deaths. IUGR is the

TABLE 58.1 Major Causes of Perinatal and Neonatal Mortality
FETUS
Abruptio placentae
Chromosomal anomalies
Congenital malformations (heart, CNS, renal)
Hydrops fetalis
Intrauterine asphyxia*
Intrauterine infection*
Maternal underlying disease (chronic hypertension, autoimmune disease, diabetes mellitus)
Multiple gestation*
Placental insufficiency*
Umbilical cord accident
PRETERM INFANT
Respiratory distress syndrome/bronchopulmonary dysplasia (chronic lung disease)*
Severe immaturity*
Congenital anomalies
Infection
Intraventricular hemorrhage*
Necrotizing enterocolitis
FULL-TERM INFANT
Birth asphyxia*
Birth trauma
Congenital anomalies*
Infection*
Macrosomia
Meconium aspiration pneumonia
Persistent pulmonary hypertension

**Common.*
CNS, Central nervous system.

most common cause of LBW in developing countries, whereas prematurity is the cause in developed countries.

Very low birth weight (VLBW) infants, weighing less than 1,500 g at birth, represent about 1% of all births but account for 50% of neonatal deaths. Compared with infants weighing 2,500 g or more, LBW infants are 40 times more likely to die in the neonatal period; VLBW infants have a 200-fold higher risk of neonatal death. The LBW rate has not improved in recent years and is one of the major reasons that the U.S. infant mortality rate is high compared with other large, modern, industrialized countries.

Maternal factors associated with a LBW caused by premature birth or IUGR include a previous LBW birth, low socioeconomic status, low level of maternal education, no antenatal care, maternal age younger than 16 years or older than 35 years, short interval between pregnancies, cigarette smoking, alcohol and illicit drug use, physical (excessive standing or walking) or psychological (poor social support) stresses, unmarried status, low prepregnancy weight (<45 kg), poor weight gain during pregnancy (<10 lb), and African American race. LBW and VLBW rates for African American women are twice the rates for white women. The neonatal and infant mortality rates are nearly twofold higher among African American infants. These racial differences are only partly explained by poverty.

ASSESSMENT OF THE FETUS

Fetal size can be determined accurately by ultrasound techniques. **Fetal growth** can be assessed by determining the fundal height of the uterus through bimanual examination of the gravid abdomen. Ultrasound measurements of the fetal biparietal diameter, femur length, and abdominal circumference are used to estimate fetal growth. A combination of these measurements predicts fetal weight. Deviations from the normal fetal growth curve are associated with high-risk conditions.

IUGR is present when fetal growth stops and, over time, declines to less than the 5th percentile of growth for gestational age or when growth proceeds slowly, but absolute size remains less than the 5th percentile. Growth restriction may result from fetal conditions that reduce the innate growth potential, such as fetal rubella infection, primordial dwarfing syndromes, chromosomal abnormalities, and congenital malformation syndromes. Reduced fetal production of insulin and insulin-like growth factor I is associated with fetal growth restriction. Placental causes of IUGR include villitis (congenital infections), placental tumors, chronic abruptio placentae, twin-to-twin transfusion syndrome, and placental insufficiency. Maternal causes include severe peripheral vascular diseases that reduce uterine blood flow (chronic hypertension, diabetic vasculopathy, and preeclampsia/eclampsia), reduced nutritional intake, alcohol or drug abuse, cigarette smoking, and uterine constraint (noted predominantly in mothers of small stature with a low prepregnancy weight) and reduced weight gain during pregnancy. The outcome of IUGR depends on the cause of the reduced fetal growth and the associated complications after birth (Table 58.2). Fetuses subjected to chronic intrauterine hypoxia as a result of uteroplacental insufficiency are at an increased risk for the comorbidities of birth asphyxia, polycythemia, and hypoglycemia. Fetuses with reduced tissue mass due to chromosomal, metabolic, or multiple congenital anomaly syndromes have poor outcomes based on the prognosis for the particular syndrome. Fetuses born to small mothers and fetuses of mothers with poor nutritional intake usually show catch-up growth after birth.

Fetal size does not always correlate with functional or structural maturity. Determining **fetal maturity** is crucial when making a decision to deliver a fetus because of fetal or maternal disease. Fetal gestational age may be determined accurately on the basis of a correct estimate of the last menstrual period. Clinically relevant landmark dates can be used to determine gestational age; the first audible heart tones by fetoscope are detected at 18-20 weeks (12-14 weeks by Doppler methods), and quickening of fetal movements usually is perceived at 18-20 weeks. However, it is not always possible to determine fetal maturity by such dating, especially in a high-risk situation, such as preterm labor or a diabetic pregnancy.

Surfactant, a combination of surface-active phospholipids and proteins, is produced by the maturing fetal lung and eventually is secreted into the amniotic fluid. The amount of surfactant in amniotic fluid is a direct reflection of surface-active material in the fetal lung and can be used to predict the presence or absence of **pulmonary maturity**. Because phosphatidylcholine, or lecithin, is a principal component of

TABLE 58.2 Problems of Intrauterine Growth Restriction and Small for Gestational Age

PROBLEM*	PATHOGENESIS
Intrauterine fetal demise	Placental insufficiency, hypoxia, acidosis, infection, lethal anomaly
Temperature instability	Cold stress, ↓ fat stores, hypoxia, hypoglycemia
Perinatal asphyxia	↓ Uteroplacental perfusion during labor with or without chronic fetal hypoxia-acidosis, meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores; ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, relatively large brain
Polycythemia-hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/ hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformations
Pulmonary hemorrhage	Hypothermia, polycythemia, hypoxia

**Other problems are common to the gestational age–related risks of prematurity if born before 37 weeks.*
Modified from Carlo WA. The high-risk infant. In: Kliegman RM, Stanton BF, St. Geme JW, et al., eds. Nelson Textbook of Pediatrics. *19th ed. Philadelphia: Elsevier Science; 2011.*

surfactant, the determination of lecithin in amniotic fluid is used to predict a mature fetus. Lecithin concentration increases with increasing gestational age, beginning at 32-34 weeks.

Methods used to assess **fetal well-being** before the onset of labor are focused on identifying a fetus at risk for asphyxia or a fetus already compromised by uteroplacental insufficiency. The **oxytocin challenge test** simulates uterine contractions through an infusion of oxytocin sufficient to produce three contractions in a 10-minute period. The development of periodic fetal bradycardia out of phase with uterine contractions (late deceleration) is a positive test result and predicts an at-risk fetus.

The **nonstress test** examines the heart rate response to fetal body movements. Heart rate increases of more than 15 beats/min lasting 15 seconds are reassuring. If two such episodes occur in 30 minutes, the test result is considered reactive (versus nonreactive), and the fetus is not at risk. Additional signs of fetal well-being are fetal breathing movements, gross body movements, fetal tone, and the presence of amniotic fluid pockets more than 2 cm in size, detected by ultrasound. The **biophysical profile** combines the nonstress test with these four parameters and offers the most accurate fetal assessment.

Doppler examination of the fetal aorta or umbilical arteries permits identification of decreased or reversed diastolic blood flow associated with increased peripheral vascular resistance, fetal hypoxia with acidosis, and placental insufficiency. **Cordocentesis** (percutaneous umbilical blood sampling) can provide fetal blood for Pao_2, pH, lactate, and hemoglobin measurements to identify a hypoxic, acidotic, or anemic fetus that is at risk for intrauterine fetal demise or birth asphyxia. Cordocentesis also can be used to determine fetal blood type, platelet count, microbial testing, antibody titer, and rapid karyotype.

In a high-risk pregnancy, the fetal heart rate should be monitored continuously during labor, as should uterine contractions. Fetal heart rate abnormalities may indicate baseline tachycardia (>160 beats/min as a result of anemia, β-sympathomimetic drugs, maternal fever, hyperthyroidism, arrhythmia, or fetal distress), baseline **bradycardia** (<120 beats/min as a result of fetal distress, complete heart block, or local anesthetics), or reduced beat-to-beat variability (flattened tracing resulting from fetal sleep, tachycardia, atropine, sedatives, prematurity, or fetal distress). Periodic changes of the heart rate relative to uterine pressure help determine the presence of hypoxia and acidosis caused by uteroplacental insufficiency or maternal hypotension (late or type II decelerations) or by umbilical cord compression (variable decelerations). In the presence of severe decelerations (late or repeated prolonged variable), a fetal scalp blood gas level should be obtained to assess **fetal acidosis**. A scalp pH of less than 7.20 indicates fetal hypoxic compromise. A pH between 7.20 and 7.25 is in a borderline zone and warrants repeat testing.

Fetal anomalies may be detected by ultrasonography. Emphasis should be placed on visualization of the genitourinary tract; the head (for anencephaly or hydrocephaly), neck (for thickened nuchal translucency), and back (for spina bifida); skeleton; gastrointestinal tract; and heart. Four-chamber and great artery views are required for detection of heart anomalies. **Chromosomal anomaly syndromes** are often associated with an abnormal "quadruple test" (low unconjugated estriols, low maternal serum alpha-fetoprotein levels, high inhibin A, and elevated placental chorionic gonadotropin levels). Fetal genetic and chromosomal disorders can also be detected by analyzing free fetal DNA that is present in the maternal circulation. If a fetal abnormality is detected, fetal therapy or delivery with therapy in the neonatal intensive care unit may be lifesaving.

ASSESSMENT OF THE NEWBORN

The approach to the birth of an infant requires a detailed history (Table 58.3). Knowing the mother's risk factors enables the delivery room team to anticipate problems that may occur after birth. The history of a woman's labor and delivery can reveal events that might lead to complications affecting either the mother or the neonate, even when the pregnancy was previously considered low risk. Anticipating the need to resuscitate a newborn as a result of fetal distress increases the likelihood of successful resuscitation.

The **transition from fetal to neonatal physiology** occurs at birth. Oxygen transport across the placenta results in a gradient between the maternal and fetal Pao_2. Although fetal oxygenated blood has a low Pao_2 level compared with that of adults and infants, the fetus is not anaerobic. Fetal oxygen uptake and consumption are similar to neonatal rates, even though the thermal environments and activity levels of fetuses and neonates differ. The oxygen content of fetal blood is almost equal to the oxygen content in older infants and children because fetal blood has a much higher concentration of hemoglobin.

Fetal hemoglobin (two alpha and two gamma chains) has a higher affinity for oxygen than adult hemoglobin, facilitating oxygen transfer across the placenta. The fetal hemoglobin-oxygen dissociation curve is shifted to the left of the adult curve (Fig. 58.1); at the same Pao_2 level, fetal hemoglobin is more saturated than adult hemoglobin. Because fetal hemoglobin functions on the steep, lower end of the oxygen saturation curve (Pao_2,

TABLE 58.3 Components of the Perinatal History

DEMOGRAPHIC SOCIAL INFORMATION
Age
Race
Sexually transmitted infections, hepatitis, AIDS
Illicit drugs, cigarettes, ethanol, cocaine, opiates
Immune status (syphilis, rubella, hepatitis B, HIV, blood group)
Occupational exposure
PAST MEDICAL DISEASES
Chronic hypertension
Heart disease
Diabetes mellitus
Thyroid disorders
Hematological/malignancy
Collagen-vascular disease (SLE)
Genetic history—inborn errors of metabolism, bleeding, jaundice
Drug therapy
PRIOR PREGNANCY
Abortion/stillbirths
Intrauterine fetal demise
Congenital malformation
Incompetent cervix
Birth weight
Prematurity
Twins
Blood group sensitization/neonatal jaundice
Hydrops
Infertility
PRESENT PREGNANCY
Current gestational age
Method of assessing gestational age
Fetal surveillance (OCT, NST, biophysical profile)
Ultrasonography (anomalies, hydrops)
Amniotic fluid analysis (L/S ratio)
Oligohydramnios-polyhydramnios
Vaginal bleeding
Preterm labor
Premature (prolonged) rupture of membranes (duration)
Preeclampsia
Urinary tract infection
Colonization status (herpes simplex, group B streptococcus)
Medications/drugs
Acute medical illness/exposure to infectious agents
Fetal therapy
LABOR AND DELIVERY
Duration of labor
Presentation—vertex, breech
Vaginal versus cesarean section
Spontaneous labor versus augmented or induced with oxytocin (Pitocin)
Forceps delivery
Presence of meconium-stained fluid
Maternal fever/amnionitis
Fetal heart rate patterns (distress)
Scalp pH
Maternal analgesia, anesthesia
Nuchal cord
Apgar score/methods of resuscitation
Gestational age assessment
Growth status (AGA, LGA, SGA)

AGA, Average for gestational age; *AIDS*, acquired immunodeficiency syndrome; *HIV*, human immunodeficiency virus; *LGA*, large for gestational age; *L/S*, lecithin-to-sphingomyelin ratio; *NST*, nonstress test; *OCT*, oxytocin challenge test; *SGA*, small for gestational age; *SLE*, systemic lupus erythematosus.

20-30 mm Hg), however, oxygen unloading to the tissue is not deficient. In contrast, at the higher oxygen concentrations present in the placenta, oxygen loading is enhanced. In the last trimester, fetal hemoglobin production begins to decrease as adult hemoglobin production begins to increase, becoming the only hemoglobin available to the infant by 3-6 months of life. At this time, the fetal hemoglobin dissociation curve has shifted to the adult position.

A portion of well-oxygenated umbilical venous blood returning to the heart from the placenta perfuses the liver. The remainder bypasses the liver through a shunt (the **ductus venosus**) and enters the inferior vena cava. This oxygenated blood in the vena cava constitutes 65-70% of venous return to the right atrium. The crista dividens in the right atrium directs one third of this blood across the patent foramen ovale to the left atrium, where it subsequently is pumped to the coronary, cerebral, and upper extremity circulations by the left ventricle. Venous return from the upper body combines with the remaining two thirds of the vena caval blood in the right atrium and is directed to the right ventricle. This mixture of venous low-oxygenated blood from the upper and lower body enters the pulmonary artery. Only 8-10% of it is pumped to the pulmonary circuit; the remaining 80-92% of the right ventricular output bypasses the lungs through a **patent ductus arteriosus** and enters the descending aorta. The amount of blood flowing to the pulmonary system is low because vasoconstriction produced by medial muscle hypertrophy of the pulmonary arterioles and fluid in the fetal lung increases resistance to blood flow. Pulmonary artery tone also responds to hypoxia, hypercapnia, and acidosis with vasoconstriction, a response that may increase pulmonary vascular resistance further. The ductus arteriosus remains patent in the fetus because of low Pa_{O_2} levels and dilating prostaglandins. In utero, the right ventricle is the dominant ventricle, pumping 65% of the combined ventricular output,

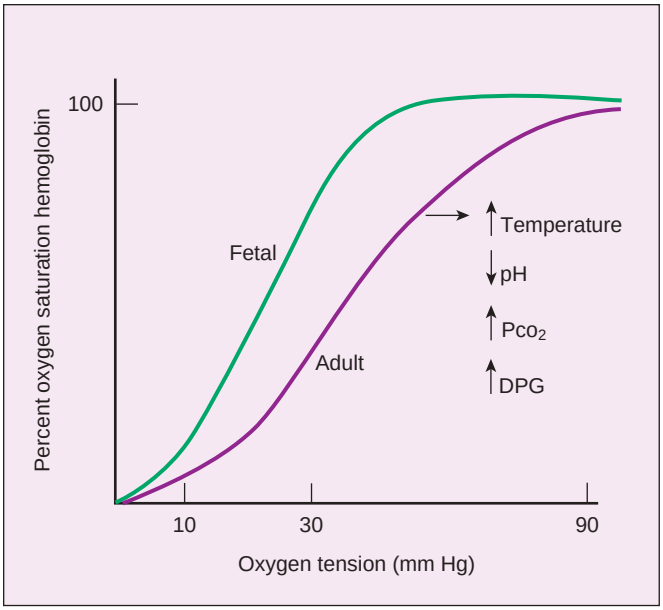

FIGURE 58.1 Hemoglobin-oxygen dissociation curves. The position of the adult curve depends on the binding of adult hemoglobin to 2,3-diphosphoglycerate (DPG), temperature, P_{CO_2}, and hydrogen ion concentration (pH).

which is a high volume (450 mL/kg/min) compared with that pumped by an older infant's right ventricle (200 mL/kg/min).

The **transition of the circulation**, occurring between the fetal and neonatal periods, involves the removal of the low-resistance circulation of the placenta, the onset of breathing, reduction of pulmonary arterial resistance, and closure of in utero shunts. Clamping the umbilical cord eliminates the low-pressure system of the placenta and increases systemic blood pressure. Decreased venous return from the placenta decreases right atrial pressure. As breathing begins, air replaces lung fluid, maintaining the functional residual capacity. Fluid leaves the lung, in part, through the trachea; it is either swallowed or squeezed out during vaginal delivery. The pulmonary lymphatic and venous systems reabsorb the remaining fluid.

Most normal infants require little pressure to spontaneously open the lungs after birth (5-10 cm H_2O). With the onset of breathing, pulmonary vascular resistance decreases, partly a result of the mechanics of breathing and partly a result of the elevated arterial oxygen tensions. The increased blood flow to the lungs increases the volume of pulmonary venous blood returning to the left atrium; left atrial pressure now exceeds right atrial pressure, and the foramen ovale closes. As the flow through the pulmonary circulation increases and arterial oxygen tensions rise, the ductus arteriosus begins to constrict. In a term infant, this constriction functionally closes the ductus arteriosus within 1 day after birth. A permanent closure requires thrombosis and fibrosis, a process that may take several weeks. In a premature infant, the ductus arteriosus is less sensitive to the effects of oxygen; if circulating levels of vasodilating prostaglandins are elevated, the ductus arteriosus may remain patent. This patency is a common problem in a premature infant with respiratory distress syndrome.

Ventilation, oxygenation, and normal pH and P_{CO_2} levels immediately reduce pulmonary artery vasoconstriction by causing smooth muscle relaxation. Remodeling of the medial muscle hypertrophy begins at birth and continues for the next 3 months, resulting in a further reduction of pulmonary vascular resistance and a further increase of pulmonary blood flow. Persistence or aggravation of pulmonary vasoconstriction caused by acidosis, hypoxia, hypercapnia, hypothermia, polycythemia, asphyxia, shunting of blood from the lungs, or pulmonary parenchymal hypoplasia results in **persistent pulmonary hypertension of the newborn (PPHN)**. Failure to replace pulmonary alveolar fluid completely with air can lead to respiratory distress **(transient tachypnea of the newborn)**.

Routine Delivery Room Care and Resuscitation

Silver nitrate (1%) instilled into both eyes without being washed out is an indicated effective therapy for the prevention of neonatal gonococcal ophthalmia, which can result in severe panophthalmitis and subsequent blindness. Silver nitrate may produce a chemical conjunctivitis with a mucopurulent discharge and is not effective against *C. trachomatis*. Many hospitals use erythromycin drops to prevent neonatal gonococcal and chlamydial eye disease.

Bacterial colonization of a newborn may begin in utero if the fetal membranes have been ruptured. Most infants undergo colonization after birth and acquire the bacteria present in the mother's genitourinary system, such as group B streptococci, staphylococci, *E. coli*, and clostridia. Antiseptic skin or cord care is routine in most nurseries to prevent the spread of pathological bacteria from one infant to another and to prevent disease in the individual infant. Staphylococcal bullous impetigo, omphalitis, diarrhea, and systemic disease may result from colonization with virulent *S. aureus*. Triple antibiotic ointment (polymyxin B, neomycin, and bacitracin) or bacitracin may be applied to the umbilical cord to reduce its colonization with gram-positive bacteria. Epidemics of *S. aureus* nursery infections are managed with strict infectious disease control measures (cohorting, hand washing, and monitoring for colonization).

Vitamin K prophylaxis (intramuscular) should be given to all infants to prevent hemorrhagic disease of the newborn. Before discharge, infants should receive the hepatitis B vaccine and be screened for various diseases (Tables 58.4 and 58.5).

Fetal or neonatal hypoxia, hypercapnia, poor cardiac output, and a metabolic acidosis can result from numerous conditions affecting the fetus, the placenta, or the mother. Whether in utero or after birth, asphyxia-caused **hypoxic-ischemic brain injury** is the result of reduced gaseous exchange through the placenta or through the lungs. Asphyxia associated with severe bradycardia or cardiac insufficiency reduces or eliminates tissue blood flow, resulting in ischemia. The fetal and neonatal circulatory systems respond to reduced oxygen availability by shunting the blood preferentially to the brain, heart, and adrenal glands and away from the intestine, kidneys, lungs, and skin.

Metabolic acidosis during asphyxia is caused by the combined effects of poor cardiac output secondary to hypoxic depression of myocardial function, systemic hypoxia, and tissue anaerobic metabolism. With severe or prolonged intrauterine or neonatal asphyxia, multiple vital organs are affected (Table 58.6).

Many conditions that contribute to **fetal or neonatal asphyxia** are the same medical or obstetric problems associated with high-risk pregnancy (Table 58.7). Maternal diseases that interfere with uteroplacental perfusion (chronic hypertension, preeclampsia, and diabetes mellitus) place the fetus at risk for intrauterine asphyxia. Maternal epidural anesthesia and the development of the vena caval compression syndrome may produce maternal

TABLE 58.4 Core Disorders Recommended for Screening by American College of Medical Genetics

DISORDER	ACRONYM	PRIMARY MARKER
METABOLIC DISORDERS DETECTED USING TANDEM MASS SPECTROMETRY		
Organic Acid Disorders		
Beta-ketothiolase deficiency (mitochondrial acetoacetyl coenzyme A [CoA] thiolase deficiency)	BKT	C5:1/C5OH
Cobalamin defects A, B	CBL (A,B)	C3
Isovaleric academia*	IVA	C5
Glutaric aciduria I	GA-I	C5DC
3-Hydroxy 3-methylglutaryl-CoA lyase deficiency*	HMG	C5OH/C5-3M-DC
Multiple carboxylase deficiency*	MCD	C3/C5OH
3-Methylcrotonyl-CoA carboxylase deficiency	3MCC	C5OH
Methylmalonic aciduria (mutase)*	MMA	C3
Propionic academia*	PA	C3
Fatty Acid Oxidation Defects		
Carnitine uptake defect (carnitine transporter defect)	CUD	C0
Long-chain hydroxyacyl-CoA dehydrogenase deficiency*	LCHAD/D	C16OH/C18:1OH
Medium-chain acyl-CoA dehydrogenase deficiency	MCAD/D	C8
Trifunctional protein deficiency*	TFP	C16OH/C18:1OH
Very-long-chain acyl-CoA dehydrogenase deficiency	VLCAD/D	C14:1/C14
Amino Acid Disorders		
Argininosuccinic aciduria (argininosuccinate lyase deficiency)*	ASA	ASA
Citrullinemia I (argininosuccinate synthase deficiency)*	CIT-I	Citrulline
Phenylketonuria	PKU	Phenylalanine
Maple syrup urine disease*	MSUD	Leucine
Homocystinuria	HCY	Methionine
Tyrosinemia type I	TYR-I	Tyrosine
OTHER METABOLIC DISORDERS		
Biotinidase deficiency	BIOT	Biotinidase activity
Galactosemia*	GALT	Total galactose, GALT activity
ENDOCRINE DISORDERS		
Congenital adrenal hyperplasia*	CAH	17-Hydroxyprogesterone
Congenital hypothyroidism	CH	T_4, TSH
HEMOGLOBIN DISORDERS		
Sickle cell anemia	HbSS	Hb variants
Sickle cell disorder	HbS/C	Hb variants
Hemoglobin S/β-thalassemia	HbS/betaTh	Hb variants
OTHER DISORDERS		
Cystic fibrosis	CF	Immunoreactive trypsinogen
Hearing	HEAR	

**Can manifest acutely in the first week of life.*
From Sahai I, Levy H. Newborn screening. In: Gleason C, Devasker D, eds. Avery's Diseases of the Newborn. *9th ed. Philadelphia: Saunders; 2012.*

hypotension, which decreases uterine perfusion. Maternal medications given to relieve pain during labor may cross the placenta and depress the infant's respiratory center, resulting in apnea at the time of birth.

Fetal conditions associated with asphyxia usually do not become manifested until delivery, when the infant must initiate and sustain ventilation. In addition, the upper and lower airways must be patent and unobstructed. Alveoli must be free from foreign material, such as meconium, amniotic fluid debris, and infectious exudates, which increases airway resistance, reduces lung compliance, and leads to respiratory distress and hypoxia. Some extremely immature infants weighing less than 1,000 g at birth may be unable to expand their lungs, even in the absence of other pathology. Their compliant chest walls and surfactant

TABLE 58.5 Abnormal Newborn Screening Results: Possible Implications and Initial Action to Be Taken

NEWBORN SCREENING FINDING	DIFFERENTIAL DIAGNOSIS	INITIAL ACTION
↑ Phenylalanine	PKU, non-PKU hyperphenylalaninemia, pterin defect, galactosemia, transient hyperphenylalaninemia	Repeat blood specimen
↓ T_4, ↑ TSH	Congenital hypothyroidism, iodine exposure	Repeat blood specimen or thyroid function testing, begin thyroxine treatment
↓ T_4, normal TSH	Maternal hyperthyroidism, thyroxine-binding globulin deficiency, secondary hypothyroidism, congenital hypothyroidism with delayed TSH elevation	Repeat blood specimen
↑ Galactose (1-P) transferase	Galactosemia, liver disease, reducing substance, repeat deficiency variant (Duarte), transient	Clinical evaluation, urine for blood specimen. If reducing substance positive, begin lactose-free formula
↓ Galactose-1-phosphate uridyltransferase	Galactosemia, transferase deficiency variant (Duarte), transient	Clinical evaluation, urine for reducing substance, repeat blood specimen. If reducing substance positive, begin lactose-free formula
↑ Methionine	Homocystinuria, isolated liver dysfunction, tyrosinemia type I, transient hypermethioninemia	Repeat blood and urine specimen
↑ Leucine	Maple syrup urine disease, transient elevation	Clinical evaluation including urine for ketones, acid-base status, amino acid studies, immediate neonatal ICU care if urine ketones positive
↑ Tyrosine	Tyrosinemia type I or type II, transient tyrosinemia, liver disease	Repeat blood specimen
↑ 17α-Hydroxyprogesterone	Congenital adrenal hyperplasia, prematurity, transient (residual fetal adrenal cortex), stress in neonatal period, early specimen collection	Clinical evaluation including genital examination, serum electrolytes, repeat blood specimen
S-hemoglobin	Sickle cell disease, sickle cell trait	Hemoglobin electrophoresis
↑ Trypsinogen	Cystic fibrosis, transient, intestinal anomalies, perinatal stress, trisomies 13 and 18, renal failure	Repeat blood specimen, possible sweat test and DNA testing
↑ Creatinine phosphokinase	Duchenne muscular dystrophy, other type of muscular dystrophy, birth trauma, invasive procedure	Repeat blood test
↓ Biotinidase	Biotinidase deficiency	Serum biotinidase assay, biotin therapy
↓ G6PD	G6PD deficiency	Complete blood count, bilirubin determination
↓ α_1-Antitrypsin	α_1-Antitrypsin deficiency	Confirmatory test
Toxoplasma antibody (IgM)	Congenital toxoplasmosis	Infectious disease consultation
HIV antibody (IgG)	Maternally transmitted HIV, possible AIDS	Infectious disease consultation
↑ Organic acids	Fatty acid oxidation defects (medium-chain acyl-CoA dehydrogenase deficiency)	Perform specific assay (tandem mass spectroscopy); frequent feeds

AIDS, Acquired immunodeficiency syndrome; *G6PD*, glucose-6-phosphate dehydrogenase; *HIV*, human immunodeficiency virus; *ICU*, intensive care unit; *PKU*, phenylketonuria; T_4, thyroxine; *TSH*, thyroid-stimulating hormone.
From Kim SZ, Levy HL. Newborn screening. In: Taeusch HW, Ballard RA, eds. Avery's Diseases of the Newborn. *7th ed. Philadelphia: Saunders; 1998.*

TABLE 58.6 Effects of Asphyxia

SYSTEM	EFFECT
Central nervous system	Hypoxic-ischemic encephalopathy, IVH, PVL, cerebral edema, seizures, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, tricuspid insufficiency, hypotension
Pulmonary	Persistent pulmonary hypertension, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration, necrosis
Metabolic	Inappropriate ADH, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

ADH, Antidiuretic hormone; *IVH*, intraventricular hemorrhage; *PVL*, periventricular leukomalacia.

TABLE 58.7 Etiology of Birth Asphyxia

TYPE	EXAMPLE
INTRAUTERINE	
Hypoxia-ischemia	Uteroplacental insufficiency, abruptio placentae, prolapsed cord, maternal hypotension, unknown
Anemia-shock	Vasa previa, placenta previa, fetomaternal hemorrhage, erythroblastosis
INTRAPARTUM	
Birth trauma	Cephalopelvic disproportion, shoulder dystocia, breech presentation, spinal cord transection
Hypoxia-ischemia	Umbilical cord compression, tetanic uterine contraction, abruptio placentae
POSTPARTUM	
Central nervous system	Maternal medication, trauma, previous episodes of fetal hypoxia-acidosis
Congenital neuromuscular disease	Congenital myasthenia gravis, myopathy, myotonic dystrophy
Infection	Consolidated pneumonia, shock
Airway disorder	Choanal atresia, severe obstructing goiter or tumor, laryngeal webs
Pulmonary disorder	Severe immaturity, pneumothorax, pleural effusion, diaphragmatic hernia, pulmonary hypoplasia
Renal disorder	Pulmonary hypoplasia, pneumothorax

TABLE 58.8 Apgar Score

	POINTS		
SIGNS	**0**	**1**	**2**
Heart rate	0	<100/min	>100/min
Respiration	None	Weak cry	Vigorous cry
Muscle tone	None	Some extremity flexion	Arms, legs well flexed
Reflex irritability	None	Some motion	Cry, withdrawal
Color of body	Blue	Pink body, blue extremities	Pink all over

deficiency may result in poor air exchange, retractions, hypoxia, and apnea.

The newborn (particularly a preterm infant) responds paradoxically to hypoxia with apnea rather than tachypnea as occurs in adults. Episodes of intrauterine asphyxia also may depress the neonatal central nervous system. If recovery of the fetal heart rate occurs as a result of improved uteroplacental perfusion, fetal hypoxia and acidosis may resolve. Nonetheless, if the effect on the respiratory center is more severe, a newborn may not initiate an adequate ventilatory response at birth and may undergo another episode of asphyxia.

The **Apgar examination**, a rapid scoring system based on physiological responses to the birth process, is a good method for assessing the need to resuscitate a newborn (Table 58.8). At intervals of 1 and 5 minutes after birth, each of the five physiological parameters is observed or elicited by a qualified examiner. Full-term infants with a normal cardiopulmonary adaptation should score 8-9 at 1 and 5 minutes. Apgar scores of 4-7 warrant close attention to determine whether the infant's status will improve and to ascertain whether any pathological condition is contributing to the low Apgar score.

By definition, an Apgar score of 0-3 represents either a cardiopulmonary arrest or a condition caused by severe bradycardia, hypoventilation, or central nervous system depression. Most low Apgar scores are caused by difficulty in establishing adequate ventilation and not by primary cardiac pathology. In addition to an Apgar score of 0-3, most infants with asphyxia severe enough to cause neurological injury also manifest fetal acidosis (pH <7); seizures, coma, or hypotonia; and multiorgan dysfunction. Low Apgar scores may be caused by fetal hypoxia or other factors listed in Table 58.7. Most infants with low Apgar scores respond to assisted ventilation by face mask or by endotracheal intubation and usually do not need emergency medication.

Resuscitation of a newborn with a low Apgar score follows the same systematic sequence as that for resuscitation of older patients, but in the newborn period this simplified *ABCD* approach requires some qualification (Fig. 58.2). In the ABCD approach, **A** stands for securing a patent airway by clearing amniotic fluid or meconium by suctioning; **A** is also a reminder of *anticipation* and the need for knowing the events of pregnancy, labor, and delivery. Evidence of a diaphragmatic hernia and a low Apgar score indicate that immediate endotracheal intubation is required. If a mask and bag are used, gas enters the lung and the stomach, and the latter may act as an expanding mass in the chest that compromises respiration. If fetal hydrops has occurred with pleural effusions, bilateral thoracentesis to evacuate the pleural effusions may be needed to establish adequate ventilation.

B represents **breathing**. If the neonate is apneic or hypoventilating and remains cyanotic, artificial ventilation should be initiated. Ventilation should be performed with a well-fitted mask attached to an anesthesia bag and a manometer to prevent extremely high pressures from being given to the newborn; 100% oxygen should be administered through the mask. If the infant does not revive, an endotracheal tube should be placed, attached to the anesthesia bag and manometer, and 100% oxygen should be administered. The pressure generated should begin at 20-25 cm H_2O, with a rate of 40-60 breaths/minute. An adequate response to ventilation includes good chest rise, return of breath sounds, well-oxygenated color, heart rate returning to the normal range (120-160 beats/min), normal end-tidal carbon dioxide, and, later, increased muscle activity and wakefulness. The usual recovery after a cardiac arrest first involves a return to a normal heart rate, followed by disappearance of cyanosis and noticeably improved perfusion.

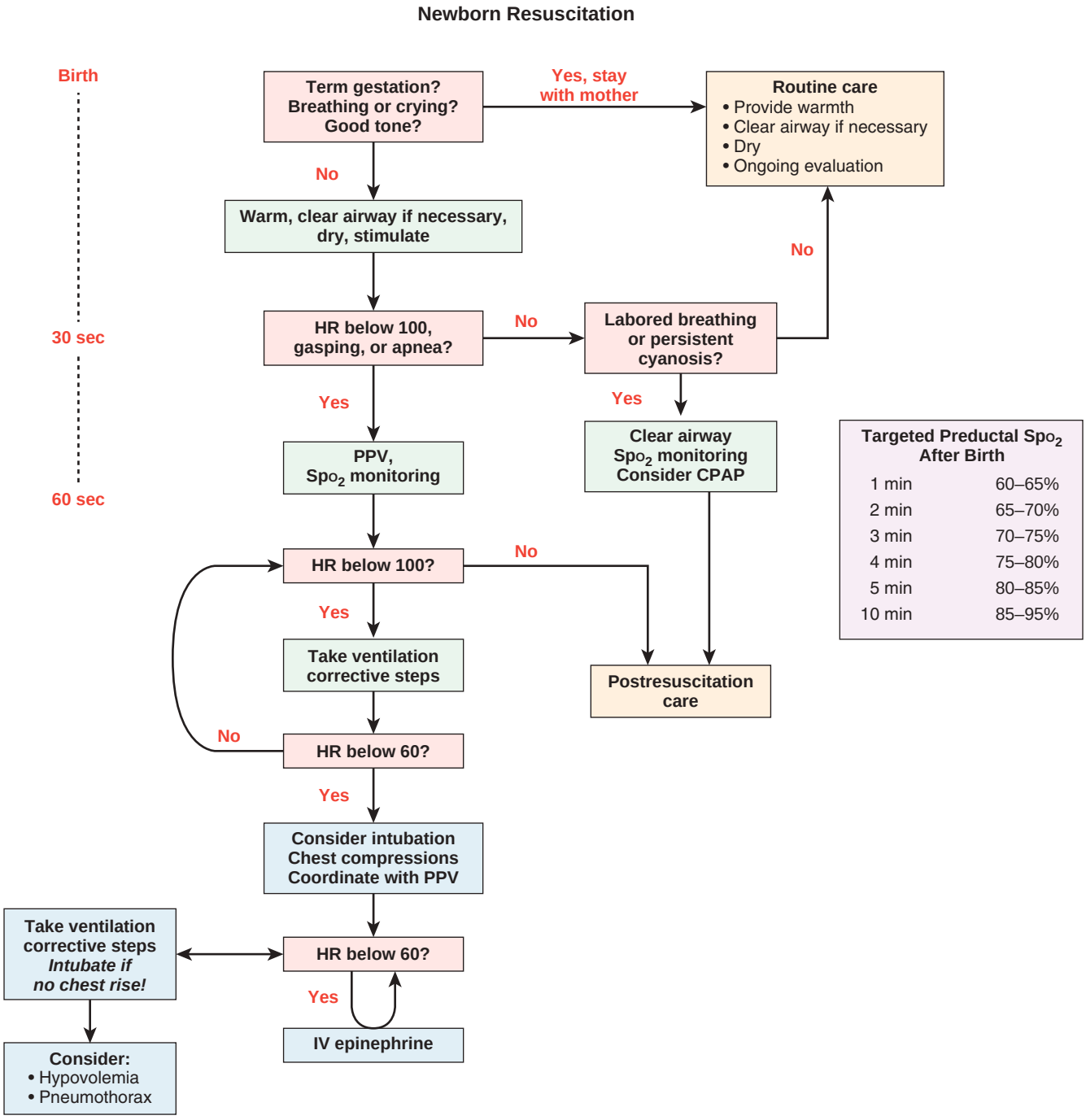

FIGURE 58.2 New guidelines and algorithm for neonatal resuscitation. *CPAP*, Continuous positive airway pressure; *IV*, intravenous; *HR*, heart rate; *PPV*, positive pressure ventilation; *Spo_2*, blood oxygen saturation. (From Kattwinkel J, Perlman JM, Aziz K, et al. Special report—neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics*. 2010;126[5]:e1400–e1413. Erratum in Neoreviews 2011;128[1]:176.)

An infant may remain limp and be apneic for a prolonged time after return of cardiac output and correction of acidosis.

Breathing initially should be briefly delayed if meconium-stained amniotic fluid is present to avoid dissemination of meconium into the lungs, producing severe aspiration pneumonia. If meconium is noted in the amniotic fluid, the oropharynx should be suctioned when the head is delivered. After the birth of a **depressed infant**, the oral cavity should be suctioned again; the vocal cords should be visualized and the infant intubated.

C represents **circulation** and external cardiac massage. If artificial ventilation does not improve bradycardia, if asystole is present, or if peripheral pulses cannot be palpated, external cardiac massage should be performed at a rate of 120 compressions/minute with compressions and breaths given at a ratio of 3:1. External cardiac massage usually is not

TABLE 58.9 Life-Threatening Congenital Anomalies

NAME	MANIFESTATIONS
Choanal atresia (stenosis)	Respiratory distress in delivery room, apnea, unable to pass nasogastric tube through nares
Pierre Robin syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in left chest, heart shifted to right, respiratory distress, polyhydramnios
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation, unable to place nasogastric tube in stomach
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention
Gastroschisis/omphalocele	Polyhydramnios; intestinal obstruction
Renal agenesis/Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Hydronephrosis	Bilateral abdominal masses
Neural tube defects: anencephaly, meningomyelocele	Polyhydramnios, elevated α-fetoprotein; decreased fetal activity
Down syndrome (trisomy 21)	Hypotonia, congenital heart disease, duodenal atresia
Ductal-dependent congenital heart disease	Cyanosis, murmur, shock

needed because most infants in the delivery room respond to ventilation.

D represents the **administration of drugs**. If bradycardia is unresponsive to ventilation or if asystole is present, epinephrine should be administered. Intravenous (IV) epinephrine (1:10,000), 0.1-0.3 mL/kg, should be given through an umbilical venous line or injected into the endotracheal tube. However, when epinephrine is administered through the endotracheal tube, the result is often unpredictable. Before medications are administered in the presence of electrical cardiac activity with poor pulses, it is important to determine whether there is a **pneumothorax**. Transillumination of the thorax, involving the use of a bright light through each side of the thorax and over the sternum, may suggest pneumothorax if one side transmits more light than the other. Breath sounds may be decreased over a pneumothorax and there may be a shift of the heart tones away from the side of a tension pneumothorax.

If central nervous system depression in the infant may be due to a narcotic medication given to the mother, 0.1 mg/kg of naloxone (Narcan) can be given to the infant intravenously or endotracheally. Before this drug is administered, the ABCs should be followed carefully. Naloxone should not be given to a newborn of a mother who is suspected of being addicted to narcotics or is on methadone maintenance because the newborn may experience severe withdrawal seizures.

In babies of more than 35 weeks' gestation suffering moderate to severe hypoxic-ischemic injury at birth, induced therapeutic **hypothermia** (33.0-34.0°C) for 72 hours has been shown in clinical studies to be efficacious in reducing the severity of brain injury. Brain hypothermia, whether induced by whole-body or selective head cooling, provides neuroprotection against encephalopathy presumably due to hypoxic ischemia.

Physical Examination and Gestational Age Assessment

The first physical examination of a newborn may be a general physical examination of a well infant or an examination to confirm fetal diagnoses or to determine the cause of various manifestations of neonatal diseases. Problems in the transition from fetal to neonatal life may be detectable immediately in the delivery room or during the first day of life. Physical examination also may reveal effects of the labor and delivery resulting from asphyxia, drugs, or birth trauma. The first newborn examination is an important way to detect congenital malformations or deformations (Table 58.9). Significant congenital malformations may be present in 1-3% of all births.

Appearance

Signs such as cyanosis, nasal flaring, intercostal retractions, and grunting suggest pulmonary disease. Meconium staining of the umbilical cord, nails, and skin suggest fetal distress and the possibility of aspiration pneumonia. The level of spontaneous activity, passive muscle tone, quality of the cry, and apnea are useful screening signs to evaluate the state of the nervous system.

Vital Signs

The examination should proceed with an assessment of vital signs, particularly heart rate (normal rate, 120-160 beats/min), respiratory rate (normal rate, 30-60 breaths/min), temperature (usually done per rectum and later as an axillary measurement), and blood pressure (often reserved for sick infants). Length, weight, and head circumference should be measured and plotted on growth curves to determine whether growth is normal, accelerated, or retarded for the specific gestational age.

Gestational Age

Gestational age is determined by an assessment of various physical signs (Fig. 58.3) and neuromuscular characteristics (Fig. 58.4) that vary according to fetal age and maturity. **Physical criteria** mature with advancing fetal age, including increasing firmness of the pinna of the ear; increasing size of the breast tissue; decreasing fine, immature lanugo hair over the back; and decreasing opacity of the skin. **Neurological criteria** mature with gestational age, including increasing flexion of the legs, hips, and arms; increasing tone of the flexor muscles of the neck; and decreasing laxity of the joints. These signs are determined during the first day of life and are assigned scores.

Physical maturity	–1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel–toe 40-50 mm: –1 Less than 40 mm: –2	<50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola–no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused, loosely (–1), tightly (–2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft, slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm; instant recoil	Thick cartilage, ear stiff	
Genitals male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

FIGURE 58.3 Physical criteria for assessment of maturity and gestational age. Expanded New Ballard Score includes extremely premature infants and has been refined to improve accuracy in more mature infants. (From Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr.* 1991;119:417–423.)

The cumulative score is correlated with a gestational age, which is usually accurate to within 2 weeks (Fig. 58.5).

Gestational age assessment permits the detection of abnormal fetal growth patterns, aiding in predicting the neonatal complications of largeness or smallness for gestational age (Fig. 58.6). Infants born at a weight greater than the 90th percentile for age are considered **large for gestational age**. Among the risks associated with being large for gestational age are all the risks of the infant of a diabetic mother and risks associated with postmaturity. Infants born at a weight less than 10th percentile for age (some growth curves use <2 standard deviations or the 5th percentile) are **small for gestational age** and have IUGR. Problems associated with small for gestational age infants include congenital malformations, in addition to the problems listed in Table 58.2.

Skin

The skin should be evaluated for pallor, plethora, jaundice, cyanosis, meconium staining, petechiae, ecchymoses, congenital nevi, and neonatal rashes. Vasomotor instability with cutis marmorata, telangiectasia, phlebectasia (intermittent mottling with venous prominence), and acrocyanosis (feet and hands) is normal in a premature infant. Acrocyanosis also may be noted in a healthy term infant in the first days after birth.

The skin is covered with lanugo hair, which disappears by term gestation. **Hair tufts** over the lumbosacral spine suggest a spinal cord defect. **Vernix caseosa**, a soft, white, creamy layer covering the skin in preterm infants, disappears by term. Postterm infants often have peeling, parchment-like skin. **Mongolian spots** are transient, dark blue to black pigmented macules seen over the lower back and buttocks in 90% of African American, Indian, and Asian infants. **Nevus simplex** *(salmon patch)*, or pink macular hemangioma, is common, usually transient, and noted on the back of the neck, eyelids, and forehead. **Nevus flammeus**, or **port-wine stain**, is seen on the face and should cause the examiner to consider Sturge-Weber syndrome (trigeminal angiomatosis, convulsions, and ipsilateral intracranial *tram-line* calcifications).

Congenital melanocytic nevi are pigmented lesions of varying size noted in 1% of neonates. **Giant pigmented nevi** are uncommon but have malignant potential. **Capillary hemangiomas** are raised, red lesions, whereas **cavernous hemangiomas** are deeper, blue masses. Both lesions increase in size after birth then resolve when the child is 1-4 years of age. When enlarged, these hemangiomas may produce high-output heart failure or platelet trapping and hemorrhage. **Erythema toxicum** is an erythematous, papular-vesicular rash common in neonates that develops after birth and involves

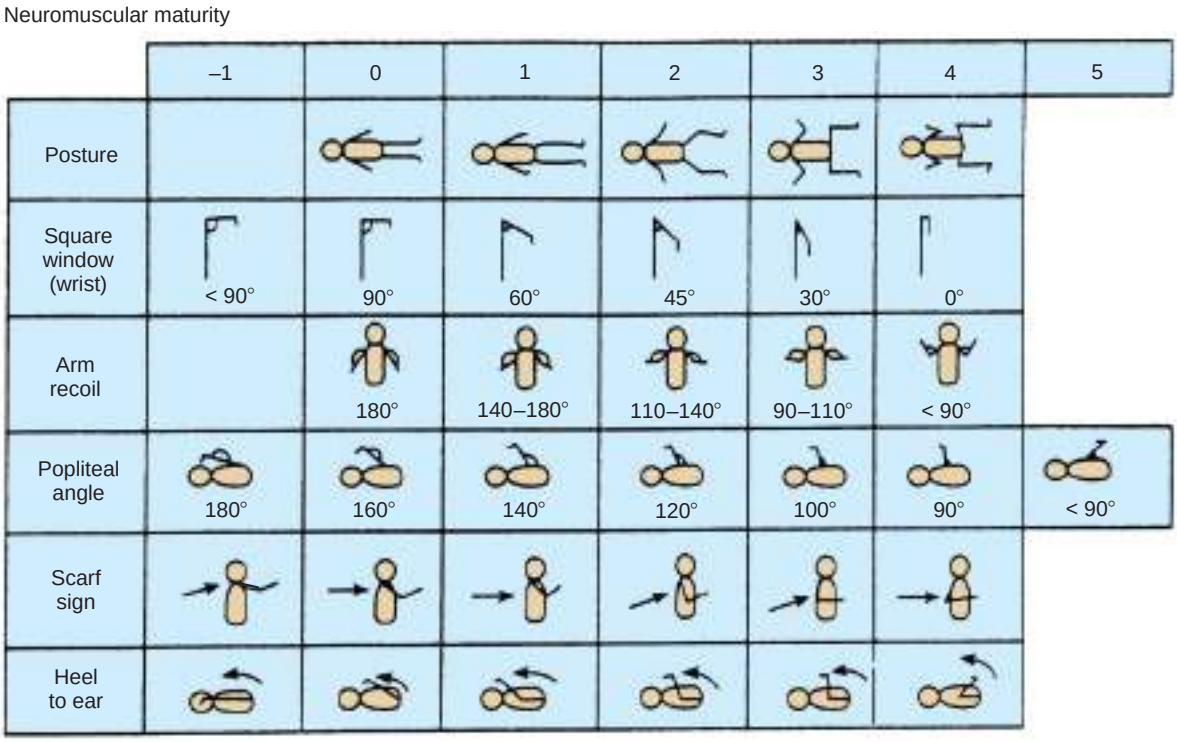

FIGURE 58.4 Neuromuscular criteria for assessment of maturity and gestational age. Expanded New Ballard Score includes extremely premature infants and has been refined to improve accuracy in more mature infants. (From Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr.* 1991;119:417–423.)

Maturity rating

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

FIGURE 58.5 Maturity rating as calculated by adding the physical and neurological scores, calculating the gestational age. (From Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr.* 1991;119:417–423.)

eosinophils in the vesicular fluid. **Pustular melanosis**, more common in African American infants, may be seen at birth and consists of a small, dry vesicle on a pigmented brown macular base. Erythema toxicum and pustular melanosis are benign lesions but may mimic more serious conditions, such as the vesicular rash of disseminated herpes simplex or the bullous eruption of *S. aureus* impetigo. Tzanck smear, Gram stain, Wright stain, direct fluorescent antibody stain, polymerase chain reaction for herpes DNA, and appropriate cultures may be needed to distinguish these rashes. Other common characteristic rashes are **milia** (yellow-white epidermal cysts of the pilosebaceous follicles that are noted on the nose) and **miliaria** (prickly heat), which is caused by obstructed sweat glands. **Edema** may be present in preterm infants, but also suggests hydrops fetalis, sepsis, hypoalbuminemia, or lymphatic disorders.

Skull

The skull may be elongated and molded after a prolonged labor; this resolves 2-3 days after birth. The sutures should be palpated to determine the width and the presence of premature fusion or cranial synostosis. The anterior and posterior fontanelles should be soft and nonbulging, with the anterior larger than the posterior. A large fontanelle is associated with hydrocephalus, hypothyroidism, rickets, and other disorders. Soft areas away from the fontanelle are **craniotabes**; these lesions feel like a Ping-Pong ball when they are palpated. They may be a result of in utero compression. The skull should be examined carefully for signs of trauma or lacerations from internal fetal electrode sites or fetal scalp pH sampling; abscesses may develop in these areas.

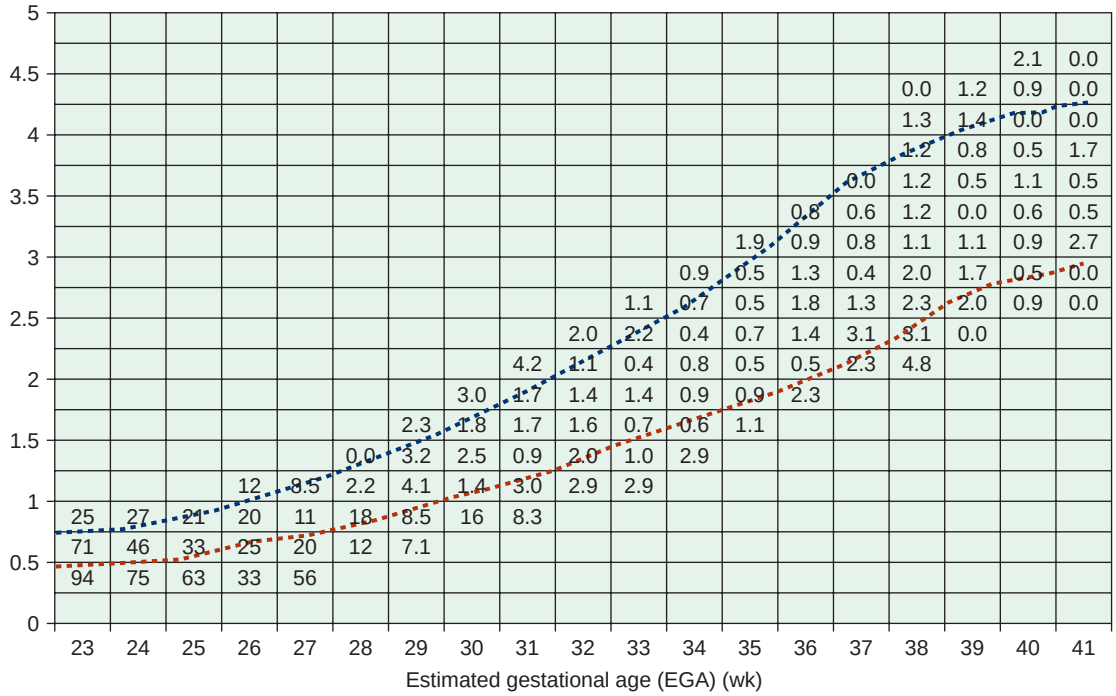

FIGURE 58.6 Birth weight–specific and estimated gestational age–specific mortality rates. The dashed lines of the figure represent the 10th and 90th percentile weights. The grid lines are plotted by each gestational age and in 250-g weight increments. Each number in the box is the percent mortality rate for the grid defined by gestational age and birth weight range. (From Thomas P, Peabody J, Turnier V, et al. A new look at intrauterine growth and impact of race, attitude, and gender. *Pediatrics.* 2000;106:E21.)

Face, Eyes, and Mouth

The face should be inspected for dysmorphic features, such as epicanthal folds, hypertelorism, preauricular tags or sinuses, low-set ears, long philtrum, and cleft lip or palate. Facial asymmetry may be a result of seventh nerve palsy; head tilt may be caused by torticollis.

The eyes should open spontaneously, especially in an upright position. Before 28 weeks' gestational age, the eyelids may be fused. Coloboma, megalocornea, and microphthalmia suggest other malformations or intrauterine infections. A cloudy cornea greater than 1 cm in diameter also may be seen in congenital glaucoma, uveal tract dysgenesis, and storage diseases. Conjunctival and retinal hemorrhages are common and usually of no significance. The pupillary response to light is present at 28 weeks of gestation. The **red reflex** of the retina is shown easily. A white reflex, or **leukokoria**, is abnormal and may be the result of cataracts, ocular tumor, severe chorioretinitis, persistent hyperplastic primary vitreous, or retinopathy of prematurity.

The mouth should be inspected for the presence of natal teeth, clefts of the soft and hard palate and uvula, and micrognathia. A bifid uvula suggests a submucosal cleft. White, shiny, multiple transient epidermal inclusion cysts (Epstein pearls) on the hard palate are normal. Hard, marble-sized masses in the buccal mucosa are usually transient idiopathic fat necrosis. The **tympanic membranes** are dull, gray, opaque, and immobile in the first 1-4 weeks. These findings should not be confused with otitis media.

Neck and Chest

The neck appears short and symmetrical. Abnormalities include midline clefts or masses caused by thyroglossal duct cysts or by goiter and lateral neck masses (or sinuses), which are the result of branchial clefts. Cystic hygromas and hemangiomas may be present. Shortening of the sternocleidomastoid muscle with a fibrous tumor over the muscle produces head tilt and asymmetrical facies (neonatal torticollis). Arnold-Chiari malformation and cervical spine lesions also produce torticollis. Edema and webbing of the neck suggest Turner syndrome. Both clavicles should be palpated for fractures.

Examination of the **chest** includes inspection of the chest wall to identify asymmetry resulting from absence of the pectoralis muscle and inspection of the breast tissue to determine gestational age and detect a breast abscess. Boys and girls may have breast engorgement and produce milk; milk expression should not be attempted. **Supernumerary nipples** may be bilateral and may be associated with renal anomalies.

Lungs

Examination of the lungs includes observations of the rate, depth, and nature of intercostal or sternal retractions. Breath sounds should be equal on both sides of the chest, and rales should not be heard after the first 1-2 hours of life. Diminished or absent breath sounds on one side suggest pneumothorax, collapsed lung, pleural effusion, or diaphragmatic hernia. Shift of the cardiac impulse away from a tension pneumothorax and diaphragmatic hernia and toward the collapsed lung is a helpful physical finding for differentiating these disorders. Subcutaneous emphysema of the neck or chest also suggests a pneumothorax or pneumomediastinum, whereas bowel sounds auscultated in the chest in the presence of a scaphoid abdomen suggest a diaphragmatic hernia.

Heart

The position of the heart in infants is more midline than in older children. The first heart sound is normal, whereas the second heart sound may not be split in the first day of life. Decreased splitting of the second heart sound is noted in PPHN, transposition of the great vessels, and pulmonary atresia. Heart murmurs in newborns are common in the delivery room and during the first day of life. Most of these murmurs are transient and are due to closure of the ductus arteriosus, peripheral pulmonary artery stenosis, or a small ventral septal defect. Pulses should be palpated in the upper and lower extremities (over the brachial and femoral arteries). Blood pressure in the upper and lower extremities should be measured in all patients with a murmur or heart failure. An upper-to-lower extremity gradient of more than 10-20 mm Hg suggests coarctation of the aorta.

Abdomen

The liver may be palpable 2 cm below the right costal margin. The spleen tip is less likely to be palpable. A left-sided liver suggests situs inversus and asplenia syndrome. Both kidneys should be palpable in the first day of life with gentle, deep palpation. The first urination occurs during the first day of life in more than 95% of normal term infants.

Abdominal masses usually represent hydronephrosis or dysplastic-multicystic kidney disease. Less often, masses indicate ovarian cysts, intestinal duplication, neuroblastoma, or mesoblastic nephroma. Masses should be evaluated immediately with ultrasound. Abdominal distention may be caused by intestinal obstructions, such as ileal atresia, meconium ileus, midgut volvulus, imperforate anus, or Hirschsprung disease. Meconium stool is passed normally within 48 hours of birth in 99% of term infants. The anus should be patent. An imperforate anus is not always visible; the first temperature taken with a rectal thermometer should be taken carefully. The abdominal wall musculature may be absent, as in prune-belly syndrome, or weak, resulting in diastasis recti. **Umbilical hernias** are common in African American infants. The umbilical cord should be inspected to determine the presence of two arteries and one vein and the absence of an urachus or a herniation of abdominal contents, as occurs with an **omphalocele**. The latter is associated with extraintestinal problems, such as genetic trisomies and hypoglycemia (Beckwith-Wiedemann syndrome). Bleeding from the cord suggests a coagulation disorder, and a chronic discharge may be a granuloma of the umbilical stump or, less frequently, a draining omphalomesenteric cyst or urachus. Erythema around the umbilicus is **omphalitis** and may cause portal vein thrombophlebitis and subsequent extrahepatic portal hypertension. The herniation of bowel through the abdominal wall 2-3 cm lateral to the umbilicus is a **gastroschisis**.

Genitalia

Decision-Making Algorithm
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Ambiguous Genitalia

At term, the testes should be descended into a well-formed pigmented and rugated scrotum. The testes occasionally are in the inguinal canal; this is more common among preterm infants, as is cryptorchidism. Scrotal swelling may represent a hernia, transient hydrocele, in utero torsion of the testes, or, rarely, dissected meconium from meconium ileus and peritonitis. Hydroceles are clear and readily seen by transillumination, whereas testicular torsion in the newborn may present as a painless, dark swelling. The urethral opening should be at the end of the penis. Epispadias or hypospadias alone should not raise concern about pseudohermaphroditism. However, if no testes are present in the scrotum and hypospadias is present, problems of sexual development should be suspected. Circumcision should be deferred with hypospadias because the foreskin is often needed for the repair. The normal prepuce is often too tight to retract in the neonatal period.

The female genitalia normally may reveal a milky white or blood-streaked vaginal discharge as a result of maternal hormone withdrawal. Mucosal tags of the labia majora are common. Distention of an imperforate hymen may produce hydrometrocolpos and a lower midline abdominal mass as a result of an enlarged uterus. Clitoral enlargement with fusion of the labial-scrotal folds (labia majora) suggests adrenogenital syndrome or exposure to masculinizing maternal hormones.

Extremities

Examination of the extremities should involve assessment of length, symmetry, and presence of hemihypertrophy, atrophy, polydactyly, syndactyly, simian creases, absent fingers, overlapping fingers, rocker-bottom feet, clubfoot, congenital bands, fractures, and amputations.

Spine

The spine should be examined for evidence of sacral hair tufts, a dermal sinus tract above the gluteal folds, congenital scoliosis (a result of hemivertebra), and soft tissue masses such as lipomas or meningomyeloceles.

Hips

The hips should be examined for congenital dysplasia (dislocation). Gluteal fold asymmetry or leg length discrepancy is suggestive of dysplasia, but the examiner should perform the Barlow test and the Ortolani maneuver to evaluate the stability of the hip joint. These tests determine whether the femoral head can be displaced from the acetabulum **(Barlow test)** and then replaced **(Ortolani maneuver)**.

NEUROLOGICAL ASSESSMENT

The neurological examination should include assessment of active and passive tone, level of alertness, primary neonatal (primitive) reflexes, deep tendon reflexes, spontaneous motor activity, and cranial nerves (involving retinal examination, extraocular muscle movement, masseter power as in sucking, facial motility, hearing, and tongue function). The Moro reflex, present at birth and gone in 3-6 months, is one of the primary newborn reflexes. It is elicited by sudden, slight dropping of the supported head from a slightly raised supine position, which should elicit opening of the hands and extension and abduction of the arms, followed by upper extremity flexion and a cry. The palmar grasp is present by 28 weeks' gestation and gone by 4 months of age. Deep tendon reflexes may be brisk in a normal newborn; 5-10 beats of ankle clonus are normal. The Babinski sign is extensor (upgoing). The sensory examination can be evaluated by withdrawal of an extremity, grimace, and cry in response to painful stimuli. The rooting reflex (turning of the

TABLE 58.10 Differential Diagnosis of Neonatal Cyanosis

SYSTEM/DISEASE	MECHANISM
PULMONARY	
Respiratory distress syndrome	Surfactant deficiency
Sepsis, pneumonia	Inflammation, pulmonary hypertension, ARDS
Meconium aspiration pneumonia	Mechanical obstruction, inflammation, pulmonary hypertension
Persistent pulmonary hypertension of the newborn	Pulmonary hypertension
Diaphragmatic hernia	Pulmonary hypoplasia, pulmonary hypertension
Transient tachypnea	Retained lung fluid
CARDIOVASCULAR	
Cyanotic heart disease with decreased pulmonary blood flow	Right-to-left shunt as in pulmonary atresia, tetralogy of Fallot
Cyanotic heart disease with increased pulmonary blood flow	Mixing lesion as in single ventricle or truncus arteriosus
Cyanotic heart disease with congestive heart failure	Pulmonary edema and poor cardiac output as in hypoplastic left heart and coarctation of aorta
Heart failure alone	Pulmonary edema and poor cardiac contractility as in sepsis, myocarditis, supraventricular tachycardia, or complete heart block; high-output failure as in PDA or vein of Galen or other arteriovenous malformations
CENTRAL NERVOUS SYSTEM (CNS)	
Maternal sedative drugs	Hypoventilation, apnea
Asphyxia	CNS depression
Intracranial hemorrhage	CNS depression, seizure
Neuromuscular disease	Hypotonia, hypoventilation, pulmonary hypoplasia
HEMATOLOGICAL	
Acute blood loss	Shock
Chronic blood loss	Heart failure
Polycythemia	Pulmonary hypertension
Methemoglobinemia	Low-affinity hemoglobin or red blood cell enzyme defect
METABOLIC	
Hypoglycemia	CNS depression, congestive heart failure
Adrenogenital syndrome	Shock (salt-losing)

ARDS, Acute respiratory distress syndrome; *CNS*, central nervous system; *PDA*, patent ductus arteriosus.

head toward light tactile stimulation of the perioral area) is present by 32 weeks' gestation.

Special Conditions Requiring Resuscitation in the Delivery Room

Cyanosis

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Cyanosis

Acrocyanosis (blue color of the hands and feet with pink color of the rest of the body) is common in the delivery room and is usually normal. **Central cyanosis** of the trunk, mucosal membranes, and tongue can occur at any time after birth and is always a manifestation of a serious underlying condition. Cyanosis is noted with 4-5 g/dL of deoxygenated hemoglobin. Central cyanosis can be caused by problems in many different organ systems, although cardiopulmonary diseases are the most common (Table 58.10). Respiratory distress syndrome, sepsis, and cyanotic heart disease are the three most common causes of cyanosis in infants admitted to a neonatal intensive care unit. A systematic evaluation of these and other causes of cyanosis is required for every cyanotic infant after prompt administration of oxygen, with or without assisted ventilation.

Life-Threatening Congenital Malformations

Various congenital anomalies can interfere with vital organ function after birth (see Table 58.9). Some malformations, such as choanal atresia and other lesions obstructing the airway, may complicate ventilation. Intrathoracic lesions, such as cysts or diaphragmatic hernia, interfere with respiration. Other malformations that obstruct the gastrointestinal system at the level of the esophagus, duodenum, ileum, or colon may lead to aspiration pneumonia, intestinal perforation, or gangrene. Gastroschisis and omphalocele are associated with exposed

bowel on the abdominal wall. Omphalocele is often associated with other malformations, whereas intestinal necrosis is more common in gastroschisis.

Shock

Shock in the delivery room is manifested by pallor, poor capillary refill time, lack of palpable pulses, hypotonia, cyanosis, and eventually cardiopulmonary arrest. Blood loss before or during labor and delivery is a common cause of shock in the delivery room. Blood loss may be caused by fetal-maternal hemorrhage, placenta previa, vasa previa, twin-to-twin transfusion syndrome, or displacement of blood from the fetus to the placenta as during asphyxia *(asphyxia pallida)*. Hemorrhage into a viscus, such as the liver or spleen, may be noted in macrosomic infants, and hemorrhage into the cerebral ventricles may produce shock and apnea in preterm infants. Anemia, hypoalbuminemia, hypovolemia, and shock at birth are common manifestations of Rh immune hydrops.

Severe intrauterine bacterial sepsis may present with shock in the delivery room or immediately after the infant is transferred to the nursery. Typically these infants are mottled, hypotonic, and cyanotic and have diminished peripheral pulses. They have a normal hemoglobin concentration but may manifest neutropenia, thrombocytopenia, and disseminated intravascular coagulation. Peripheral symmetrical gangrene (purpuric rash) often is a sign of hypotensive shock in infants with severe congenital bacterial infections. Congenital left ventricular cardiac obstruction (critical aortic stenosis or hypoplastic left heart syndrome) also produces shock, although not usually in the delivery room.

Treatment of newborn infants with shock should involve the management approaches used for the sick infant. Problems may be anticipated through knowledge of the infant's immune status, evidence of hydrops, or suspicion of intrauterine infection or anomalies. Stabilization of the airway and institution of respiratory support are essential. Hypovolemic shock should be managed with repeated boluses of 10-15 mL/kg of normal saline or lactated Ringer solution. If severe immune hemolysis is predicted, blood typed against the mother's blood should be available in the delivery room and should be given to the newborn if signs of anemia and shock are present. Thereafter, all blood should be crossmatched with the infant's and mother's blood before transfusion. Drugs such as dopamine, epinephrine, or cortisol may improve cardiac output and tissue perfusion.

Birth Injury

Birth injury refers to avoidable and unavoidable injury to the fetus during the birth process. **Caput succedaneum** is a diffuse, edematous, often dark swelling of the soft tissue of the scalp that extends across the midline and suture lines. In infants delivered from a face presentation, soft tissue edema of the eyelids and face is an equivalent phenomenon. Caput succedaneum may be seen after prolonged labor in full-term and preterm infants. Molding of the head often is associated with caput succedaneum and is the result of pressure that is induced from overriding the parietal and frontal bones against their respective sutures.

A **cephalhematoma** is a subperiosteal hemorrhage that does not cross the suture lines surrounding the respective bones. A linear skull fracture rarely may be seen underlying a cephalhematoma. With time, the cephalhematoma may organize, calcify, and form a central depression.

Infants with cephalhematoma and caput succedaneum require no specific treatment. Occasionally a premature infant may develop a massive scalp hemorrhage. This **subgaleal bleeding** and the bleeding noted from a cephalhematoma may cause indirect hyperbilirubinemia requiring phototherapy. **Retinal and subconjunctival hemorrhages** are common but usually are small and insignificant; no treatment is necessary.

Spinal cord or **spine injuries** may occur in the fetus as a result of the hyperextended *star gazing* posture. Injuries also may occur in infants after excessive rotational (at C3-4) or longitudinal (at C7-T1) force is transmitted to the neck during vertex or breech delivery. Fractures of vertebrae are rare; trauma may cause direct damage to the spinal cord, leading to transection and permanent sequelae, hemorrhage, edema, and neurological signs. Rarely, a snapping sound indicating cord transection rather than vertebral displacement is heard at the time of delivery. Neurological dysfunction usually involves complete flaccid paralysis, absence of deep tendon reflexes, and absence of responses to painful stimuli below the lesion. Painful stimuli may elicit reflex flexion of the legs. Infants with spinal cord injury often are flaccid, apneic, and asphyxiated, all of which may mask the underlying spinal cord transection.

Injury to the nerves of the **brachial plexus** may result from excessive traction on the neck, producing paresis or complete paralysis. The mildest injury (neurapraxia) is edema; axonotmesis is more severe and consists of disrupted nerve fibers with an intact myelin sheath; neurotmesis, or complete nerve disruption or root avulsion, is most severe. **Erb-Duchenne paralysis** involves the fifth and sixth cervical nerves and is the most common and usually mildest injury. The infant cannot abduct the arm at the shoulder, externally rotate the arm, or supinate the forearm. The usual picture is one of painless adduction, internal rotation of the arm, and pronation of the forearm. The **Moro reflex** is absent on the involved side, and the hand grasp is intact. **Phrenic nerve palsy** (C3, C4, and C5) may lead to diaphragmatic paralysis and respiratory distress. Elevation of the diaphragm caused by nerve injury must be differentiated from elevation caused by eventration resulting from congenital weakness or absence of diaphragm muscle. **Klumpke paralysis** is caused by injury to the seventh and eighth cervical nerves and the first thoracic nerve, resulting in a paralyzed hand and, if the sympathetic nerves are injured, an ipsilateral **Horner syndrome** (ptosis, miosis). Complete arm and hand paralysis is noted with the most severe form of damage to C5, C6, C7, C8, and T1. **Treatment** of brachial plexus injury is supportive and includes positioning to avoid contractures. Active and passive range of motion exercises also may be beneficial. If the deficit persists, nerve grafting may be beneficial.

Facial nerve injury may be the result of compression of the seventh nerve between the facial bone and the mother's pelvic bones or the physician's forceps. This peripheral nerve injury is characterized by an asymmetric crying face whose normal side, including the forehead, moves in a regular manner. The affected side is flaccid, the eye does not close, the nasolabial fold is absent, and the side of the mouth droops at rest. If there is a central injury to the facial nerve, only the lower two thirds of the face (not the forehead) are involved. Complete agenesis of the facial nucleus results in a central facial paralysis; when this is bilateral, as in **Möbius syndrome**, the face appears expressionless.

Skull fractures are rare, are usually linear, and require no treatment other than observation for very rare, delayed (1-3

months) complications (e.g., leptomeningeal cyst). Depressed skull fractures are unusual but may be seen with complicated forceps delivery and may need surgical elevation. Fractures of the **clavicle** usually are unilateral and are noted in macrosomic infants after shoulder dystocia. Often a snap is heard after a difficult delivery, and the infant exhibits an asymmetrical Moro response and decreased movement of the affected side. The prognosis is excellent; many infants require no treatment or a simple figure of eight bandage to immobilize the bone.

Extremity fractures are less common than fractures of the clavicle and involve the humerus more often than the femur. **Treatment** involves immobilization and a triangular splint bandage for the humerus and traction suspension of the legs for femoral fractures. The prognosis is excellent.

Fractures of the **facial bones** are rare, but dislocation of the cartilaginous part of the nasal septum out of the vomeral groove and columella is common. Clinical manifestations include feeding difficulty, respiratory distress, asymmetrical nares, and a flattened, laterally displaced nose. Treatment reduces the dislocation by elevating the cartilage back into the vomeral groove.

Visceral trauma to the liver, spleen, or adrenal gland occurs in macrosomic infants and in extremely premature infants, with or without breech or vaginal delivery. Rupture of the liver with subcapsular hematoma formation may lead to anemia, hypovolemia, shock, hemoperitoneum, and disseminated intravascular coagulation. Infants with anemia and shock who are suspected to have an intraventricular hemorrhage but with a normal head ultrasound examination should be evaluated for hepatic or splenic rupture. Adrenal hemorrhage may be asymptomatic, detected only by finding calcified adrenal glands in normal infants. Infants with severe adrenal hemorrhage may exhibit a flank mass, jaundice, and hematuria, with or without shock.

Temperature Regulation

After birth, a newborn remains covered by amniotic fluid and situated in a cold environment (20-25°C). An infant's skin temperature may decrease 0.3°C/min, and the core temperature may decrease 0.1°C/min in the delivery room. In the absence of an external heat source, the infant must increase metabolism substantially to maintain body temperature.

Heat loss occurs through four basic mechanisms. In the cold delivery room, the wet infant loses heat predominantly by **evaporation** (cutaneous and respiratory loss when wet or in low humidity), **radiation** (loss to nearby cold, solid surfaces), and **convection** (loss to air current). When the infant is dry, radiation, convection, and **conduction** (loss to object in direct contact with infant) are important causes of heat loss. After birth, all high-risk infants should be dried immediately to eliminate evaporative heat losses. A radiant or convective heat source should be provided for these high-risk infants. Normal term infants should be dried and wrapped in a blanket.

The ideal environmental temperature is the **neutral thermal environment**, the ambient temperature that results in the lowest rate of heat being produced by the infant and maintains normal body temperature. The neutral thermal environmental temperature decreases with increasing gestational and postnatal age. Ambient temperatures less than the neutral thermal environment result in increasing rates of oxygen consumption for heat production, which is designed to maintain normal body temperature. If the ambient temperature decreases further or if oxygen consumption cannot increase sufficiently (due to hypoxia, hypoglycemia, or drugs), the core body temperature decreases.

Heat production by a newborn is created predominantly by nonshivering thermogenesis in specialized areas of tissue containing brown adipose tissue. Brown fat is highly vascular, contains many mitochondria per cell, and is situated around large blood vessels, resulting in rapid heat transfer to the circulation. The vessels of the neck, thorax, and interscapular region are common locations of brown fat. These tissues also are innervated by the sympathetic nervous system, which serves as a primary stimulus for heat production by brown adipose cells. Shivering does not occur in newborns.

Severe **cold injury** in an infant is manifested by acidosis, hypoxia, hypoglycemia, apnea, bradycardia, pulmonary hemorrhage, and a pink skin color. The color is caused by trapping of oxygenated hemoglobin in the cutaneous capillaries. Many of these infants appear dead, but most respond to treatment and recover. Milder degrees of cold injury in the delivery room may contribute to metabolic acidosis and hypoxia after birth. Conversely, hypoxia delays heat generation in cold-stressed infants.

Treatment of severe hypothermia should involve resuscitation and rapid warming of core (e.g., lung and stomach) and external surfaces. Fluid resuscitation also is needed to treat hypovolemia seen in many of these infants. Reduced core temperature (32-35°C) in the immediate newborn period often requires only external warming with a radiant warmer, incubator, or both.

Elevated Temperature

Exposure to ambient temperatures above the neutral thermal environment results in *heat stress* and an elevated core temperature. Sweating is uncommon in newborns and may be noted only on the forehead. In response to moderate heat stress, infants may increase their respiratory rate to dissipate heat. Excessive environmental temperatures may result in heatstroke or in hemorrhagic shock encephalopathy syndrome.

MISCELLANEOUS DISORDERS

Hypocalcemia

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Hypocalcemia

Hypocalcemia is common in sick and premature newborns. Calcium levels are higher in cord blood than in maternal blood because of active placental transfer of calcium to the fetus. Fetal calcium accretion in the third trimester approaches 150 mg/kg/24 hr; fetal bone mineral content doubles between 30 and 40 weeks of gestation. All infants show a slight decline of serum calcium levels after birth, reaching a trough level at 24-48 hours, the point at which hypocalcemia usually occurs. Total serum calcium levels of less than 7 mg/dL and ionized calcium levels of less than 3-3.5 mg/dL are considered hypocalcemia.

The etiology of hypocalcemia varies with the time of onset and the associated illnesses of the child. **Early neonatal hypocalcemia** occurs in the first 3 days of life and is often asymptomatic. Transient hypoparathyroidism and a reduced

parathyroid response to the usual postnatal decline of serum calcium levels may be responsible for hypocalcemia in premature infants and infants of diabetic mothers. Congenital absences of the parathyroid gland with DiGeorge syndrome is a cause of hypocalcemia. **Hypomagnesemia** (<1.5 mg/dL) may be seen simultaneously with hypocalcemia, especially in infants of diabetic mothers. Treatment with calcium alone does not relieve symptoms or increase serum calcium levels until hypomagnesemia is also treated. Sodium bicarbonate therapy, phosphate release from cell necrosis, transient hypoparathyroidism, and hypercalcitoninemia may be responsible for early neonatal hypocalcemia associated with asphyxia. Early-onset hypocalcemia associated with asphyxia often occurs with seizures as a result of hypoxic-ischemic encephalopathy.

Late neonatal hypocalcemia, or **neonatal tetany**, often is the result of ingestion of high phosphate–containing milk or the inability to excrete the usual phosphorus in commercial infant formula. Hyperphosphatemia (>8 mg/dL) usually occurs in infants with hypocalcemia after the first week of life. Vitamin D deficiency states and malabsorption also have been associated with late-onset hypocalcemia.

The clinical manifestations of hypocalcemia and hypomagnesemia include apnea, muscle twitching, seizures, laryngospasm, **Chvostek sign** (facial muscle spasm when the side of the face over the seventh nerve is tapped), and **Trousseau sign** (carpopedal spasm induced by partial inflation of a blood pressure cuff). The latter two signs are rare in the immediate newborn period.

Neonatal hypocalcemia may be prevented in high-risk neonates by administration of IV or oral calcium supplementation at a rate of 25-75 mg/kg/24 hr. Early asymptomatic hypocalcemia of preterm infants and infants of diabetic mothers often resolves spontaneously. Symptomatic hypocalcemia should be treated with 2-4 mL/kg of 10% calcium gluconate given intravenously and slowly over 10-15 minutes, followed by a continuous infusion of 75 mg/kg/24 hr of elemental calcium. If hypomagnesemia is associated with hypocalcemia, 50% magnesium sulfate, 0.1 mL/kg, should be given by intramuscular injection and repeated every 8-12 hours.

The **treatment** of late hypocalcemia includes immediate management, as in early hypocalcemia, plus the initiation of feedings with low-phosphate formula. Subcutaneous infiltration of IV calcium salts can cause tissue necrosis; oral supplements are hypertonic and may irritate the intestinal mucosa.

Neonatal Drug Addiction and Withdrawal

Infants may become passively and physiologically addicted to medications or to drugs of abuse (heroin, methadone, barbiturates, tranquilizers, amphetamines) taken chronically by the mother during pregnancy; these infants subsequently may have signs and symptoms of drug withdrawal. Many of these pregnancies are at high risk for other complications related to IV drug abuse, such as hepatitis, acquired immunodeficiency syndrome (AIDS), and syphilis. In addition, the LBW rate and the long-term risk for sudden infant death syndrome are higher in the infants of these high-risk women.

Opiates

Neonatal withdrawal signs and symptoms usually begin at 1-5 days of life with maternal heroin use and at 1-4 weeks with maternal methadone addiction. Clinical manifestations of withdrawal include sneezing, yawning, ravenous appetite, emesis, diarrhea, fever, diaphoresis, tachypnea, high-pitched cry, tremors, jitteriness, poor sleep, poor feeding, and seizures. The illness tends to be more severe during methadone withdrawal. The initial treatment includes swaddling in blankets in a quiet, dark room. When hyperactivity is constant, and irritability interferes with sleeping and feeding, or when diarrhea or seizures are present, pharmacological treatment is indicated. Seizures usually are treated with phenobarbital. The other symptoms may be managed with replacement doses of a narcotic (oral morphine, methadone, buprenorphine) to calm the infant; weaning from narcotics may be prolonged over 1-2 months.

Cocaine

Cocaine use during pregnancy is associated with preterm labor, abruptio placentae, neonatal irritability, and decreased attentiveness. Infants may be small for gestational age and have small head circumferences. Usually no treatment is needed.

CHAPTER 59

Maternal Diseases Affecting the Newborn

Maternal diseases during pregnancy can affect the fetus directly or indirectly (Table 59.1). Autoantibody-mediated diseases can have direct consequences on the fetus and neonate because the antibodies are usually of the immunoglobulin G (IgG) type and can cross the placenta to the fetal circulation.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is associated with thrombophilia and recurrent pregnancy loss. Antiphospholipid antibodies are found in 2-5% of the general healthy population, but they also may be associated with systemic lupus erythematosus (SLE) and other rheumatic diseases. Obstetric complications arise from the prothrombotic effects of the antiphospholipid antibodies on placental function. Vasculopathy, infarction, and thrombosis have been identified in mothers with antiphospholipid syndrome. Antiphospholipid syndrome can include fetal growth impairment, placental insufficiency, maternal preeclampsia, and premature birth.

IDIOPATHIC (IMMUNE) THROMBOCYTOPENIA

Idiopathic thrombocytopenic purpura (ITP) is seen in approximately 1-2 per 1,000 live births and is an immune process in which antibodies are directed against platelets. Platelet-associated IgG antibodies can cross the placenta and cause thrombocytopenia in the fetus and newborn. The severely thrombocytopenic fetus is at increased risk for intracranial hemorrhage. ITP during pregnancy requires close maternal and fetal management to reduce the risks of life-threatening maternal hemorrhage and trauma to the fetus at delivery. Postnatal management involves observation of the infant's platelet count. For infants

TABLE **59.1** Maternal Disease Affecting the Fetus or Neonate

MATERNAL DISORDER	FETAL/NEONATAL EFFECTS	MECHANISM
Cyanotic heart disease	Intrauterine growth restriction	Low fetal oxygen delivery
Diabetes mellitus		
Mild	Large for gestational age, hypoglycemia	Fetal hyperglycemia—produces hyperinsulinemia promoting growth
Severe	Growth retardation	Vascular disease, placental insufficiency
Drug abuse	Intrauterine growth restriction, neonatal withdrawal	Direct drug effect, plus poor diet
Endemic goiter	Hypothyroidism	Iodine deficiency
Graves disease	Transient thyrotoxicosis	Placental immunoglobulin passage of thyrotropin receptor antibody
Hyperparathyroidism	Hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Hypertension	Intrauterine growth restriction, intrauterine fetal demise	Placental insufficiency, fetal hypoxia
Idiopathic thrombocytopenic purpura	Thrombocytopenia	Nonspecific platelet antibodies cross placenta
Infection	Neonatal sepsis (see Chapter 66)	Transplacental or ascending infection
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetal neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Metastasis
Myasthenia gravis	Transient neonatal myasthenia	Immunoglobulin to acetylcholine receptor crosses the placenta
Myotonic dystrophy	Neonatal myotonic dystrophy	Autosomal dominant with genetic anticipation
Phenylketonuria	Microcephaly, retardation, ventricular septal defect	Elevated fetal phenylalanine levels
Rh or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	Antibody crosses placenta directed at fetal cells with antigen
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia, cardiomyopathy, stillbirth	Antibody directed at fetal heart, red and white blood cells, and platelets; lupus anticoagulant

From Stoll BJ, Kliegman RM. The fetus and neonatal infant. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. *16th ed. Philadelphia: Saunders; 2000.*

who have evidence of hemorrhage, single-donor irradiated platelets may be administered to control the bleeding. The infant may benefit from an infusion of intravenous immunoglobulin. Neonatal thrombocytopenia usually resolves within 4-6 weeks.

SYSTEMIC LUPUS ERYTHEMATOSUS

Immune abnormalities in SLE can lead to the production of anti-Ro (SS-A) and anti-La (SS-B) antibodies that can cross the placenta and injure fetal tissue. The most serious complication is damage to the cardiac conducting system, which results in **congenital heart block**. The heart block observed in association with maternal SLE tends to be complete (third degree), although less advanced blocks have been observed. The mortality rate is approximately 20%; most surviving infants require pacing. Neonatal lupus may occur and is characterized by skin lesions (sharply demarcated erythematous plaques or central atrophic macules with peripheral scaling with predilection for the eyes, face, and scalp), thrombocytopenia, autoimmune hemolysis, and hepatic involvement.

NEONATAL HYPERTHYROIDISM

Graves disease is associated with thyroid-stimulating antibodies. The prevalence of clinical hyperthyroidism in pregnancy has been reported to be about 0.1-0.4%; it is the second most common endocrine disorder during pregnancy (after diabetes). Neonatal hyperthyroidism is due to the transplacental passage of thyroid-stimulating antibodies; hyperthyroidism can appear rapidly within the first 12-48 hours. Symptoms may include intrauterine growth restriction, prematurity, goiter (may cause tracheal obstruction), exophthalmos, stare, craniosynostosis (usually coronal), flushing, heart failure, tachycardia, arrhythmias, hypertension, hypoglycemia, thrombocytopenia, and hepatosplenomegaly. Treatment includes propylthiouracil, iodine drops, and propranolol. Autoimmune induced neonatal hyperthyroidism usually resolves in 2-4 months.

TABLE 59.2 Problems of Diabetic Pregnancy

MATERNAL
Ketoacidosis
Hyperglycemia/hypoglycemia
Nephritis
Preeclampsia
Polyhydramnios
Retinopathy
NEONATAL
Birth asphyxia
Birth injury (macrosomia, shoulder dystocia)
Congenital anomalies (lumbosacral dysgenesis—caudal regression)
Congenital heart disease (ventricular and atrial septal defects, transposition of the great arteries, truncus arteriosus, double-outlet right ventricle, coarctation of the aorta)
Hyperbilirubinemia (unconjugated)
Hypocalcemia
Hypoglycemia
Hypomagnesemia
Neurological disorders (neural tube defects, holoprosencephaly)
Organomegaly
Polycythemia (hyperviscosity)
Renal disorders (double ureter, renal vein thrombosis, hydronephrosis, renal agenesis)
Respiratory distress syndrome
Small left colon syndrome
Transient tachypnea of the newborn

TABLE 59.3 Common Teratogenic Drugs

DRUG	RESULTS
Alcohol	Fetal alcohol syndrome, microcephaly, congenital heart disease
Aminopterin	Mesomelia, cranial dysplasia
Coumarin	Hypoplastic nasal bridge, chondrodysplasia punctata
Fluoxetine	Minor malformations, low birth weight, poor neonatal adaptation
Folic acid antagonists*	Neural tube, cardiovascular, renal, and oral cleft defects
Isotretinoin and vitamin A	Facial and ear anomalies, congenital heart disease
Lithium	Ebstein anomaly
Methyl mercury	Microcephaly, blindness, deafness, retardation (Minamata disease)
Misoprostol	Arthrogryposis
Penicillamine	Cutis laxa syndrome
Phenytoin	Hypoplastic nails, intrauterine growth restriction, typical facies
Radioactive iodine	Fetal hypothyroidism
Radiation	Microcephaly
Stilbestrol (DES)	Vaginal adenocarcinoma during adolescence
Streptomycin	Deafness
Testosterone-like drugs	Virilization of female
Tetracycline	Enamel hypoplasia
Thalidomide	Phocomelia
Toluene (solvent abuse)	Fetal alcohol–like syndrome, preterm labor
Trimethadione	Congenital anomalies, typical facies
Valproate	Spina bifida
Vitamin D	Supravalvular aortic stenosis

**Trimethoprim, triamterene, phenytoin, primidone, phenobarbital, carbamazepine.*

DIABETES MELLITUS

Diabetes mellitus that develops during pregnancy (*gestational diabetes* is noted in about 5% of women) or diabetes that is present before pregnancy adversely influences fetal and neonatal well-being. The effect of diabetes on the fetus depends, in part, on the severity of the diabetic state: age of onset of diabetes, duration of treatment with insulin, and presence of vascular disease. Poorly controlled maternal diabetes leads to maternal and fetal hyperglycemia that stimulates the fetal pancreas, resulting in hyperplasia of the islets of Langerhans. Fetal hyperinsulinemia results in increased fat and protein synthesis, producing a fetus that is large for gestational age. After birth, hyperinsulinemia persists, resulting in fasting neonatal hypoglycemia. Strictly controlling maternal diabetes during pregnancy and preventing hyperglycemia during labor and delivery prevent macrosomic fetal growth and neonatal hypoglycemia. Additional problems of the diabetic mother and her fetus and newborn are summarized in Table 59.2.

OTHER CONDITIONS

Other maternal illnesses, such as severe pulmonary disease (cystic fibrosis), cyanotic heart disease, and sickle cell anemia, may reduce oxygen availability to the fetus. Severe hypertensive or diabetic vasculopathy can result in uteroplacental insufficiency. The fetus and the newborn may also be adversely affected by the medications used to treat maternal illnesses. These effects may appear as teratogenesis (Table 59.3) or as an adverse metabolic, neurological, or cardiopulmonary adaptation to extrauterine life (Table 59.4). Acquired infectious diseases of the mother also may affect the fetus or newborn adversely.

TABLE **59.4** Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant

AGENT	POTENTIAL CONDITION(S)
Acebutolol	IUGR, hypotension, bradycardia
Acetazolamide	Metabolic acidosis
Adrenal corticosteroids	Adrenocortical failure (rare)
Amiodarone	Bradycardia, hypothyroidism
Anesthetic agents (volatile)	CNS depression
Aspirin	Neonatal bleeding, prolonged gestation
Atenolol	IUGR, hypoglycemia
Blue cohosh herbal tea	Neonatal heart failure
Bromides	Rash, CNS depression, IUGR
Captopril, enalapril	Transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of infant)	Bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)	Transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor	CNS depression, hypotonia
Cephalothin	Positive direct Coombs test reaction
Fluoxetine	Possible transient neonatal withdrawal, hypertonicity, minor anomalies
Haloperidol	Withdrawal
Hexamethonium bromide	Paralytic ileus
Ibuprofen	Oligohydramnios, PPHN
Imipramine	Withdrawal
Indomethacin	Oliguria, oligohydramnios, intestinal perforation, PPHN
Intravenous fluids during labor (e.g., salt-free solutions)	Electrolyte disturbances, hyponatremia, hypoglycemia
Iodide (radioactive)	Goiter
Iodides	Neonatal goiter
Lead	Reduced intellectual function
Magnesium sulfate	Respiratory depression, meconium plug, hypotonia
Methimazole	Goiter, hypothyroidism
Morphine and its derivatives (addiction)	Withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene	Hemolytic anemia (in G6PD-deficient infants)
Nitrofurantoin	Hemolytic anemia (in G6PD-deficient infants)
Oxytocin	Hyperbilirubinemia, hyponatremia
Phenobarbital	Bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine	Hemolytic anemia (in G6PD-deficient infants)
Propranolol	Hypoglycemia, bradycardia, apnea
Propylthiouracil	Goiter, hypothyroidism
Reserpine	Drowsiness, nasal congestion, poor temperature stability
Sulfonamides	Interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea	Refractory hypoglycemia
Sympathomimetic (tocolytic–β agonist) agents	Tachycardia
Thiazides	Neonatal thrombocytopenia (rare)

CNS, Central nervous system; *G6PD*, glucose-6-phosphate dehydrogenase; *IUGR*, intrauterine growth restriction; *PPHN*, persistent pulmonary hypertension of the newborn.

From Stoll BJ, Kliegman RM. The fetus and neonatal infant. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. *16th ed. Philadelphia: Saunders; 2000.*

CHAPTER 60

Diseases of the Fetus

The principal determinants of fetal disease include the fetal genotype and the in utero environment. Variation in environmental factors rather than the fetal genetics plays a more significant role in determining overall fetal well-being, although a genetically abnormal fetus may not thrive as well or survive. The ability to assess a fetus genetically, biochemically, and physically is greatly enhanced through the development of amniocentesis, fetoscopy, chorionic villus sampling, fetal blood sampling, genetic testing of circulating fetal DNA in the mother's blood, and real-time ultrasonography.

INTRAUTERINE GROWTH RESTRICTION AND SMALL FOR GESTATIONAL AGE

Fetuses subjected to abnormal maternal, placental, or fetal conditions that restrain growth are a high-risk group and traditionally classified as having intrauterine growth restriction (IUGR). The terms *IUGR* and *small for gestational age (SGA)* are not synonymous. IUGR represents a deviation from expected growth patterns. The decreased fetal growth associated with IUGR is an adaptation to unfavorable intrauterine conditions that result in permanent alterations in metabolism, growth, and development. IUGR most frequently occurs with a variety of maternal conditions that are associated with preterm delivery. SGA describes an infant whose birth weight is statistically less than the 10th percentile or two standard deviations below the mean birth weight for gestational age. The cause of SGA may be pathological, as in an infant with IUGR, or nonpathological, as in an infant who is small but otherwise healthy (Table 60.1).

Only about 50% of IUGR infants are identified before delivery. Measurement and recording of maternal fundal height in conjunction with serial ultrasound assessment of the fetus (growth rate, amniotic fluid volume, malformations, anomalies, and Doppler velocimetry of uterine, placental, and fetal blood flow) can aid detection. When suspected and identified, IUGR and SGA fetuses must be monitored for fetal well-being, and appropriate maternal care needs to be instituted (see Chapter 58).

At birth, infants who are mildly to moderately SGA appear smaller than normal with decreased subcutaneous fat. More severely affected infants may present with a *wasted appearance* with asymmetrical findings, including larger heads for the size of the body (central nervous system sparing), widened anterior fontanelles, small abdomen, thin arms and legs, decreased subcutaneous fat, dry and redundant skin, decreased muscle mass, and thin (often meconium-stained) umbilical cord. Gestational age is often difficult to assess when based on physical appearance and perceived advanced neurological maturity. Physical examination should detail the presence of dysmorphic features, abnormal extremities, or gross anomalies that might suggest underlying congenital malformations, chromosomal defects, or exposure to teratogens. Hepatosplenomegaly, jaundice, and skin rashes in addition to ocular disorders, such as chorioretinitis, cataracts, glaucoma, and cloudy cornea, suggest the presence of a congenital infection or inborn error of metabolism. Infants with severe IUGR or SGA, particularly in conjunction with fetal distress, may have problems at birth that include respiratory acidosis, metabolic acidosis, asphyxia, hypoxemia, hypotension, hypoglycemia, polycythemia, meconium aspiration syndrome, and persistent pulmonary hypertension of the newborn.

Management of IUGR and SGA infants is usually symptomatic and supportive. The diagnostic evaluation at birth should be directed at identifying the cause of the IUGR and SGA, if possible. The consequences of IUGR and SGA depend on the etiology, severity, and duration of growth retardation. The mortality rates of infants who are severely affected are 5-20 times

TABLE 60.1 Etiologies for Intrauterine Growth Restriction and Small for Gestational Age at Birth

MATERNAL FACTORS
Age (young and advanced)
Cigarette smoking
Genetics (short stature, weight)
Illnesses during pregnancy (preeclampsia, severe diabetes, chronic hypertension, connective tissue disease)
Infections (intrauterine)
Lack of good prenatal care
Oligohydramnios
Poor nutrition
Race (African American)
FETAL FACTORS
Chromosomal abnormality and nonchromosomal syndromes
Congenital infections
Inborn errors of metabolism
Multiple gestations
Insulin resistance or reduced insulin or insulin-like growth factor-1 production
MATERNAL MEDICATIONS
Antimetabolites (methotrexate)
Heavy metals (mercury, lead)
Hydantoin
Narcotics (morphine, methadone)
Steroids (prednisone)
Substance and illicit drug use (alcohol, cocaine)
Warfarin
PLACENTAL AND UTERINE ABNORMALITIES
Abruptio placentae
Abnormal implantation
Abnormal placental vessels
Chorioangioma
Circumvallate placenta
Fetal vessel thrombosis
Ischemic villus necrosis
Multiple gestations
True knots in umbilical cord
Villitis (congenital infection)

those of infants who are appropriate for gestational age. Postnatal growth and development depend in part on the etiology, the postnatal nutritional intake, and the social environment. Infants who have IUGR and SGA secondary to congenital infection, chromosomal abnormalities, or constitutional syndromes remain small throughout life. Infants who have growth inhibited late in gestation because of uterine constraints, placental insufficiency, or poor nutrition have catch-up growth and, under optimal environmental conditions, approach their inherited growth and development potential.

HYDROPS FETALIS

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Anemia

Hydrops fetalis is caused by immune and nonimmune conditions. Hydrops fetalis is a fetal clinical condition of excessive fluid accumulation in the skin and one or more other body compartments, including the pleural space, peritoneal cavity, pericardial sac, or placenta with resultant high morbidity and mortality. Hydrops initially was described in association with Rhesus blood group isoimmunization. The use of Rho (D) immune globulin has reduced the incidence of isoimmune fetal hydrops. Concurrently the incidence of nonimmune hydrops has increased as a cause of this severe clinical condition.

Fetal hydrops results from an imbalance of interstitial fluid accumulation and decreased removal of fluid by the capillaries and lymphatic system. Fluid accumulation can be secondary to congestive heart failure, obstructed lymphatic flow, or decreased plasma oncotic pressure (hypoproteinemic states). Edema formation is the final common pathway for many disease processes that affect the fetus, including fetal cardiac, genetic, hematological, metabolic, infection, or malformation syndromes.

The diagnostic work-up of the hydropic fetus should focus on discovering the underlying cause. Maternal findings may include hypertension, anemia, multiple gestation, thickened placenta, and polyhydramnios, whereas fetal findings may include tachycardia, ascites, scalp and body wall edema, and pleural and pericardial effusion. Invasive fetal testing may be indicated. Amniocentesis provides amniotic fluid samples for karyotype, culture, alpha-fetoprotein, and metabolic and enzyme analysis. Percutaneous umbilical cord blood sampling can provide fetal blood for chromosomal analysis and hematological and metabolic studies and provide a source for intervention (fetal transfusion for profound anemia).

Management depends on the underlying cause and the gestational age of the fetus. Resuscitative efforts at delivery are often required. It is often necessary to remove ascitic fluid from the abdomen or pleural fluid to improve ventilation. Profound anemia necessitates immediate transfusion with packed red blood cells.

The overall mortality for infants with nonimmune hydrops is approximately 50%. If the diagnosis is made before 24 weeks of gestation with subsequent premature delivery, the survival rate is approximately 4-6%.

CHAPTER 61
Respiratory Diseases of the Newborn

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Acidemia

Respiratory distress that becomes manifested by tachypnea, intercostal retractions, reduced air exchange, cyanosis, expiratory grunting, and nasal flaring is a nonspecific response to serious illness. The differential diagnosis of respiratory distress includes pulmonary, cardiac, hematological, infectious, anatomical, and metabolic disorders that may involve the lungs directly or indirectly. Surfactant deficiency causes **respiratory distress syndrome (RDS)**, resulting in cyanosis and tachypnea; **infection** produces pneumonia, shown by interstitial or lobar infiltrates; **meconium aspiration** results in a chemical pneumonitis with hypoxia and pulmonary hypertension; **hydrops fetalis** causes anemia and hypoalbuminemia with high-output heart failure and pulmonary edema; and congenital or acquired **pulmonary hypoplasia** causes pulmonary hypertension and pulmonary insufficiency. It also is clinically useful to differentiate the common causes of respiratory distress according to gestational age (Table 61.1).

TABLE 61.1 Etiology of Respiratory Distress

PRETERM INFANT
Respiratory distress syndrome (RDS)*
Erythroblastosis fetalis
Nonimmune hydrops
Pulmonary hemorrhage
FULL-TERM INFANT
Primary pulmonary hypertension of the neonate*
Meconium aspiration pneumonia*
Polycythemia
Amniotic fluid aspiration
PRETERM AND FULL-TERM INFANT
Bacterial sepsis (GBS)*
Transient tachypnea*
Spontaneous pneumothorax
Congenital anomalies (e.g., congenital lobar emphysema, cystic adenomatoid malformation, diaphragmatic hernia)
Congenital heart disease
Pulmonary hypoplasia
Viral infection (e.g., herpes simplex, CMV)
Inborn metabolic errors

**Common.*
CMV, Cytomegalovirus; *GBS*, group B streptococcus.

In addition to the specific therapy for the individual disorder, supportive care and evaluation of the infant with respiratory distress can be applied to all the problems mentioned earlier (Table 61.2). Blood gas monitoring and interpretation are key components of general respiratory care.

Treatment of hypoxemia requires knowledge of normal values. In term infants, the arterial Pa_{O_2} level is 55-60 mm Hg at 30 minutes of life, 75 mm Hg at 4 hours, and 90 mm Hg at 24 hours. Preterm infants have lower values. Pa_{CO_2} levels should be 35-40 mm Hg, and the pH should be 7.35-7.40. It is imperative that arterial blood gas analysis be performed in all infants with significant respiratory distress, whether or not cyanosis is perceived. Cyanosis becomes evident when there is 5 g of unsaturated hemoglobin; anemia may interfere with the perception of cyanosis. Jaundice also may interfere with the appearance of cyanosis. Capillary blood gas determinations are useful in determining blood pH and the Pa_{CO_2} level but may result in falsely low blood Pa_{O_2} readings. Serial blood gas levels may be monitored by an indwelling arterial catheter placed in a peripheral artery or through the umbilical artery. Another method for monitoring blood gas levels is to combine capillary blood gas techniques with noninvasive methods used to monitor oxygen (pulse oximetry or transcutaneous oxygen diffusion).

Metabolic acidosis, defined as a reduced pH (<7.25) and bicarbonate concentration (<18 mEq/L) accompanied by a normal or low Pa_{CO_2} level, may be caused by hypoxia or by insufficient tissue perfusion. The origin of the disorder may be pulmonary, cardiac, infectious, renal, hematological, nutritional, metabolic, or iatrogenic. The initial approach to metabolic acidosis is to determine the cause and treat the pathophysiological problem. This approach may include, as in the sequence of therapy for hypoxia, increasing the inspired oxygen concentration; applying continuous positive airway pressure (CPAP) nasally; or initiating mechanical ventilation using positive end-expiratory pressure. Patients with hypotension produced by hypovolemia require fluids and may need inotropic or vasoactive drug support. If metabolic acidosis persists despite specific therapy, sodium bicarbonate (1 mEq/kg/dose) may be given by slow intravenous infusion. Near-normal or low P_{CO_2} levels should be documented before sodium bicarbonate infusion. The buffering effect of sodium bicarbonate results in increased P_{CO_2} levels, unless adequate ventilation is maintained.

Respiratory acidosis, defined as an elevated P_{CO_2} level and reduced pH without a reduction in the bicarbonate concentration, may be caused by pulmonary insufficiency or central hypoventilation. Most disorders producing respiratory distress can lead to hypercapnia. Treatment involves assisted ventilation but not sodium bicarbonate. If central nervous system depression of respirations is caused by placental passage of narcotic analgesics, assisted ventilation is instituted first, then the central nervous system depression is reversed by naloxone.

TABLE 61.2 Initial Laboratory Evaluation of Respiratory Distress

TEST	RATIONALE
Chest radiograph	To determine reticular granular pattern of RDS; to determine presence of pneumothorax, cardiomegaly, life-threatening congenital anomalies
Arterial blood gas	To determine severity of respiratory compromise, hypoxemia, and hypercapnia and type of acidosis; severity determines treatment strategy
Complete blood count	Hemoglobin/hematocrit to determine anemia and polycythemia; white blood cell count to determine neutropenia/sepsis; platelet count and smear to determine DIC
Blood culture	To recover potential pathogen
Blood glucose	To determine presence of hypoglycemia, which may produce or occur simultaneously with respiratory distress; to determine stress hyperglycemia
Echocardiogram, ECG	In the presence of a murmur, cardiomegaly, or refractory hypoxia; to determine structural heart disease or PPHN

DIC, Disseminated intravascular coagulation; *ECG*, electrocardiogram; *PPHN*, primary pulmonary hypertension of the newborn; *RDS*, respiratory distress syndrome.

RESPIRATORY DISTRESS SYNDROME (HYALINE MEMBRANE DISEASE)

RDS occurs after the onset of breathing and is associated with an insufficiency of pulmonary surfactant.

Lung Development

The lining of the alveolus consists of 90% type I cells and 10% type II cells. After 20 weeks of gestation, the type II cells contain vacuolated, osmophilic, lamellar inclusion bodies, which are packages of surface-active material (Fig. 61.1). This lipoprotein surfactant is 90% lipid and is composed predominantly of saturated phosphatidylcholine (lecithin), but also contains phosphatidylglycerol, other phospholipids, and neutral lipids. The surfactant proteins, SP-A, SP-B, SP-C, and SP-D, are packaged into the lamellar body and contribute to surface-active properties and recycling of surfactant. Surfactant prevents atelectasis by reducing surface tension at low lung volumes when it is concentrated at end expiration as the alveolar radius decreases; surfactant contributes to lung recoil by increasing surface tension at larger lung volumes when it is diluted during inspiration as the alveolar radius increases. Without surfactant, surface tension forces are not reduced, and atelectasis develops during end expiration as the alveolus collapses.

The timing of surfactant production in quantities sufficient to prevent atelectasis depends on an increase in fetal cortisol levels that begins between 32 and 34 weeks of gestation. By 34-36 weeks, sufficient surface-active material is produced by the type II cells in the lung, is secreted into the alveolar lumen, and is excreted into the amniotic fluid. The concentration of lecithin in amniotic fluid indicates fetal pulmonary maturity. Because the amount of lecithin is difficult to quantify, the ratio of lecithin (which increases with maturity) to sphingomyelin (which remains constant during gestation; L/S ratio) is determined. An L/S ratio of 2:1 usually indicates pulmonary maturity. The presence of minor phospholipids, such as phosphatidylglycerol, also is indicative of fetal lung maturity and may be useful in situations in which the L/S ratio is borderline or possibly affected by maternal diabetes, which reduces lung maturity. The absence of phosphatidylglycerol suggests that surfactant might not be mature.

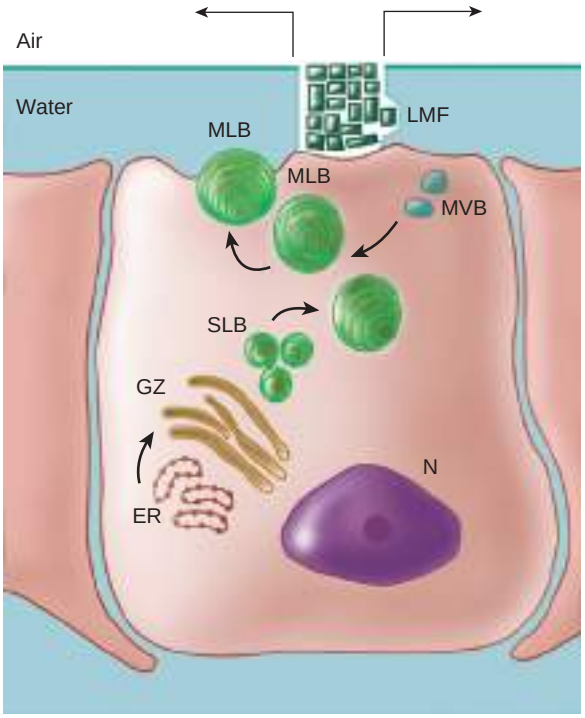

FIGURE 61.1 Proposed pathway of synthesis, transport, secretion, and reuptake of surfactant in the type II alveolar cell. Phospholipids are synthesized in the smooth endoplasmic reticulum (ER). The glucose/glycerol precursor may be derived from lung glycogen or circulating glucose. Phospholipids and surfactant proteins are packaged in the Golgi apparatus (GZ), emerge as small lamellar bodies (SLB), coalesce to mature lamellar bodies (MLB), migrate to the apical membrane, and are released by exocytosis into the liquid hypophase below the air-liquid interface. The tightly coiled lamellar body unravels to form the lattice (tubular) myelin figure (LMF), the immediate precursor to the phospholipid monolayer at the alveolar surface. Reuptake by endocytosis forms multivesicular bodies (MVB) that recycle surfactant. The enzymes, receptors, transporters, and surfactant proteins are controlled by regulatory processes at the transcriptional level in the nucleus (N). Corticosteroid and thyroid hormones are regulatory ligands that may accelerate surfactant synthesis. (From Hansen T, Corbet A. Lung development and function. In: Taeusch HW, Ballard R, Avery ME, eds. *Diseases of the Newborn*. 6th ed. Philadelphia: Saunders; 1991:465.)

Clinical Manifestations

A deficiency of pulmonary surfactant (most often due to prematurity) results in atelectasis, decreased functional residual capacity, arterial hypoxemia, and respiratory distress. Surfactant synthesis may also be reduced as a result of hypovolemia, hypothermia, acidosis, hypoxemia, and rare genetic disorders of surfactant synthesis. These factors also produce pulmonary artery vasospasm, which may contribute to RDS in larger premature infants who have developed sufficient pulmonary arteriole smooth muscle to produce vasoconstriction. Surfactant deficiency–induced atelectasis causes alveoli to be perfused but not ventilated, which results in a pulmonary shunt and hypoxemia. As atelectasis increases, the lungs become increasingly difficult to expand, and lung compliance decreases. Because the chest wall of the premature infant is very compliant, the infant attempts to overcome decreased lung compliance with increasing inspiratory pressures, resulting in retractions of the chest wall. The sequence of decreased lung compliance and chest wall retractions leads to poor air exchange, an increased physiological dead space, alveolar hypoventilation, and hypercapnia. A cycle of hypoxia, hypercapnia, and acidosis acts on type II cells to reduce surfactant synthesis and, in some infants, on the pulmonary arterioles to produce pulmonary hypertension.

Infants at greatest risk for RDS are premature and have an immature L/S ratio. The incidence of RDS increases with decreasing gestational age. RDS develops in 30-60% of infants between 28 and 32 weeks of gestation. Other risk factors include delivery of a previous preterm infant with RDS, maternal diabetes, hypothermia, fetal distress, asphyxia, male sex, white race, being the second-born of twins, and delivery by cesarean section without labor.

RDS may develop immediately in the delivery room in extremely immature infants at 26-30 weeks of gestation. Some more mature infants (34 weeks' gestation) may not show signs of RDS until 3-4 hours after birth, correlating with the initial release of stored surfactant at the onset of breathing accompanied by the ongoing inability to replace the surfactant owing to inadequate stores. **Manifestations** of RDS include cyanosis, tachypnea, nasal flaring, intercostal and sternal retractions, and grunting. Grunting is caused by closure of the glottis during expiration, the effect of which is to maintain lung volume (decreasing atelectasis) and gas exchange during exhalation. Atelectasis is well documented by radiographic examination of the chest, which shows a ground-glass haze in the lung surrounding air-filled bronchi (the air bronchogram; Fig. 61.2). Severe RDS may show an airless lung field *(whiteout)* on a radiograph, even obliterating the distinction between the atelectatic lungs and the heart.

During the first 72 hours, infants with untreated RDS have increasing distress and hypoxemia. In infants with severe RDS, the development of edema, apnea, and respiratory failure necessitates assisted ventilation. Thereafter, uncomplicated cases show a spontaneous improvement that often is heralded by diuresis and a marked resolution of edema. Complications include the development of a pneumothorax, a patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). The differential diagnosis of RDS includes diseases associated with cyanosis and respiratory distress (see Table 58.10).

Prevention and Treatment

Strategies to prevent preterm birth include maternal cervical cerclage, bed rest, treatment of infections, and administration of tocolytic medications. In addition, prevention of neonatal cold stress, birth asphyxia, and hypovolemia reduces the risk of RDS. If premature delivery is unavoidable, the antenatal administration of corticosteroids (e.g., betamethasone) to the mother (and thus to the fetus) stimulates fetal lung production of surfactant; this approach requires multiple doses for at least 48 hours.

After birth, RDS may be prevented or its severity reduced by intratracheal administration of exogenous surfactant immediately after birth in the delivery room or within a few hours of birth. Exogenous surfactant can be administered repeatedly during the course of RDS in patients receiving endotracheal intubation, mechanical ventilation, and oxygen therapy. Early application of nasal CPAP may also reduce the severity of RDS. Additional management includes the general supportive and ventilation care presented in Table 61.3.

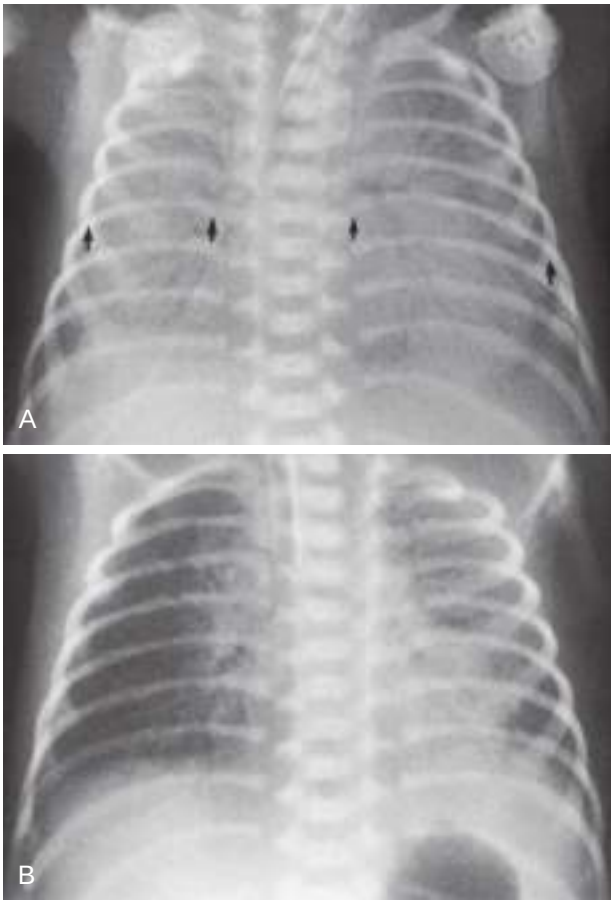

FIGURE 61.2 Respiratory distress syndrome. The infant is intubated, and the lungs show a dense reticulonodular pattern with air bronchograms **(A)**. To evaluate rotation on the frontal chest, the lengths of the posterior ribs are compared from left to right *(arrows)*. Because the infant is supine, the side of the longer ribs indicates to which side the thorax is rotated. In this case, the left ribs are longer, and this radiograph is a left posterior oblique view. Surfactant was administered, resulting in significant improvement in the density of the lung **(B)**. The right lung is slightly better aerated than the left. Uneven distribution of clearing is common. (From Hilton S, Edwards D. *Practical Pediatric Radiology*. 2nd ed. Philadelphia: Saunders; 1994.)

TABLE 61.3 Potential Causes of Neonatal Apnea

Central nervous system	IVH, drugs, seizures, hypoxic injury
Respiratory	Pneumonia, obstructive airway lesions, atelectasis, extreme prematurity (<1,000 g), laryngeal reflex, phrenic nerve paralysis, severe RDS, pneumothorax
Infectious	Sepsis, necrotizing enterocolitis, meningitis (bacterial, fungal, viral)
Gastrointestinal	Oral feeding, bowel movement, gastroesophageal reflux, esophagitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓ P_{O_2}, ↓↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, change in vagal tone
Idiopathic	Immaturity of respiratory center, sleep state, upper airway collapse

IVH, Intraventricular hemorrhage; *RDS*, respiratory distress syndrome.

The Pa_{O_2} level should be maintained between 60 and 70 mm Hg (oxygen saturation 90%), and the pH should be maintained above 7.25. An increased concentration of warm and humidified inspired oxygen administered by a nasal cannula or an oxygen hood may be all that is needed for larger premature infants. If hypoxemia (Pa_{O_2} <50 mm Hg) is present, and the needed inspired oxygen concentration is 70-100%, nasal CPAP should be added at a distending pressure of 8-10 cm H_2O. If respiratory failure ensues (P_{CO_2} >60 mm Hg, pH <7.20, and Pa_{O_2} <50 mm Hg with 100% oxygen), assisted ventilation using a ventilator is indicated. Conventional rate (25-60 breaths/min), high-frequency jet (150-600 breaths/min), and oscillatory (900-3,000 breaths/min) ventilators all have been successful in managing respiratory failure caused by severe RDS. Suggested starting settings on a conventional ventilator are fraction of inspired oxygen, 0.60-1.0; peak inspiratory pressure, 20-25 cm H_2O; positive end-expiratory pressure, 5 cm H_2O; and respiratory rate, 30-50 breaths/min.

In response to persistent hypercapnia, alveolar ventilation (tidal volume – dead space × rate) must be increased. Ventilation can be increased by an increase in the ventilator's rate or an increase in the tidal volume (the gradient between peak inspiratory pressure and positive end-expiratory pressure using a pressure-controlled ventilator). In response to hypoxia, the inspired oxygen content may be increased. Alternatively, the degree of oxygenation depends on the mean airway pressure. Mean airway pressure is directly related to positive end-expiratory pressure, flow, and inspiratory time. Increased mean airway pressure may improve oxygenation by improving lung volume, enhancing ventilation-perfusion matching. Because of the difficulty in distinguishing sepsis and pneumonia from RDS, broad-spectrum parenteral antibiotics (ampicillin and gentamicin) are administered for 48-72 hours, pending the recovery of an organism from a previously obtained blood culture.

COMPLICATIONS OF RESPIRATORY DISTRESS SYNDROME

Patent Ductus Arteriosus

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Heart Murmurs

PDA is a common complication that occurs in many low birth weight infants who have RDS. The incidence of PDA is inversely related to the maturity of the infant. In term newborns, the ductus closes within 24-48 hours after birth. However, in preterm newborns, the ductus frequently fails to close, requiring medical or surgical closure. The ductus arteriosus in a preterm infant is less responsive to vasoconstrictive stimuli, which, when complicated with hypoxemia during RDS, may lead to a persistent PDA that creates a shunt between the pulmonary and systemic circulations.

During the acute phase of RDS, hypoxia, hypercapnia, and acidosis lead to pulmonary arterial vasoconstriction. The pulmonary and systemic pressures may be equal, and flow through the ductus may be small or bidirectional. When RDS improves and pulmonary vascular resistance declines, flow through the ductus arteriosus increases in a left-to-right direction. Significant

systemic-to-pulmonary shunting may lead to heart failure and pulmonary edema. Excessive intravenous fluid administration may increase the incidence of symptomatic PDA. The infant's respiratory status deteriorates because of increased lung fluid, hypercapnia, and hypoxemia.

Clinical manifestations of a PDA usually become apparent on day 2-4 of life. Because the left-to-right shunt directs flow to a low-pressure circulation from one of high pressure, the pulse pressure widens; a previously inactive precordium shows an extremely active precordial impulse, and peripheral pulses become easily palpable and bounding. The murmur of a PDA may be continuous in systole and diastole, but usually only the systolic component is auscultated. Heart failure and pulmonary edema result in rales and hepatomegaly. A chest radiograph shows cardiomegaly and pulmonary edema; a two-dimensional echocardiogram shows ductal patency; and Doppler studies show markedly increased left-to-right flow through the ductus.

Treatment of a PDA during RDS involves initial fluid restriction and diuretic administration. If there is no improvement after 24-48 hours, a prostaglandin synthetase inhibitor, indomethacin or ibuprofen, is administered. Contraindications to using indomethacin include thrombocytopenia (platelets <50,000/mm^3), bleeding, serum creatinine measuring more than 1.8 mg/dL, and oliguria. Because 20-30% of infants do not respond initially to indomethacin and because the PDA reopens in 10-20% of infants, a repeat course of indomethacin or surgical ligation is required in some patients.

FIGURE 61.3 Pneumothorax. Right-sided hyperlucent pleural air is obvious. The findings of linear interstitial air and the resultant noncompliant but collapsed lung are noted. (From Heller RM, Kirchner SG. *Advanced Exercises in Diagnostic Radiology: the Newborn*. Philadelphia: WB Saunders; 1979.)

Pulmonary Air Leaks

Assisted ventilation with high peak inspiratory pressures and positive end-expiratory pressures may cause overdistention of alveoli in localized areas of the lung. Rupture of the alveolar epithelial lining may produce pulmonary interstitial emphysema as gas dissects along the interstitial space and the peribronchial lymphatics. Extravasation of gas into the parenchyma reduces lung compliance and worsens respiratory failure. Gas dissection into the mediastinal space produces a pneumomediastinum, occasionally dissecting into the subcutaneous tissues around the neck, causing subcutaneous emphysema.

Alveolar rupture adjacent to the pleural space produces a **pneumothorax** (Fig. 61.3). If the gas is under tension, the pneumothorax shifts the mediastinum to the opposite side of the chest, producing hypotension, hypoxia, and hypercapnia. The diagnosis of a pneumothorax may be based on unequal transillumination of the chest and may be confirmed by chest radiograph. Treatment of a symptomatic pneumothorax requires insertion of a pleural chest tube connected to negative pressure or to an underwater drain. Prophylactic or therapeutic use of exogenous surfactant has reduced the incidence of pulmonary air leaks.

Pneumothorax also is observed after vigorous resuscitation, meconium aspiration pneumonia, pulmonary hypoplasia, and diaphragmatic hernia. Spontaneous pneumothorax is seen in fewer than 1% of deliveries and may be associated with renal malformations.

Bronchopulmonary Dysplasia (Chronic Lung Disease)

BPD is a clinical diagnosis defined by oxygen dependence at 36 weeks' postconceptual age and accompanied by characteristic clinical and radiographic findings that correspond to anatomical abnormalities. Oxygen concentrations greater than 40% are toxic to the neonatal lung. Oxygen-mediated lung injury results from the generation of superoxides, hydrogen peroxide, and oxygen free radicals, which disrupt membrane lipids. Assisted ventilation with high peak pressures produces barotrauma, compounding the damaging effects of highly inspired oxygen levels. In most patients, BPD develops after ventilation for RDS that may have been complicated by PDA or pulmonary interstitial emphysema. Inflammation from prolonged assisted ventilation and repeated systemic and pulmonary infections may play a major role. Failure of RDS to improve after 2 weeks, the need for prolonged mechanical ventilation, and oxygen therapy required at 36 weeks' postconceptual age are characteristic of patients with RDS in whom BPD develops. BPD also may develop in infants weighing less than 1,000 g who require mechanical ventilation for poor respiratory drive in the absence of RDS. Fifty percent of infants of 24-26 weeks' gestational age require oxygen at 36 weeks' corrected age.

The **radiographic appearance** of BPD is characterized initially by lung opacification and subsequently by development of cysts accompanied by areas of overdistention and atelectasis, giving the lung a spongelike appearance. The histopathology of BPD reveals interstitial edema, atelectasis, mucosal metaplasia, interstitial fibrosis, necrotizing obliterative bronchiolitis, and overdistended alveoli.

The **clinical manifestations** of BPD are oxygen dependence, hypercapnia with a compensatory metabolic alkalosis, pulmonary hypertension, poor growth, and development of right-sided heart failure. Increased airway resistance with reactive airway bronchoconstriction also is noted and is treated with bronchodilating agents. Severe chest retractions produce negative interstitial pressure that draws fluid into the interstitial space. Together with cor pulmonale, these chest retractions

cause fluid retention, necessitating fluid restriction and the administration of diuretics.

Patients with severe BPD may need treatment with mechanical ventilation for many months. To reduce the risk of subglottic stenosis, a tracheotomy may be indicated. To reduce oxygen toxicity and barotrauma, ventilator settings are reduced to maintain blood gases with slightly lower Pa_{O_2} (50 mm Hg) and higher Pa_{CO_2} (50-75 mm Hg) levels than for infants during the acute phase of RDS. Dexamethasone therapy may reduce inflammation, improve pulmonary function, and enhance weaning of patients from assisted ventilation. However, dexamethasone may increase the risk of cerebral palsy or abnormal neuromotor developmental outcome. Older survivors of BPD have hyperinflation, reactive airways, and developmental delay. They are at risk for severe respiratory syncytial virus pneumonia and as infants should receive prophylaxis against respiratory syncytial virus.

Retinopathy of Prematurity (Retrolental Fibroplasia)

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Visual Impairment and Leukocoria

Retinopathy of prematurity (ROP) is caused by the acute and chronic effects of oxygen toxicity on the developing blood vessels of the premature infant's retina. The completely vascularized retina of the term infant is not susceptible to ROP. ROP is a leading cause of blindness in very low birth weight infants (<1,500 g). Excessive arterial oxygen tensions produce vasoconstriction of immature retinal vasculature in the first stage of this disease. Vaso-obliteration follows if the duration and extent of hyperoxia are prolonged beyond the time when vasoconstriction is reversible. Hypercarbia and hypoxia may contribute to ROP. The subsequent proliferative stages are characterized by extraretinal fibrovascular proliferation, forming a ridge between the vascular and avascular portions of the retina, and by the development of neovascular tufts. In mild cases, vasoproliferation is noted at the periphery of the retina. Severe cases may have neovascularization involving the entire retina, retinal detachment resulting from traction on vessels as they leave the optic disc, fibrous proliferation behind the lens producing leukokoria, and synechiae displacing the lens forward, leading to glaucoma. Both eyes usually are involved, but severity may be asymmetrical.

The incidence of ROP may be reduced by careful monitoring of arterial blood gas levels in all patients receiving oxygen. Although there is no absolutely safe Pa_{O_2} level, it is wise to keep the arterial oxygen level between 50 and 70 mm Hg in premature infants. Infants who weigh less than 1,500 g or who are born before 28 weeks' gestational age (some authors say 32 weeks) should be screened when they are 4 weeks of age or more than 34 weeks' corrected gestational age, whichever comes first. Laser therapy or (less often) cryotherapy may be used for vitreous hemorrhage or for severe, progressive vasoproliferation. Surgery is indicated for retinal detachment. Less severe stages of ROP resolve spontaneously and without visual impairment in most patients.

TRANSIENT TACHYPNEA OF THE NEWBORN

Transient tachypnea of the newborn is a self-limited condition characterized by tachypnea, mild retractions, hypoxia, and occasional grunting, usually without signs of severe respiratory distress. Cyanosis, when present, usually requires treatment with supplemental oxygen in the range of 30-40%. Transient tachypnea of the newborn usually is noted in larger premature infants and in term infants born by precipitous delivery or cesarean section without prior labor. Infants of diabetic mothers and infants with poor respiratory drive as a result of placental passage of analgesic drugs are at risk. Transient tachypnea of the newborn may be caused by retained lung fluid or slow resorption of lung fluid. Chest radiographs show prominent central vascular markings, fluid in the lung fissures, overaeration, and occasionally a small pleural effusion. Air bronchograms and a reticulogranular pattern are not seen; their presence suggests another pulmonary process, such as RDS or pneumonia.

MECONIUM ASPIRATION SYNDROME

Meconium-stained amniotic fluid is seen in 15% of predominantly term and post-term deliveries. Although the passage of meconium into amniotic fluid is common in infants born in the breech presentation, meconium-stained fluid should be considered clinically as a sign of fetal distress in all infants. The presence of meconium in the amniotic fluid suggests in utero distress with asphyxia, hypoxia, and acidosis.

Aspiration of amniotic fluid contaminated with particulate meconium may occur in utero in a distressed, gasping fetus; more often, meconium is aspirated into the lung immediately after delivery. Affected infants have abnormal chest radiographs, showing a high incidence of pneumonia and pneumothoraces.

Meconium aspiration pneumonia is characterized by tachypnea, hypoxia, hypercapnia, and small airway obstruction causing a ball-valve effect, leading to air trapping, overdistention, and extra-alveolar air leaks. Complete small-airway obstruction produces atelectasis. Within 24-48 hours, a chemical pneumonitis develops in addition to the mechanical effects of airway obstruction. Abnormal pulmonary function may be caused by the meconium, in part, through inactivation of surfactant. Primary pulmonary hypertension of the newborn (PPHN) frequently accompanies meconium aspiration, with right-to-left shunting caused by increased pulmonary vascular resistance. The chest radiograph reveals patchy infiltrates, overdistention, flattening of the diaphragm, increased anteroposterior diameter, and a high incidence of pneumomediastinum and pneumothoraces. Comorbid diseases include those associated with in utero asphyxia that initiated the passage of meconium.

Treatment of meconium aspiration includes general supportive care and assisted ventilation. Infants with a PPHN-like presentation should be treated for PPHN. If severe hypoxia does not subside with conventional or high-frequency ventilation, surfactant therapy, and inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO) may be beneficial.

Prevention of meconium aspiration syndrome involves careful in utero monitoring to prevent asphyxia. When meconium-stained fluid is observed, the obstetrician should suction the infant's oropharynx before delivering the rest of the infant's body. If the infant is depressed with poor tone, minimal respiratory effort, and cyanosis, the infant's oropharynx should

be suctioned, the vocal cords visualized, and the area below the vocal cords suctioned to remove any meconium from the trachea. Saline intrauterine amnioinfusion during labor may reduce the incidence of aspiration and pneumonia.

PRIMARY PULMONARY HYPERTENSION OF THE NEWBORN

PPHN occurs in post-term, term, or near-term infants. PPHN is characterized by severe hypoxemia, without evidence of parenchymal lung or structural heart disease. PPHN is often seen with asphyxia or meconium-stained fluid. The chest radiograph usually reveals normal lung fields rather than the expected infiltrates and hyperinflation that may accompany meconium aspiration. Additional problems that may lead to PPHN are congenital pneumonia, hyperviscosity-polycythemia, congenital diaphragmatic hernia, pulmonary hypoplasia, congenital cyanotic heart disease, hypoglycemia, and hypothermia. Total anomalous venous return associated with obstruction of blood flow may produce a clinical picture that involves severe hypoxia and that is initially indistinguishable from PPHN; however, a chest radiograph reveals severe pulmonary venous engorgement and a small heart. Echocardiography or cardiac catheterization confirms the diagnosis.

Significant right-to-left shunting through a patent foramen ovale, through a PDA, and through intrapulmonary channels is characteristic of PPHN. The pulmonary vasculature often shows hypertrophied arterial wall smooth muscle, suggesting that the process of or predisposition to PPHN began in utero as a result of previous periods of fetal hypoxia. After birth, hypoxia, hypercapnia, and acidosis exacerbate pulmonary artery vasoconstriction, leading to further hypoxia and acidosis. Some infants with PPHN have extrapulmonary manifestations as a result of asphyxia. Myocardial injuries include heart failure, transient mitral insufficiency, and papillary muscle or myocardial infarction. Thrombocytopenia, right atrial thrombi, and pulmonary embolism also may be noted.

The **diagnosis** is confirmed by echocardiographic examination, which shows elevated pulmonary artery pressures and sites of right-to-left shunting. Echocardiography also rules out structural congenital heart disease and transient myocardial dysfunction.

Treatment involves general supportive care; correction of hypotension, anemia, and acidosis; and management of complications associated with asphyxia. If myocardial dysfunction is present, dopamine or dobutamine is needed. The most important therapy for PPHN is assisted ventilation. Reversible mild pulmonary hypertension may respond to conventional assisted ventilation. Patients with severe PPHN do not always respond to conventional therapy. Paralysis with a muscle relaxant may be needed to assist vigorous ventilation. Surfactant replacement seems to have no effect when PPHN is the primary diagnosis. If mechanical ventilation and supportive care are unsuccessful in improving oxygenation, inhaled nitric oxide, a selective pulmonary artery vasodilating agent, should be administered. If hypoxia persists, the patient may be a candidate for ECMO. Infants who require extremely high ventilator settings, marked by an alveolar-to-arterial oxygen gradient greater than 620 mm Hg, have a high mortality rate and benefit from ECMO if they do not respond to nitric oxide. In addition, the oxygenation index (OI) is used to assess the severity of hypoxemia and to guide the timing of interventions such as inhaled nitric oxide and ECMO. The OI is calculated using the equation OI = [(mean airway pressure × fraction of inspired oxygen)/Pa_{O_2}] × 100. A high OI indicates severe hypoxemic respiratory failure.

APNEA OF PREMATURITY

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Apnea

Although apnea typically is associated with immaturity of the respiratory control system, it also may be the presenting sign of other diseases or pathophysiological states that affect preterm infants (see Table 61.3). A thorough consideration of possible causes is always warranted, especially with the onset or unexpected increase in the frequency of episodes of apnea (or bradycardia).

Apnea is defined as the cessation of pulmonary airflow for a specific time interval, usually longer than 10-20 seconds. Bradycardia often accompanies prolonged apnea. **Central apnea** refers to a complete cessation of airflow and respiratory efforts with no chest wall movement. **Obstructive apnea** refers to the absence of noticeable airflow but with the continuation of chest wall movements. **Mixed apnea**, a combination of these two events, is the most frequent type. It may begin as a brief episode of obstruction followed by a central apnea. Alternatively, central apnea may produce upper airway closure (passive pharyngeal hypotonia), resulting in mixed apnea.

A careful evaluation to determine the cause of apnea should be performed immediately in any infant with apnea. The incidence of apnea increases as gestational age decreases. Idiopathic apnea, a disease of premature infants, appears in the absence of any other identifiable disease states during the first week of life and usually resolves by 36-40 weeks of postconceptual age (gestational age at birth + postnatal age). The premature infant's process of regulating respiration is especially vulnerable to apnea. Preterm infants respond paradoxically to hypoxia by developing apnea rather than by increasing respirations as in mature infants. Poor tone of the laryngeal muscles also may lead to collapse of the upper airway, causing obstruction. Isolated obstructive apnea also may occur as a result of flexion or extreme lateral positioning of the premature infant's head, which obstructs the soft trachea.

Treatment of apnea of prematurity involves administration of oxygen to hypoxic infants, transfusion of anemic infants, and physical cutaneous stimulation for infants with mild apnea. Methylxanthines (caffeine or theophylline) are the mainstay of pharmacological treatment of apnea. Xanthine therapy increases minute ventilation, improves the carbon dioxide sensitivity, decreases hypoxic depression of breathing, enhances diaphragmatic activity, and decreases periodic breathing. Treatment usually is initiated with a loading dose followed by maintenance therapy. High-flow nasal cannula therapy and nasal CPAP of 4-6 cm H_2O also are effective and relatively safe methods of treating obstructive or mixed apneas; they may work by stimulating the infant and splinting the upper airway. CPAP also probably increases functional residual capacity, improving oxygenation.

CHAPTER 62

Anemia and Hyperbilirubinemia

ANEMIA

Embryonic hematopoiesis begins by the 20th day of gestation and is evidenced as blood islands in the yolk sac. In midgestation, erythropoiesis occurs in the liver and spleen; the bone marrow becomes the predominant site in the last trimester. Hemoglobin concentration increases from 8-10 g/dL at 12 weeks to 16.5-18 g/dL at 40 weeks. Fetal red blood cell (RBC) production is responsive to erythropoietin; the concentration of this hormone increases with fetal hypoxia and anemia.

After birth, hemoglobin levels increase transiently at 6-12 hours, then decline to 11-12 g/dL at 3-6 months. A premature infant (<32 weeks' gestational age) has a lower hemoglobin concentration and a more rapid postnatal decline of hemoglobin level, which achieves a nadir 1-2 months after birth. Fetal and neonatal RBCs have a shorter life span (70-90 days) and a higher mean corpuscular volume (110-120 fL) than adult cells. In the fetus, hemoglobin synthesis in the last two trimesters of pregnancy produces fetal hemoglobin (hemoglobin F), composed of two alpha chains and two gamma chains. Immediately before term, the infant begins to synthesize beta-hemoglobin chains; the term infant should have some adult hemoglobin (two alpha chains and two beta chains). Fetal hemoglobin represents 60-90% of hemoglobin at term birth. The levels decline to adult levels of less than 5% by 4 months of age.

For a term infant, blood volume is 72-93 mL/kg, and for a preterm infant, blood volume is 90-100 mL/kg. The placenta and umbilical vessels contain approximately 20-30 mL/kg of additional blood that can increase neonatal blood volume and hemoglobin levels transiently for the first 3 days of life if clamping or milking *(stripping)* of the umbilical cord is delayed at birth. Delayed clamping usually has no adverse effects but may increase the risk of polycythemia and jaundice. Early clamping may lead to anemia, a cardiac murmur, poor peripheral perfusion, and less tachypnea. Hydrostatic pressure affects blood transfer between the placenta and the infant at birth. An undesired fetal-to-placental transfusion occurs if the infant is situated above the level of the placenta.

The physiological anemia noted at 2-3 months of age in term infants and at 1-2 months of age in preterm infants is a normal process that does not result in signs of illness and does not require any treatment. It is a physiological condition believed to be related to several factors, including increased tissue oxygenation experienced at birth, shortened RBC life span, and low erythropoietin levels.

Etiology

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Gastrointestinal Bleeding
Anemia
Bleeding
Petechiae/Purpura
Pancytopenia

Symptomatic anemia in the newborn period (Fig. 62.1) may be caused by decreased RBC production, increased RBC destruction, or blood loss.

Decreased Red Blood Cell Production

Anemia caused by decreased production of RBCs appears at birth with pallor, a low reticulocyte count, and absence of erythroid precursors in the bone marrow. Potential causes of neonatal decreased RBC production include bone marrow failure syndromes (congenital RBC aplasia [Blackfan-Diamond anemia]), infection (congenital viral infections [parvovirus, rubella], acquired bacterial or viral sepsis), and congenital leukemia.

Increased Red Blood Cell Destruction

Immunologically mediated hemolysis in utero may lead to **erythroblastosis fetalis**, or the fetus may be spared and **hemolytic disease** may appear in the newborn. Hemolysis of fetal erythrocytes is a result of blood group differences between the sensitized mother and fetus, which causes production of maternal IgG antibodies directed against an antigen on fetal cells.

ABO blood group incompatibility with neonatal hemolysis develops only if the mother has IgG antibodies from a previous exposure to A or B antigens. These IgG antibodies cross the placenta by active transport and affect the fetus or newborn. Sensitization of the mother to fetal antigens may have occurred by previous transfusions or by conditions of pregnancy that result in transfer of fetal erythrocytes into the maternal circulation, such as first-trimester abortion, ectopic pregnancy, amniocentesis, manual extraction of the placenta, version (external or internal) procedures, or normal pregnancy.

ABO incompatibility with sensitization usually does not cause fetal disease other than extremely mild anemia. It may produce **hemolytic disease of the newborn**, which is manifested as significant anemia and hyperbilirubinemia. Because many mothers who have blood group O have IgG antibodies to A and B before pregnancy, the firstborn infant of A or B blood type may be affected. In contrast to Rh disease, ABO hemolytic disease does not become more severe with subsequent pregnancies. Hemolysis with ABO incompatibility is less severe than hemolysis in Rh-sensitized pregnancy, either because the anti-A or anti-B antibody may bind to nonerythrocytic cells that contain A or B antigen or because fetal erythrocytes have fewer A or B antigenic determinants than they have Rh sites. With the declining incidence of Rh hemolytic disease, ABO incompatibility has become the most common cause of neonatal hyperbilirubinemia requiring therapy, currently accounting for approximately 20% of clinically significant jaundice in the newborn.

Erythroblastosis fetalis classically is caused by Rh blood group incompatibility. Most Rh-negative women have no anti-Rh antibodies at the time of their first pregnancy. The Rh antigen system consists of five antigens: C, D, E, c, and e; the d type is not antigenic. In most Rh-sensitized cases, the D antigen of the fetus sensitizes the Rh-negative (d) mother, resulting in IgG antibody production during the first pregnancy. Because most mothers are not sensitized to Rh antigens at the start of pregnancy, Rh erythroblastosis fetalis is usually a disease of the

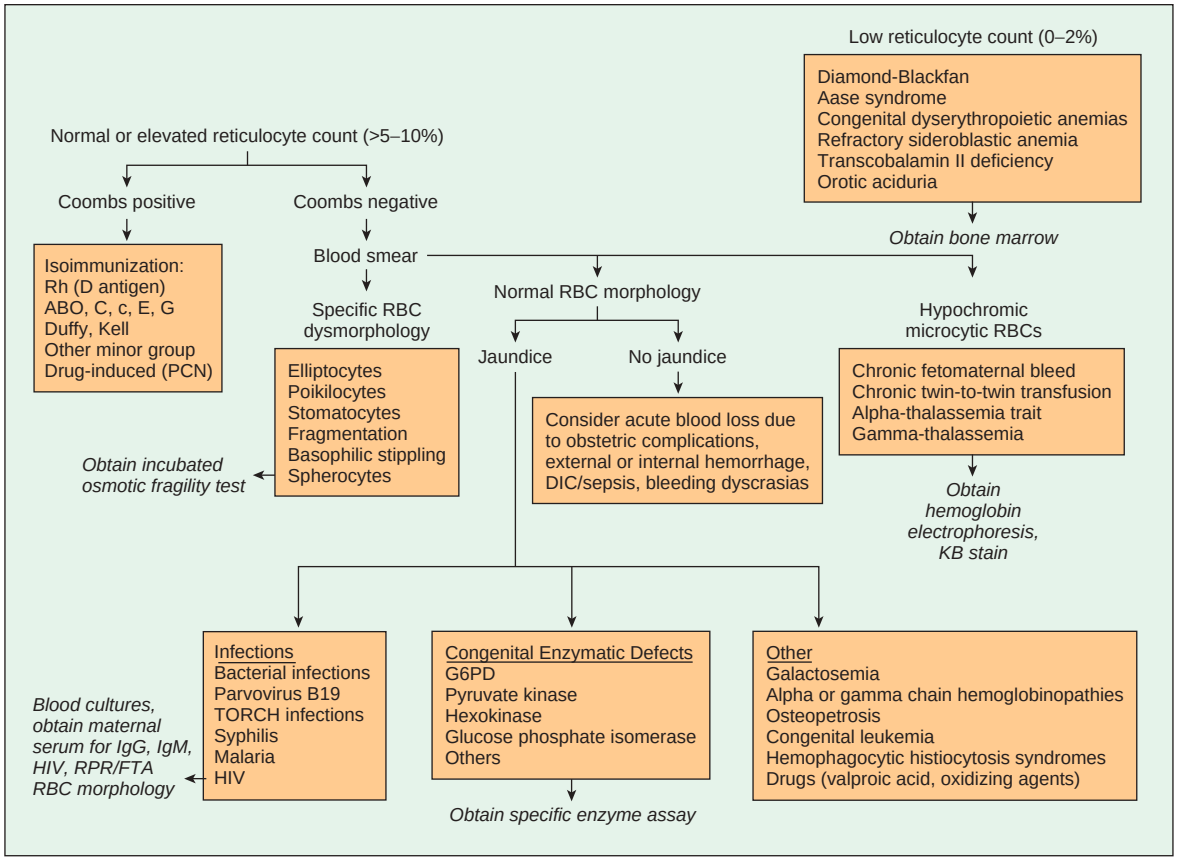

FIGURE 62.1 Differential diagnosis of neonatal anemia. The physician obtains information from the family, maternal and labor and delivery histories, and laboratory tests, including hemoglobin, reticulocyte count, blood type, direct Coombs test, peripheral smear, red blood cell (RBC) indices, and bilirubin concentration. *DIC*, Disseminated intravascular coagulation; *FTA*, fluorescent treponemal antibody test; *G6PD*, glucose-6-phosphate dehydrogenase; *HIV*, human immunodeficiency virus; *KB*, Kleihauer-Betke; *PCN*, penicillin; *RPR*, rapid plasma reagin tests; *TORCH*, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex. (From Ohls RK. Anemia in the neonate. In: Christensen RD, ed. *Hematologic Problems of the Neonate*. Philadelphia: Saunders; 2000:162.)

second and subsequent pregnancies. The first affected pregnancy results in an antibody response in the mother, which may be detected during antenatal screening with the Coombs test and determined to be anti-D antibody. The first affected newborn may show no serious fetal disease and may manifest hemolytic disease of the newborn only by the development of anemia and hyperbilirubinemia. Subsequent pregnancies result in an increasing severity of response because of an earlier onset of hemolysis in utero. Fetal anemia, heart failure, elevated venous pressure, portal vein obstruction, and hypoalbuminemia result in **fetal hydrops**, which is characterized by ascites, pleural and pericardial effusions, and anasarca (see Chapter 60). The risk of fetal death is high.

The **management** of a pregnancy complicated by Rh sensitization depends on the severity of hemolysis, its effects on the fetus, and the maturity of the fetus at the time it becomes affected. The severity of the hemolysis can be assessed by the quantity of bilirubin transferred from the fetus to the amniotic fluid, quantified by spectrophotometric analysis of the optical density (at 450 nm) of amniotic fluid.

Three zones of optical densities with decreasing slopes toward term gestation have been developed to predict the severity of the illness. The high optical density zone 3 is associated with severe hemolysis. Fetuses in the lower zones probably are not affected. If a fetus's optical density measurement for bilirubin falls into zone 3, and the fetus has pulmonary maturity as determined by the lecithin-to-sphingomyelin ratio, the infant should be delivered and treated in the neonatal intensive care unit. If the lungs are immature and the fetus is between 22 and 33 weeks of gestational age, an ultrasound-guided intrauterine transfusion with O-negative blood into the umbilical vein is indicated and may have to be repeated until pulmonary maturity is reached or fetal distress is detected. Indications for fetal intravascular transfusion in sensitized fetuses between 22 and 32 weeks of gestational age include a fetal hematocrit of less than 25-30%, fetal hydrops, and fetal distress too early in gestation for delivery. Intravascular intrauterine transfusion corrects fetal anemia, improves the outcome of severe hydrops, and reduces the need for postnatal exchange transfusion, but is associated with neonatal anemia as a result of continued hemolysis plus suppressed erythropoiesis.

Prevention of sensitization of the mother carrying an Rh-positive fetus is possible by treating the mother during gestation (>28 weeks' gestational age) and within 72 hours after birth with anti-Rh-positive immune globulin (RhoGAM). The dose of RhoGAM (300 μg) is based on the ability of this amount

of anti-Rh-positive antibody to bind all the possible fetal Rh-positive erythrocytes entering the maternal circulation during the fetal-to-maternal transfusion at birth (approximately 30 mL). RhoGAM may bind Rh-positive fetal erythrocytes or interfere with maternal anti-Rh-positive antibody production by another, unknown mechanism. RhoGAM is effective only in preventing sensitization to the D antigen. Other blood group antigens that can cause immune hydrops and erythroblastosis include Rh C, E, Kell, and Duffy. Anti-Kell alloimmunity produces lower amniotic bilirubin levels and a lower reticulocyte count because, in addition to hemolysis, it inhibits erythropoiesis.

Nonimmune causes of hemolysis in the newborn include RBC enzyme deficiencies of the Embden-Meyerhof pathway, such as pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency. RBC membrane disorders are another cause of nonimmune hemolysis. Hereditary spherocytosis is inherited as a severe autosomal recessive form or less severe autosomal dominant form and is the result of a deficiency of spectrin, a protein of the RBC membrane. Hemoglobinopathies, such as thalassemia, are another cause of nonimmunologically mediated hemolysis.

Blood Loss

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Gastrointestinal Bleeding
Bleeding

Anemia from blood loss at birth is manifested by two patterns of presentation, depending on the rapidity of blood loss. **Acute blood loss** after fetal-maternal hemorrhage, rupture of the umbilical cord, placenta previa, or internal hemorrhage (hepatic or splenic hematoma; retroperitoneal) is characterized by pallor, diminished peripheral pulses, and shock. There are no signs of extramedullary hematopoiesis and no hepatosplenomegaly. The hemoglobin content and serum iron levels initially are normal, but the hemoglobin levels decline during the subsequent 24 hours. Newborns with **chronic blood loss** caused by chronic fetal-maternal hemorrhage or a twin-to-twin transfusion present with marked pallor, heart failure, hepatosplenomegaly with or without hydrops, a low hemoglobin level at birth, a hypochromic microcytic blood smear, and decreased serum iron stores. Fetal-maternal bleeding occurs in 50-75% of all pregnancies, with fetal blood losses ranging from 1 to 50 mL; most blood losses are 1 mL or less, 1 in 400 are approximately 30 mL, and 1 in 2,000 are approximately 100 mL.

The diagnosis of fetal-maternal hemorrhage is confirmed by the Kleihauer-Betke acid elution test. Pink fetal RBCs are observed and counted in the mother's peripheral blood smear because fetal hemoglobin is resistant to acid elution; adult hemoglobin is eluted, leaving discolored maternal cells (patients with sickle cell anemia or hereditary persistence of fetal hemoglobin may have a false-positive result, and ABO incompatibility may produce a false-negative result).

Diagnosis and Management

Hemolysis in utero resulting from any cause may produce a spectrum of clinical manifestations at birth. Severe hydrops with anasarca, heart failure, and pulmonary edema may prevent adequate ventilation at birth, resulting in asphyxia. Infants affected with hemolysis in utero have hepatosplenomegaly and pallor and become jaundiced within the first 24 hours after birth. Less severely affected infants manifest pallor and hepatosplenomegaly at birth and become jaundiced subsequently. Patients with ABO incompatibility often are asymptomatic and show no physical signs at birth; mild anemia with jaundice develops during the first 24-72 hours of life.

Because hydrops, anemia, or jaundice is secondary to many diverse causes of hemolysis, a laboratory evaluation is needed in all patients with suspected hemolysis. A complete blood count, blood smear, reticulocyte count, blood type, and direct Coombs test (to determine the presence of antibody-coated RBCs) should be performed in the initial evaluation of all infants with hemolysis. Reduced hemoglobin levels, reticulocytosis, and a blood smear characterized by polychromasia and anisocytosis are expected with isoimmune hemolysis. Spherocytes commonly are observed in ABO incompatibility. The determination of the blood type and the Coombs test identify the responsible antigen and antibody in immunologically mediated hemolysis.

In the absence of a positive Coombs test and blood group differences between the mother and fetus, other causes of nonimmune hemolysis must be considered. RBC enzyme assays, hemoglobin electrophoresis, or RBC membrane tests (osmotic fragility, spectrin assay) should be performed. Internal hemorrhage also may be associated with anemia, reticulocytosis, and jaundice when the hemorrhage reabsorbs; ultrasound evaluation of the brain, liver, spleen, or adrenal gland may be indicated when nonimmune hemolysis is suspected. Shock is more typical in patients with internal hemorrhage, whereas in hemolytic diseases, heart failure may be seen with severe anemia. Evaluation of a possible fetal-maternal hemorrhage should include the Kleihauer-Betke test.

The **treatment** of *symptomatic* neonatal anemia is transfusion of cross-matched packed RBCs. If immune hemolysis is present, the cells to be transfused must be cross-matched against maternal and neonatal plasma. Acute volume loss may necessitate resuscitation with nonblood products, such as saline if blood is not available; packed RBCs can be given subsequently. To correct anemia and any remaining blood volume deficit, 10-15 mL/kg of packed RBCs should be sufficient. Cytomegalovirus-seronegative blood should be given to cytomegalovirus-seronegative infants, and all blood products should be irradiated to reduce the risk of graft-versus-host disease; blood should be screened for HIV, hepatitis B and C, and syphilis. Recombinant erythropoietin may improve the hematocrit in infants with a hyporegenerative anemia after in utero transfusion.

HYPERBILIRUBINEMIA

Hemolytic disease of the newborn is a common cause of neonatal jaundice. Nonetheless, because of the immaturity of the pathways of bilirubin metabolism, many newborn infants without evidence of hemolysis become jaundiced.

Bilirubin is produced by the catabolism of hemoglobin in the reticuloendothelial system. The tetrapyrrole ring of heme is cleaved by heme oxygenase to form equivalent quantities of biliverdin and carbon monoxide. Because no other biologic source of carbon monoxide exists, the excretion of this gas is stoichiometrically identical to the production of bilirubin.

Biliverdin is converted to bilirubin by biliverdin reductase. One gram of hemoglobin produces 35 mg of bilirubin. Sources of bilirubin other than circulating hemoglobin represent 20% of bilirubin production; these sources include inefficient (shunt) hemoglobin production and lysis of precursor cells in bone marrow. Compared with adults, newborns have a twofold to threefold greater rate of bilirubin production (6-10 mg/kg/24 hr vs. 3 mg/kg/24 hr). This increased production is caused, in part, by an increased RBC mass (higher hematocrit) and a shortened erythrocyte life span of 70-90 days compared with the 120-day erythrocyte life span in adults.

Bilirubin produced after hemoglobin catabolism is lipid soluble and unconjugated and reacts as an indirect reagent in the van den Bergh test. Indirect-reacting, unconjugated bilirubin is toxic to the central nervous system and is insoluble in water, limiting its excretion. Unconjugated bilirubin binds to albumin on specific bilirubin binding sites; 1 g of albumin binds 8.5 mg of bilirubin in a newborn. If the binding sites become saturated or if a competitive compound binds at the site, displacing bound bilirubin, free bilirubin becomes available to enter the central nervous system. Organic acids such as free fatty acids and drugs such as sulfisoxazole can displace bilirubin from its binding site on albumin.

Bilirubin dissociates from albumin at the hepatocyte and becomes bound to a cytoplasmic liver protein Y (ligandin). Hepatic conjugation results in the production of bilirubin diglucuronide, which is water soluble and capable of biliary and renal excretion. The enzyme glucuronosyltransferase represents the rate-limiting step of bilirubin conjugation. The concentrations of ligandin and glucuronosyltransferase are lower in newborns, particularly in premature infants, than in older children.

Conjugated bilirubin gives a direct reaction in the van den Bergh test. Most conjugated bilirubin is excreted through the bile into the small intestine and eliminated in the stool. Some bilirubin may undergo hydrolysis back to the unconjugated fraction by intestinal glucuronidase, however, and may be reabsorbed (enterohepatic recirculation). In addition, bacteria in the neonatal intestine convert bilirubin to urobilinogen and stercobilinogen, which are excreted in urine and stool and usually limit bilirubin reabsorption. Delayed passage of meconium, which contains bilirubin, also may contribute to the enterohepatic recirculation of bilirubin.

Bilirubin is produced in utero by the normal fetus and by the fetus affected by erythroblastosis fetalis. Indirect, unconjugated, lipid-soluble fetal bilirubin is transferred across the placenta and becomes conjugated by maternal hepatic enzymes. The placenta is impermeable to conjugated water-soluble bilirubin. Fetal bilirubin levels become only mildly elevated in the presence of severe hemolysis, but may increase when hemolysis produces fetal hepatic inspissated bile stasis and conjugated hyperbilirubinemia. Maternal indirect (but not direct) hyperbilirubinemia also may increase fetal bilirubin levels.

Etiology of Indirect Unconjugated Hyperbilirubinemia

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Jaundice

Physiological jaundice is a common cause of hyperbilirubinemia among newborns. It is a diagnosis of exclusion, made after careful evaluation has ruled out more serious causes of jaundice, such as hemolysis, infection, and metabolic diseases. Physiological jaundice is the result of many factors that are normal physiological characteristics of newborns: increased bilirubin production resulting from an increased RBC mass, shortened RBC life span, and hepatic immaturity of ligandin and glucuronosyltransferase. Physiological jaundice may be exaggerated among infants of Greek and Asian ancestry.

The clinical pattern of physiological jaundice in term infants includes a peak indirect-reacting bilirubin level of no more than 12 mg/dL on day 3 of life. In premature infants, the peak is higher (15 mg/dL) and occurs later (fifth day). The peak level of indirect bilirubin during physiological jaundice may be higher in breast milk–fed infants than in formula-fed infants (15-17 mg/dL versus 12 mg/dL). This higher level may be partly a result of the decreased fluid intake of infants fed breast milk. Jaundice is unphysiological or pathological if it is clinically evident on the first day of life, if the bilirubin level increases more than 0.5 mg/dL/hr, if the peak bilirubin is greater than 13 mg/dL in term infants, if the direct bilirubin fraction is greater than 1.5 mg/dL, or if hepatosplenomegaly and anemia are present.

Crigler-Najjar syndrome is a serious, rare, autosomal recessive, permanent deficiency of glucuronosyltransferase that results in severe indirect hyperbilirubinemia. Type II responds to enzyme induction by phenobarbital, producing an increase in enzyme activity and a reduction of bilirubin levels. Type I does not respond to phenobarbital and manifests as persistent indirect hyperbilirubinemia, often leading to kernicterus. **Gilbert disease** is caused by a mutation of the promoter region of glucuronosyltransferase and results in a mild indirect hyperbilirubinemia. In the presence of another icterogenic factor (hemolysis), more severe jaundice may develop.

Breast milk jaundice may be associated with unconjugated hyperbilirubinemia without evidence of hemolysis during the first to second week of life. Bilirubin levels rarely increase to more than 20 mg/dL. Interruption of breast feeding for 1-2 days results in a rapid decline of bilirubin levels, which do not increase significantly after breast feeding resumes. Breast milk may contain an inhibitor of bilirubin conjugation or may increase enterohepatic recirculation of bilirubin because of breast milk glucuronidase.

Jaundice on the first day of life is always pathological, and immediate attention is needed to establish the cause. Early onset often is a result of hemolysis, internal hemorrhage (cephalhematoma, hepatic or splenic hematoma), or infection (Table 62.1). Infection also is often associated with direct-reacting bilirubin resulting from perinatal congenital infections or from bacterial sepsis.

Physical evidence of jaundice is observed in infants when bilirubin levels reach 5-10 mg/dL (versus 2-3 mg/dL in adults). When jaundice is observed, the laboratory evaluation for hyperbilirubinemia should include a total bilirubin measurement to determine the magnitude of hyperbilirubinemia. Bilirubin levels greater than 5 mg/dL on the first day of life or greater than 13 mg/dL thereafter in term infants should be evaluated further with measurement of indirect and direct bilirubin levels, blood typing, Coombs test, complete blood count, blood smear, and reticulocyte count. These tests must be performed before treatment of hyperbilirubinemia with phototherapy or exchange transfusion. In the absence of hemolysis or evidence

TABLE 62.1 Etiology of Unconjugated Hyperbilirubinemia

	HEMOLYSIS PRESENT	HEMOLYSIS ABSENT
Common	*Blood group incompatibility:* ABO, Rh, Kell, Duffy infection	Physiological jaundice, breast milk jaundice, internal hemorrhage, polycythemia, infant of diabetic mother
Rare	*Red blood cell enzyme defects:* glucose-6-phosphate dehydrogenase, pyruvate kinase *Red blood cell membrane disorders:* spherocytosis, ovalocytosis *Hemoglobinopathy:* thalassemia	Mutations of glucuronyl transferase enzyme (Crigler-Najjar syndrome, Gilbert disease), pyloric stenosis, hypothyroidism, immune thrombocytopenia

for either the common or the rare causes of nonhemolytic indirect hyperbilirubinemia, the diagnosis is either physiological or breast milk jaundice. Jaundice appearing or increasing after 2 weeks of age is pathological and suggests a direct-reacting hyperbilirubinemia.

Etiology of Direct Conjugated Hyperbilirubinemia

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Jaundice

Direct-reacting hyperbilirubinemia (defined as a direct bilirubin level >2 mg/dL or >20% of the total bilirubin) is never physiological and should always be evaluated thoroughly according to the diagnostic categories (Table 62.2). Direct-reacting bilirubin (composed mostly of conjugated bilirubin) is not neurotoxic to the infant but signifies a serious underlying disorder involving cholestasis or hepatocellular injury. The diagnostic evaluation of patients with direct-reacting hyperbilirubinemia involves the determination of the levels of liver enzymes (aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, and γ-glutamyl transpeptidase), bacterial and viral cultures, metabolic screening tests, hepatic ultrasound, sweat chloride test, and occasionally liver biopsy. In addition, the presence of dark urine and gray-white (acholic) stools with jaundice after the second week of life strongly suggests biliary atresia. The treatment of disorders manifested by direct bilirubinemia is specific for the diseases that are listed in Table 62.2. These diseases do not respond to phototherapy or exchange transfusion.

TABLE 62.2 Etiology of Conjugated Hyperbilirubinemia

COMMON
Hyperalimentation cholestasis
CMV infection
Other perinatal congenital infections (TORCH)
Inspissated bile from prolonged hemolysis
Neonatal hepatitis
Sepsis
UNCOMMON
Hepatic infarction
Inborn errors of metabolism (galactosemia, tyrosinemia)
Cystic fibrosis
Biliary atresia
Choledochal cyst
α_1-Antitrypsin deficiency
Neonatal iron storage disease (neonatal hemochromatosis)
Alagille syndrome (arteriohepatic dysplasia)
Byler disease, progressive familial intrahepatic cholestasis types 1, 2, 3

CMV, Cytomegalovirus; *TORCH*, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex.

Kernicterus (Bilirubin Encephalopathy)

Lipid-soluble, unconjugated, indirect bilirubin fraction is toxic to the developing central nervous system, especially when indirect bilirubin concentrations are high and exceed the binding capacity of albumin. Kernicterus results when indirect bilirubin is deposited in brain cells and disrupts neuronal metabolism and function, especially in the basal ganglia. Indirect bilirubin may cross the blood-brain barrier because of its lipid solubility. Other theories propose that a disruption of the blood-brain barrier permits entry of a bilirubin-albumin or free bilirubin–fatty acid complex.

Kernicterus usually is noted when the bilirubin level is excessively high for gestational age. It usually does not develop in term infants when bilirubin levels are less than 20-25 mg/dL, but the incidence increases as serum bilirubin levels exceed 25 mg/dL. Kernicterus may be noted at bilirubin levels less than 20 mg/dL in the presence of sepsis, meningitis, hemolysis, asphyxia, hypoxia, hypothermia, hypoglycemia, bilirubin-displacing drugs (sulfa drugs), and prematurity. Other risks for kernicterus in term infants are hemolysis, jaundice noted within 24 hours of birth, and delayed diagnosis of hyperbilirubinemia. Kernicterus has developed in extremely immature infants weighing less than 1,000 g when bilirubin levels are less than 10 mg/dL because of a more permeable blood-brain barrier associated with prematurity.

The earliest clinical manifestations of kernicterus are lethargy, hypotonia, irritability, poor Moro response, and poor feeding. A high-pitched cry and emesis also may be present. Early signs are noted after day 4 of life. Later signs include bulging fontanelle, opisthotonic posturing, pulmonary hemorrhage, fever, hypertonicity, paralysis of upward gaze, and seizures. Infants with severe cases of kernicterus die in the neonatal period. Spasticity resolves in surviving infants, who may manifest later nerve deafness, choreoathetoid cerebral palsy, mental retardation, enamel dysplasia, and discoloration of teeth as permanent sequelae. Kernicterus may be prevented by avoiding excessively high indirect bilirubin levels and by avoiding conditions or drugs that may displace bilirubin from albumin. Early signs of kernicterus occasionally may be reversed by immediately instituting an exchange transfusion (see later).

Therapy of Indirect Hyperbilirubinemia

Phototherapy is an effective and safe method for reducing indirect bilirubin levels, particularly when initiated before serum bilirubin increases to levels associated with kernicterus. In term infants, phototherapy is begun when indirect bilirubin levels are between 16 and 18 mg/dL. Phototherapy is initiated in premature infants when bilirubin is at lower levels, to prevent bilirubin from reaching the high concentrations necessitating exchange transfusion. Blue lights and white lights are effective in reducing bilirubin levels.

Under the effects of phototherapy light with maximal irradiance in the 425- to 475-nm wavelength band, bilirubin is transformed into isomers that are water soluble and easily excreted. Unconjugated bilirubin (IX) is in the 4Z, 15Z configuration. Phototherapy causes a photochemical reaction producing the reversible, more water-soluble isomer 4Z, 15E bilirubin IX. This isomer can be excreted easily, bypassing the liver's conjugation system. Another photochemical reaction results in the rapid production of lumirubin, a more water-soluble isomer than the aforementioned isomer, which does not spontaneously revert to unconjugated native bilirubin and can be excreted in urine.

Complications of phototherapy include an increased insensible water loss, diarrhea, and dehydration. Additional problems are macular-papular red skin rash, lethargy, masking of cyanosis, nasal obstruction by eye pads, and potential for retinal damage. Skin bronzing may be noted in infants with direct-reacting hyperbilirubinemia. Infants with mild hemolytic disease of the newborn occasionally may be managed successfully with phototherapy for hyperbilirubinemia, but care must be taken to follow these infants for the late occurrence of anemia from continued hemolysis.

Exchange transfusion usually is reserved for infants with dangerously high indirect bilirubin levels who are at risk for kernicterus. As a rule of thumb, a level of 20 mg/dL for indirect-reacting bilirubin is the *exchange number* for infants *with hemolysis* who weigh more than 2,000 g. Asymptomatic infants with physiological or breast milk jaundice may not require exchange transfusion, unless the indirect bilirubin level exceeds 25 mg/dL. The exchangeable level of indirect bilirubin for other infants may be estimated by calculating 10% of the birth weight in grams: the level in an infant weighing 1,500 g would be 15 mg/dL. Infants weighing less than 1,000 g usually do not require an exchange transfusion until the bilirubin level exceeds 10 mg/dL.

The exchange transfusion usually is performed through an umbilical venous catheter placed in the inferior vena cava or, if free flow is obtained, at the confluence of the umbilical vein and the portal system. The level of serum bilirubin immediately after the exchange transfusion declines to levels that are about half of those before the exchange; levels rebound 6-8 hours later as a result of continued hemolysis and redistribution of bilirubin from tissue stores.

Complications of exchange transfusion include problems related to the blood (transfusion reaction, metabolic instability, or infection), the catheter (vessel perforation or hemorrhage), or the procedure (hypotension or necrotizing enterocolitis [NEC]). Unusual complications include thrombocytopenia and graft-versus-host disease. Continuation of phototherapy may reduce the necessity for subsequent exchange transfusions.

Polycythemia (Hyperviscosity Syndrome)

Polycythemia is an excessively high hematocrit (≥65%), which may lead to hyperviscosity that produces symptoms related to vascular stasis, hypoperfusion, and ischemia. As the hematocrit increases from 40% to 60%, there is a small increase in blood viscosity. When the central hematocrit increases to greater than 65%, the blood viscosity begins to increase markedly, and symptoms may appear. Neonatal erythrocytes are less filterable or deformable than adult erythrocytes, which further contributes to hyperviscosity. A central venous hematocrit of 65% or greater is noted in 3-5% of infants. Infants at special risk for polycythemia are term and post-term small for gestational age infants, infants of diabetic mothers, infants with delayed cord clamping, and infants with neonatal hyperthyroidism, adrenogenital syndrome, trisomy 13, trisomy 18, trisomy 21, twin-to-twin transfusion syndrome (recipient), or Beckwith-Wiedemann syndrome. In some infants, polycythemia may reflect a compensation for prolonged periods of fetal hypoxia caused by placental insufficiency; these infants have increased erythropoietin levels at birth.

Polycythemic patients appear plethoric or ruddy and may develop acrocyanosis. Symptoms are a result of the increased RBC mass and of vascular compromise. Seizures, lethargy, and irritability reflect abnormalities of microcirculation of the brain, whereas hyperbilirubinemia may reflect the poor hepatic circulation or the increased amount of hemoglobin that is being broken down into bilirubin. Additional problems include respiratory distress and primary pulmonary hypertension of the newborn (PPHN) that result in part from elevated pulmonary vascular resistance. The chest radiograph often reveals cardiomegaly, increased vascular markings, pleural effusions, and interstitial edema. Other problems are NEC, hypoglycemia, thrombocytopenia, priapism, testicular infarction, hemiplegic stroke, and feeding intolerance. Many of these complications also are related to the primary condition associated with polycythemia (small for gestational age infants are at risk for hypoglycemia and PPHN after periods of hypoxia in utero).

Long-term sequelae of neonatal polycythemia relate to neurodevelopmental abnormalities that may be prevented by treatment of symptomatic infants with partial exchange transfusion after birth. A partial exchange transfusion removes whole blood and replaces it with normal saline.

Coagulation Disorders

Disorders of coagulation are common in the neonatal period. Hemorrhage during this time may be a result of trauma, inherited permanent deficiency of coagulation factors, transient deficiencies of vitamin K–dependent factors, disorders of platelets, and disseminated intravascular coagulation (DIC) seen in sick newborns with shock or hypoxia. Thrombosis also is a potential problem in the newborn because of developmentally lower circulating levels of antithrombin III, protein C (a vitamin K–dependent protein that inhibits factors VIII and V), and the fibrinolytic system.

Coagulation factors do not pass through the placenta to the fetus, and newborn infants have relatively low levels of the vitamin K–dependent factors II, VII, IX, and X. Contact factors XI and XII, prekallikrein, and kininogen also are lower in newborns than in adults. Fibrinogen (factor I); plasma levels

of factors V, VIII, and XIII; and platelet counts are within the adult normal range.

Because of the transient, relative deficiencies of the contact and vitamin K–dependent factors, the *partial thromboplastin time* (PTT), which is dependent on factors XII, IX, VIII, X, V, II, and I, is prolonged in the newborn period. Preterm infants have the most marked prolongation of the PTT (50-80 seconds) compared with term infants (35-50 seconds) and older, more mature infants (25-35 seconds). The administration of heparin and the presence of DIC, hemophilia, and severe vitamin K deficiency prolong the PTT.

The *prothrombin time* (PT), which is dependent on factors X, VII, V, II, and I, is a more sensitive test for vitamin K deficiency. The PT is only slightly prolonged in term infants (13-20 seconds) compared with preterm infants (13-21 seconds) and more mature patients (12-14 seconds). Abnormal prolongations of the PT occur with vitamin K deficiency, hepatic injury, and DIC. Levels of *fibrinogen* and *fibrin degradation products* are similar in infants and adults. The *bleeding time,* which reflects platelet function and number, is normal during the newborn period in the absence of maternal salicylate therapy.

Vitamin K is a necessary cofactor for the carboxylation of glutamate on precursor proteins, converting them into the more active coagulation factors II, VII, IX, and X; γ-carboxyglutamic acid binds calcium, which is required for the immediate activation of factors during hemorrhage. There is no congenital deficiency of hepatic synthesis of these precursor proteins, but in the absence of vitamin K, their conversion to the active factor is not possible. Levels of *protein induced by vitamin K absence* increase in vitamin K deficiency and are helpful diagnostic markers; vitamin K administration rapidly corrects the coagulation defects, reducing protein induced by vitamin K absence to undetectable levels.

Although most newborns are born with reduced levels of vitamin K–dependent factors, hemorrhagic complications develop only rarely. Infants at risk for **hemorrhagic disease of the newborn** have the most profound deficiency of vitamin K–dependent factors, and these factors decline further after birth. Because breast milk is a poor source of vitamin K, breast fed infants are at increased risk for hemorrhage that usually occurs between days 3 and 7 of life. Bleeding usually ensues from the umbilical cord, circumcision site, intestines, scalp, mucosa, and skin, but internal hemorrhage places the infant at risk for fatal complications, such as intracranial bleeding.

Hemorrhage on the first day of life resulting from a deficiency of the vitamin K–dependent factors often is associated with administration to the mother of drugs that affect vitamin K metabolism in the infant. This early pattern of hemorrhage has been seen with maternal warfarin or antibiotic (e.g., isoniazid or rifampin) therapy and in infants of mothers receiving phenobarbital and phenytoin. Bleeding also may occur 1-3 months after birth, particularly among breast fed infants. Vitamin K deficiency in breast fed infants also should raise suspicion about the possibility of vitamin K malabsorption resulting from cystic fibrosis, biliary atresia, hepatitis, or antibiotic suppression of the colonic bacteria that produce vitamin K.

Bleeding associated with vitamin K deficiency may be **prevented** by administration of vitamin K to all infants at birth. Before routine administration of vitamin K, 1-2% of all newborns had hemorrhagic disease of the newborn. One intramuscular dose (1 mg) of vitamin K prevents vitamin K–deficiency bleeding. **Treatment** of bleeding resulting from vitamin K deficiency involves intravenous administration of 1 mg of vitamin K. If severe, life-threatening hemorrhage is present, fresh frozen plasma also should be given. Unusually high doses of vitamin K may be needed for hepatic disease and for maternal warfarin or anticonvulsant therapy.

Clinical Manifestations and Differential Diagnoses of Bleeding Disorders

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Bleeding
Petechiae/Purpura

Bleeding disorders in a newborn may be associated with cutaneous bleeding, such as cephalhematoma, subgaleal hemorrhage, ecchymosis, and petechiae. Facial petechiae are common in infants born by vertex presentation, with or without a nuchal cord, and usually are insignificant. Mucosal bleeding may appear as hematemesis, melena, or epistaxis. Internal hemorrhage results in organ-specific dysfunction, such as seizures associated with intracranial hemorrhage. Bleeding from venipuncture or heelstick sites, circumcision sites, or the umbilical cord also is common with bleeding disorders.

The differential diagnosis depends partly on the clinical circumstances associated with the hemorrhage. In a **sick newborn**, the differential diagnosis should include DIC, hepatic failure, and thrombocytopenia. Thrombocytopenia in an ill neonate may be secondary to consumption by trapping of platelets in a hemangioma **(Kasabach-Merritt syndrome)** or may be associated with perinatal, congenital, or bacterial infections; NEC; thrombotic endocarditis; PPHN; organic acidemia; maternal preeclampsia; or asphyxia. Thrombocytopenia also may be due to peripheral washout of platelets after an exchange transfusion. Treatment of a sick infant with thrombocytopenia should be directed at the underlying disorder, supplemented by infusions of platelets, blood, or both.

The etiology of DIC in a newborn includes hypoxia, hypotension, asphyxia, bacterial or viral sepsis, NEC, death of a twin while in utero, cavernous hemangioma, nonimmune hydrops, neonatal cold injury, neonatal neoplasm, and hepatic disease. The treatment of DIC should be focused primarily on therapy for the initiating or underlying disorder. Supportive management of consumptive coagulopathy involves platelet transfusions and factor replacement with fresh frozen plasma. Heparin and factor C concentrate should be reserved for infants with DIC who also have thrombosis.

Disorders of hemostasis in a *well child* are not associated with systemic disease in a newborn, but reflect coagulation factor or platelet deficiency. Hemophilia initially is associated with cutaneous or mucosal bleeding and no systemic illness. If bleeding continues, hypovolemic shock may develop. Bleeding into the brain, liver, or spleen may result in organ-specific signs and shock.

In a *well child,* thrombocytopenia may be part of a syndrome such as Fanconi anemia syndrome (involving hypoplasia and aplasia of the thumb), radial aplasia-thrombocytopenia syndrome (thumbs present), or Wiskott-Aldrich syndrome. Various maternal drugs also may reduce the neonatal platelet

count without producing other adverse effects. These drugs include sulfonamides, quinidine, quinine, and thiazide diuretics.

The most common causes of thrombocytopenia in well newborns are transient isoimmune thrombocytopenia and transient neonatal thrombocytopenia. **Isoimmune thrombocytopenia** is caused by antiplatelet antibodies produced by the HPLA1-negative mother after her sensitization to specific paternal platelet antigen (HPA-1a and HPA-5b represent 85% and 10% of cases, respectively) expressed on the fetal platelet. The incidence is 1 in 1,000 to 1 in 2,000 births. This response to maternal-sensitized antibodies that produce isoimmune thrombocytopenia is analogous to the response that produces erythroblastosis fetalis. The maternal antiplatelet antibody does not produce maternal thrombocytopenia, but after crossing the placenta this IgG antibody binds to fetal platelets that are trapped by the reticuloendothelial tissue, resulting in thrombocytopenia. Infants with thrombocytopenia produced in this manner are at risk for development of petechiae, purpura, and intracranial hemorrhage (an incidence of 10-15%) before or after birth. Vaginal delivery may increase the risk of neonatal bleeding; cesarean section may be indicated.

Specific **treatment** for severe thrombocytopenia (<20,000 platelets/mm^3) or significant bleeding is transfusion of ABO-compatible and RhD-compatible, HPA-1a-negative and HPA-5b-negative maternal platelets. Because the antibody in isoimmune thrombocytopenia is directed against the fetal rather than the maternal platelet, thrombocytapheresis of the mother yields sufficient platelets to treat the affected infant. After one platelet transfusion, the infant's platelet count dramatically increases and usually remains in a safe range. Without treatment, thrombocytopenia resolves during the first month of life as the maternal antibody level declines. *Treatment* of the mother with intravenous immunoglobulin or the thrombocytopenic fetus with intravascular platelet transfusion (cordocentesis) is also effective. Cesarean section reduces the risk of intracranial hemorrhage.

Neonatal thrombocytopenia in infants born to women with idiopathic thrombocytopenic purpura (ITP) also is a result of placental transfer of maternal IgG antibodies. In ITP, these autoantibodies are directed against all platelet antigens; mother and newborn may have low platelet counts. The risks of hemorrhage in an infant born to a mother with ITP may be lessened by cesarean section and by treatment of the mother with corticosteroids.

Treatment of an affected infant born to a mother with ITP may involve prednisone and intravenous immunoglobulin. In an emergency, random donor platelets may be used and may produce a transient increase in the infant's platelet count. Thrombocytopenia resolves spontaneously during the first month of life as maternal-derived antibody levels decline. Elevated levels of platelet-associated antibodies also have been noted in thrombocytopenic infants with sepsis and thrombocytopenia of unknown cause who were born to mothers without demonstrable platelet antibodies.

The laboratory evaluation of an infant (well or sick) with bleeding must include a platelet count, blood smear, and evaluation of PTT and PT. Isolated thrombocytopenia in a well infant suggests immune thrombocytopenia. Laboratory evidence of DIC includes a markedly prolonged PTT and PT (minutes rather than seconds), thrombocytopenia, and a blood smear suggesting a microangiopathic hemolytic anemia (burr or fragmented blood cells). Further evaluation reveals low levels of fibrinogen (<100 mg/dL) and elevated levels of fibrin degradation products. Vitamin K deficiency prolongs the PT more than the PTT, whereas hemophilia resulting from factors VIII and IX deficiency prolongs only the PTT. Specific factor levels confirm the diagnosis of hemophilia.

CHAPTER 63

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a syndrome of intestinal injury and is the most common intestinal emergency occurring in preterm infants admitted to the neonatal intensive care unit. NEC occurs in 1-3 per 1,000 live births and 1-8% of admissions to the neonatal intensive care unit. Prematurity is the most consistent and significant factor associated with neonatal NEC. The disease occurs in 4-13% of infants who weigh less than 1,500 g at birth. NEC is infrequent in term infants (<10% of affected infants).

Most cases of NEC occur in premature infants born before 34 weeks' gestation who have been fed enterally. Prematurity is associated with immaturity of the gastrointestinal tract, including decreased integrity of the intestinal mucosal barrier, depressed mucosal enzymes, suppressed gastrointestinal hormones, suppressed intestinal host defense system, decreased coordination of intestinal motility, and differences in blood flow autoregulation, which is thought to play a significant role in the pathogenesis of NEC. More than 90% of infants diagnosed with NEC have been fed enterally, but NEC has been reported in infants who have never been fed. Feeding with human milk has shown a beneficial role in reducing the incidence of NEC. In addition, probiotics may offer potential benefits for the preterm infant by increasing mucosal barrier function, improving nutrition, upregulating the immune system, and reducing mucosal colonization by potential pathogens. It also is theorized that compromised intestinal blood flow contributes to NEC.

Early clinical signs of NEC include abdominal distention, feeding intolerance/increased gastric residuals, emesis, rectal bleeding, and occasional diarrhea. As the disease progresses, patients may develop marked abdominal distention, bilious emesis, ascites, abdominal wall erythema, lethargy, temperature instability, increased episodes of apnea/bradycardia, disseminated intravascular coagulation, and shock. With abdominal perforation, the abdomen may develop a bluish discoloration.

The white blood cell count can be elevated, but often it is depressed. Thrombocytopenia is common. In addition, infants may develop coagulation abnormalities along with metabolic derangements, including metabolic acidosis, electrolyte imbalance, and hypoglycemia and hyperglycemia. No unique infectious agent has been associated with NEC; bacteriological and fungal cultures may prove helpful but not conclusive.

Radiographic imaging is essential to the diagnosis of NEC. The earliest radiographic finding is intestinal ileus, often associated with thickening of the bowel loops and air-fluid levels. The pathognomonic radiographic finding is **pneumatosis intestinalis** caused by hydrogen gas production from pathogenic bacteria present between the subserosal and muscularis layers of the bowel wall. Radiographic findings also may include a fixed or

persistent dilated loop of bowel, intrahepatic venous gas, and *pneumoperitoneum* seen with bowel perforation.

The **differential diagnosis** of NEC includes sepsis with intestinal ileus or a volvulus. Both conditions can present with systemic signs of sepsis and abdominal distention. The absence of pneumatosis on abdominal radiographs does not rule out the diagnosis of NEC; other causes of abdominal distention and perforation (gastric or ileal perforation) should be considered and investigated. Patients diagnosed with Hirschsprung enterocolitis or severe gastroenteritis may present with pneumatosis intestinalis.

The **management** of NEC includes the discontinuation of enteral feedings, gastrointestinal decompression with nasogastric suction, fluid and electrolyte replacement, total parenteral nutrition, and systemic broad-spectrum antibiotics. When the diagnosis of NEC is made, consultation with a pediatric surgeon should be obtained. Even with aggressive and appropriate medical management, 25-50% of infants with NEC require surgical intervention. The decision to perform surgery is obvious when the presence of a pneumoperitoneum is observed on abdominal radiograph. Other, not so obvious indications for surgical intervention include rapid clinical deterioration despite medical therapy, rapid onset and progression of pneumatosis, abdominal mass, and intestinal obstruction. The surgical procedure of choice is laparotomy with removal of the frankly necrotic and nonviable bowel. Many extremely small infants are managed initially with primary peritoneal drainage followed by surgical intervention as needed later, when the infant is stable and a laparotomy can be performed safely. The long-term outcome includes intestinal strictures requiring further surgical intervention, short bowel syndrome with poor absorption of enteral fluids and nutrients, associated cholestasis with resultant cirrhosis and liver failure from prolonged parenteral nutrition, and neurodevelopmental delay from prolonged hospitalization.

CHAPTER 64

Hypoxic-Ischemic Encephalopathy, Intracranial Hemorrhage, and Seizures

The human newborn spends more time asleep (predominantly in rapid eye movement or active sleep) than in a wakeful state and is totally dependent on adults. Primitive reflexes, such as the Moro, grasp, stepping, rooting, sucking, and crossed extensor reflexes, are readily elicited and are normal for this age. In addition, the newborn has a wealth of cortical functions that are less easily shown (e.g., the ability to extinguish repetitive or painful stimuli). The newborn also has the capacity for attentive eye fixation and differential responses to the mother's voice. During the perinatal period, many pathophysiological mechanisms can adversely and permanently affect the developing brain, including prenatal events, such as hypoxia, ischemia, infections, inflammation, malformations, maternal drugs, and coagulation disorders, as well as postnatal events, such as birth trauma, hypoxia-ischemia, inborn errors of metabolism, hypoglycemia, hypothyroidism, hyperthyroidism, polycythemia, hemorrhage, and meningitis.

NEONATAL SEIZURES

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Seizures and Other Paroxysmal Disorders
Hypocalcemia

Seizures during the neonatal period may be the result of multiple causes, with characteristic **historical and clinical manifestations**. Seizures caused by **hypoxic-ischemic encephalopathy** (postasphyxial seizures), a common cause of seizures in the full-term infant, usually occur 12-24 hours after a history of birth asphyxia and often are refractory to conventional doses of anticonvulsant medications. Postasphyxial seizures also may be caused by metabolic disorders associated with neonatal asphyxia, such as hypoglycemia and hypocalcemia. **Intraventricular hemorrhage (IVH)** is a common cause of seizures in premature infants and often occurs between 1 and 3 days of age. Seizures with IVH are associated with a bulging fontanelle, hemorrhagic spinal fluid, anemia, lethargy, and coma. Seizures caused by **hypoglycemia** often occur when blood glucose levels decline to the lowest postnatal value (at 1-2 hours of age or after 24-48 hours of poor nutritional intake). Seizures caused by **hypocalcemia** and **hypomagnesemia** develop in high-risk infants and respond well to therapy with calcium, magnesium, or both.

Seizures noted in the delivery room often are caused by direct *injection of local anesthetic agents* into the fetal scalp (associated with transient bradycardia and fixed dilated pupils), severe *anoxia*, or *congenital brain malformation*. Seizures after the first 5 days of life may be the result of *infection* or *drug withdrawal*. Seizures associated with lethargy, acidosis, and a family history of infant deaths may be the result of an *inborn error of metabolism*. An infant whose parent has a history of a neonatal seizure also is at risk for *benign familial seizures*. In an infant who appears well, a sudden onset on day 1-3 of life of seizures that are of short duration and that do not recur may be the result of a *subarachnoid hemorrhage*. Focal seizures often are the result of local cerebral infarction.

Seizures may be difficult to differentiate from benign jitteriness or from tremulousness in infants of diabetic mothers, in infants with narcotic withdrawal syndrome, and in any infants after an episode of asphyxia. In contrast to seizures, jitteriness and tremors are sensory dependent, elicited by stimuli, and interrupted by holding the extremity. Seizure activity becomes manifested as coarse, fast and slow clonic activity, whereas jitteriness is characterized by fine, rapid movement. Seizures may be associated with abnormal eye movements, such as tonic deviation to one side. The electroencephalogram often shows seizure activity when the clinical diagnosis is uncertain. Identifying seizures in the newborn period is often difficult because the infant, especially the low birth weight infant, usually does not show the tonic-clonic major motor activity typical of the older child (Table 64.1). Subtle seizures are a common manifestation in newborns. The subtle signs of seizure activity include apnea, eye deviation, tongue thrusting, eye blinking, fluctuation of vital

TABLE **64.1** Clinical Characteristics of Neonatal Seizures

DESIGNATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unilateral or multifocal May appear synchronously or asynchronously in various body regions Cannot be suppressed by restraint
Focal tonic	Sustained posturing of single limbs Sustained asymmetrical posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint
Myoclonic	Arrhythmic contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation
Generalized tonic	Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked by stimulation May be suppressed by restraint or repositioning
Ocular signs	Random and roving eye movements or nystagmus Distinct from tonic eye deviation
Orobuccolingual movements	Sucking, chewing, tongue protrusions May be provoked by stimulation
Progression movements	Rowing or swimming movements of the arms Pedaling or bicycling movements of the legs May be provoked by stimulation May be suppressed by restraint or repositioning

From Mizrahi EM. Neonatal seizures. In: Shinnar S, Branski D, eds. Pediatric and Adolescent Medicine, *vol 6,* Childhood Seizures. *Basel: S. Karger; 1995.*

signs, and staring. Continuous bedside electroencephalographic monitoring can help identify subtle seizures.

The **diagnostic evaluation** of infants with seizures should involve an immediate determination of capillary blood glucose levels with a Chemstrip. In addition, blood concentrations of sodium, calcium, glucose, and bilirubin should be determined. When infection is suspected, cerebrospinal fluid and blood specimens should be obtained for culture. After the seizure has stopped, a careful examination should be done to identify signs of increased intracranial pressure, congenital malformations, and systemic illness. If signs of elevated intracranial pressure are absent, a lumbar puncture should be performed. If the diagnosis is not apparent at this point, further evaluation should involve magnetic resonance imaging, computed tomography, or cerebral ultrasound and tests to determine the presence of an inborn error of metabolism. Determinations of inborn errors of metabolism are especially important in infants with unexplained lethargy, coma, acidosis, ketonuria, or respiratory alkalosis.

The **treatment** of neonatal seizures may be specific, such as treatment of meningitis or the correction of **hypoglycemia**, **hypocalcemia**, **hypomagnesemia**, **hyponatremia**, or **vitamin B_6 deficiency** or **dependency**. In the absence of an identifiable cause, therapy should involve an anticonvulsant agent, such as 20-40 mg/kg of phenobarbital, 10-20 mg/kg of phenytoin, or 0.1-0.3 mg/kg of diazepam. Treatment of status epilepticus requires repeated doses of phenobarbital and may require diazepam or midazolam, titrated to clinical signs. The long-term outcome for neonatal seizures usually is related to the underlying cause and to the primary pathology, such as hypoxic-ischemic encephalopathy, meningitis, drug withdrawal, stroke, or hemorrhage.

INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage may be confined to one anatomical area of the brain, such as the subdural, subarachnoid, periventricular, intraventricular, intraparenchymal, or cerebellar region. **Subdural hemorrhages** are seen in association with birth trauma, cephalopelvic disproportion, forceps delivery, large for gestational age infants, skull fractures, and postnatal head trauma. The subdural hematoma does not always cause symptoms immediately after birth; with time, however, the red blood cells (RBCs) undergo hemolysis and water is drawn into the hemorrhage because of the high oncotic pressure of protein, resulting in an expanding symptomatic lesion. Anemia, vomiting, seizures, and macrocephaly may occur in an infant who is 1-2 months of age and has a subdural hematoma. **Child abuse** in this situation should be suspected and appropriate diagnostic evaluation undertaken to identify other possible signs of skeletal, ocular, or soft tissue injury. Occasionally, a massive subdural hemorrhage in the neonatal period is caused by rupture of the vein of Galen or by an inherited coagulation disorder, such as hemophilia. Infants with these conditions exhibit shock, seizures,

and coma. The **treatment** of all symptomatic subdural hematomas is surgical evacuation.

Subarachnoid hemorrhages may be spontaneous, associated with hypoxia, or caused by bleeding from a cerebral arteriovenous malformation. Seizures are a common presenting manifestation, and the *prognosis* depends on the underlying injury. Treatment is directed at the seizure and the rare occurrence of posthemorrhagic hydrocephalus.

Periventricular hemorrhage and **IVH** are common in very low birth weight infants; the risk decreases with increasing gestational age. Fifty percent of infants weighing less than 1,500 g have evidence of intracranial bleeding. The pathogenesis for these hemorrhages is unknown (they usually are not caused by coagulation disorders), but the initial site of bleeding may be the weak blood vessels in the periventricular germinal matrix. The vessels in this area have poor structural support. These vessels may rupture and hemorrhage because of passive changes in cerebral blood flow occurring with the variations of blood pressure that sick premature infants often exhibit (failure of autoregulation). In some sick infants, these blood pressure variations are the only identifiable etiological factors. In others, the disorders that may cause the elevation or depression of blood pressure or that interfere with venous return from the head (venous stasis) increase the risk of IVH; these disorders include asphyxia, pneumothorax, mechanical ventilation, hypercapnia, hypoxemia, prolonged labor, breech delivery, patent ductus arteriosus, heart failure, and therapy with hypertonic solutions such as sodium bicarbonate.

Most periventricular hemorrhages and IVHs occur in the first 3 days of life. It is unusual for IVH to occur after day 5 of life. The clinical manifestations of IVH include seizures, apnea, bradycardia, lethargy, coma, hypotension, metabolic acidosis, anemia not corrected by blood transfusion, bulging fontanelle, and cutaneous mottling. Many infants with small hemorrhages (grade 1 or 2) are asymptomatic; infants with larger hemorrhages (grade 4) often have a catastrophic event that rapidly progresses to shock and coma.

The diagnosis of IVH is confirmed and the severity graded by ultrasound through the anterior fontanelle or computed tomography examination. Grade 1 IVH is confined to the germinal matrix; grade 2 is an extension of grade 1, with blood noted in the ventricle without ventricular enlargement; grade 3 is an extension of grade 2 with ventricular dilation; and grade 4 has blood in dilated ventricles and in the cerebral cortex, either contiguous with or distant from the ventricle. Grade 4 hemorrhage has a poor prognosis, as does the development of periventricular, small, echolucent cystic lesions, with or without porencephalic cysts and posthemorrhagic hydrocephalus. Periventricular cysts often are noted after the resolution of echodense areas in the periventricular white matter. The cysts may correspond to the development of **periventricular leukomalacia**, which may be a precursor to cerebral palsy. Extensive intraparenchymal echodensities represent hemorrhagic necrosis. They are associated with a high mortality rate and have a poor neurodevelopmental prognosis for survivors.

Treatment of an acute hemorrhage involves standard supportive care, including ventilation for apnea and blood transfusion for hemorrhagic shock. Posthemorrhagic hydrocephalus may be managed with serial daily lumbar punctures, an external ventriculostomy tube, or a permanent ventriculoperitoneal shunt. Implementation of the shunt often is delayed because of the high protein content of the hemorrhagic ventricular fluid.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Conditions known to reduce uteroplacental blood flow or to interfere with spontaneous respiration lead to perinatal hypoxia, lactic acidosis, and, if severe enough to reduce cardiac output or cause cardiac arrest, ischemia. The combination of the reduced availability of oxygen for the brain resulting from hypoxia and the diminished or absent blood flow to the brain resulting from ischemia leads to reduced glucose for metabolism and to an accumulation of lactate that produces local tissue acidosis. After reperfusion, hypoxic-ischemic injury also may be complicated by cell necrosis and vascular endothelial edema, reducing blood flow distal to the involved vessel. Typically, hypoxic-ischemic encephalopathy in the term infant is characterized by cerebral edema, cortical necrosis, and involvement of the basal ganglia, whereas in the preterm infant it is characterized by periventricular leukomalacia. Both lesions may result in cortical atrophy, mental retardation, and spastic quadriplegia or diplegia.

The clinical manifestations and characteristic course of hypoxic-ischemic encephalopathy vary according to the severity of the injury (Table 64.2). Infants with severe stage

TABLE 64.2 Hypoxic-Ischemic Encephalopathy in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous
Muscle tone	Normal	Hypotonic	Flaccid
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalography	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	>24 hr if progresses, otherwise may remain normal	24 hr to 14 days	Days to weeks

Modified from Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. Arch Neurol. *1976;33:696.*

3 hypoxic-ischemic encephalopathy are usually hypotonic, although occasionally they initially appear hypertonic and hyperalert at birth. As cerebral edema develops, brain functions are affected in a descending order; cortical depression produces coma, and brainstem depression results in apnea. As cerebral edema progresses, refractory seizures begin 12-24 hours after birth. Concurrently the infant has no signs of spontaneous respirations, is hypotonic, and has diminished or absent deep tendon reflexes. Hypoxic-ischemic encephalopathy in term infants is often managed with induced hyperthermia.

Survivors of stage 3 hypoxic-ischemic encephalopathy have a high incidence of seizures and serious neurodevelopmental handicaps. The prognosis of severe asphyxia also depends on other organ system injury (see Table 58.6). Another indicator of poor prognosis is time of onset of spontaneous respiration as estimated by Apgar score. Infants with Apgar scores of 0-3 at 10 minutes have a 20% mortality and a 5% incidence of cerebral palsy; if the score remains this low by 20 minutes, the mortality increases to 60%, and the incidence of cerebral palsy increases to 57%.

CHAPTER 65

Sepsis and Meningitis

Systemic and local infections (lung, cutaneous, ocular, umbilical, kidney, bone-joint, and meningeal) are common in the newborn period. Infection may be acquired in utero through the transplacental or transcervical routes and during or after birth. Ascending infection through the cervix, with or without rupture of the amniotic fluid membranes, may result in amnionitis, funisitis (infection of the umbilical cord), congenital pneumonia, and sepsis. The bacteria responsible for ascending infection of the fetus are common bacterial organisms of the maternal genitourinary tract, such as group B streptococci, *Escherichia coli, Haemophilus influenzae*, and *Klebsiella*. Herpes simplex virus (HSV)-1 or, more often, HSV-2 also causes ascending infection that at times may be indistinguishable from bacterial sepsis. Syphilis and *Listeria monocytogenes* are acquired by transplacental infection.

Maternal humoral immunity may protect the fetus against some neonatal pathogens, such as group B streptococci and HSV. Nonetheless, various deficiencies of the neonatal antimicrobial defense mechanism probably are more important than maternal immune status as a contributing factor for neonatal infection, especially in the low birth weight infant. The incidence of sepsis is approximately 1:1,500 in full-term infants and 1:250 in preterm infants. The sixfold-higher rate of sepsis in preterm infants relates to the more immature immunological systems of preterm infants and to their prolonged periods of hospitalization, which increase risk of nosocomially acquired infectious diseases.

Preterm infants before 32 weeks of gestational age have not received the full complement of maternal antibodies (immunoglobulin G [IgG]), which cross the placenta by active transport predominantly in the latter half of the third trimester. In addition, although low birth weight infants may generate IgM antibodies, their own IgG response to infection is reduced. These infants also have deficiencies of the alternate and, to a smaller degree, the classic complement activation pathways, which results in diminished complement-mediated opsonization. Newborn infants also show a deficit in phagocytic migration to the site of infection (to the lung) and in the bone marrow reserve pool of leukocytes. In addition, in the presence of suboptimal activation of complement, neonatal neutrophils ingest and kill bacteria less effectively than adult neutrophils do. Neutrophils from sick infants seem to have an even greater deficit in bacterial killing capacity compared with phagocytic cells from normal neonates.

Defense mechanisms against viral pathogens also may be deficient in a newborn. Neonatal antibody-dependent, cell-mediated immunity by the natural killer lymphocytes is deficient in the absence of maternal antibodies and in the presence of reduced interferon production; reduced antibody levels occur in premature infants and in infants born during a primary viral infection of the mother, such as with enteroviruses, HSV-2, or cytomegalovirus. In addition, antibody-independent cytotoxicity may be reduced in lymphocytes of newborns.

Bacterial sepsis and meningitis often are linked closely in neonates. Despite this association, the incidence of meningitis relative to neonatal sepsis has been on a steady decline. The incidence of meningitis is approximately 1 in 20 cases of sepsis. The causative organisms isolated most frequently are the same as for neonatal sepsis: group B streptococci, *E. coli*, and *L. monocytogenes*. Gram-negative organisms, such as *Klebsiella*, *Salmonella*, and *Serratia marcescens*, are more common in less developed countries, and coagulase-negative staphylococcus needs to be considered in very low birth weight infants. Male infants seem to be more susceptible to neonatal infection than female infants. Severely premature infants are at even greater risk secondary to less effective defense mechanisms and deficient transfer of antibodies from the mother to the fetus (which occurs mostly after 32 weeks' gestation). Neonates in the neonatal intensive care unit live in a hostile environment, with exposure to endotracheal tubes, central arterial and venous catheters, and blood draws, all predisposing to bacteremia and meningitis. Genetic factors have been implicated in the ability of bacteria to cross the blood-brain barrier. This penetration has been noted for group B streptococci, *E. coli*, *Listeria*, *Citrobacter*, and *Streptococcus pneumoniae*.

Neonatal sepsis presents during three periods. **Early-onset sepsis** often begins in utero and usually is a result of infection caused by the bacteria in the mother's genitourinary tract. Organisms related to this sepsis include group B streptococci, *E. coli*, *Klebsiella*, *L. monocytogenes*, and nontypeable *H. influenzae*. Most infected infants are premature and show nonspecific cardiorespiratory signs, such as grunting, tachypnea, and cyanosis at birth. Risk factors for early-onset sepsis include vaginal colonization with group B streptococci, prolonged rupture of the membranes (>24 hours), amnionitis, maternal fever or leukocytosis, fetal tachycardia, and preterm birth. African American race and male sex are unexplained additional risk factors for neonatal sepsis.

Early-onset sepsis (birth to 7 days) is an overwhelming multiorgan system disease frequently manifested as respiratory failure, shock, meningitis (in 30% of cases), disseminated intravascular coagulation, acute tubular necrosis, and symmetrical peripheral gangrene. Early manifestations—grunting, poor feeding, pallor, apnea, lethargy, hypothermia, or an abnormal cry—may be nonspecific. Profound neutropenia, hypoxia, and hypotension may be refractory to treatment with broad-spectrum

antibiotics, mechanical ventilation, and vasopressors such as dopamine. In the initial stages of early-onset septicemia in a preterm infant, it is often difficult to differentiate sepsis from respiratory distress syndrome. Because of this difficulty, premature infants with respiratory distress syndrome receive broad-spectrum antibiotics.

The clinical manifestations of sepsis are difficult to separate from the manifestations of meningitis in the neonate. Infants with early-onset sepsis should be evaluated by blood and cerebrospinal fluid (CSF) cultures, CSF Gram stain, cell count, and protein and glucose levels. Normal newborns generally have an elevated CSF protein content (100-150 mg/dL) and may have 25-30/mm^3 white blood cells (mean, 9/mm^3), which are 75% lymphocytes in the absence of infection. Some infants with neonatal meningitis caused by group B streptococci do not have an elevated CSF leukocyte count but are seen to have microorganisms in the CSF on Gram stain. In addition to culture, other methods of identifying the pathogenic bacteria are the determination of bacterial DNA in samples of CSF. In cases of neonatal meningitis, the ratio of CSF glucose to blood glucose usually is less than 50%. The polymerase chain reaction test primarily is used to identify viral infections. Serial complete blood counts should be performed to identify neutropenia, an increased number of immature neutrophils (bands), and thrombocytopenia. C-reactive protein levels are often elevated in neonatal patients with bacterial sepsis.

A chest radiograph also should be obtained to determine the presence of pneumonia. In addition to the traditional neonatal pathogens, pneumonia in very low birth weight infants may be the result of acquisition of maternal genital mycoplasmal agent (e.g., *Ureaplasma urealyticum* or *Mycoplasma hominis*). Arterial blood gases should be monitored to detect hypoxemia and metabolic acidosis that may be caused by hypoxia, shock, or both. Blood pressure, urine output, and peripheral perfusion should be monitored to determine the need to treat septic shock with fluids and vasopressor agents.

The mainstay of treatment for sepsis and meningitis is antibiotic therapy. Antibiotics are used to suppress bacterial growth, allowing the infant's defense mechanisms time to respond. In addition, support measures, such as assisted ventilation and cardiovascular support, are equally important to the management of the infant. A combination of ampicillin and an aminoglycoside (usually gentamicin) for 10-14 days is effective treatment against most organisms responsible for early-onset sepsis. The combination of ampicillin and cefotaxime also is proposed as an alternative method of treatment. If meningitis is present, the treatment should be extended to 21 days or 14 days after a negative result from a CSF culture. Persistently positive results from CSF cultures are common with neonatal meningitis caused by gram-negative organisms, even with appropriate antibiotic treatment, and may be present for 2-3 days after antibiotic therapy. If gram-negative meningitis is present, some authorities continue to treat with an effective penicillin derivative combined with an aminoglycoside, whereas most change to a third-generation cephalosporin. High-dose penicillin (250,000-450,000 U/kg/24 hr) is appropriate for group B streptococcal meningitis. Inhaled nitric oxide, extracorporeal membrane oxygenation (in term infants), or both may improve the outcome of sepsis-related pulmonary hypertension. Intratracheal surfactant may reverse respiratory failure. Intrapartum penicillin empirical prophylaxis for group B streptococcal colonized mothers or mothers with risk factors (fever, preterm labor, previous infant with group B streptococci, and amnionitis) has reduced the rate of early-onset infection.

Late-onset sepsis (8-28 days) usually occurs in a healthy full-term infant who was discharged in good health from the normal newborn nursery. Clinical manifestations may include lethargy, poor feeding, hypotonia, apathy, seizures, bulging fontanelle, fever, and direct-reacting hyperbilirubinemia. In addition to bacteremia, hematogenous seeding may result in focal infections, such as meningitis (in 75% of cases), osteomyelitis (group B streptococci, *Staphylococcus aureus*), arthritis (gonococcus, *S. aureus*, *Candida albicans*, gram-negative bacteria), and urinary tract infection (gram-negative bacteria).

The evaluation of infants with late-onset sepsis is similar to that for infants with early-onset sepsis, with special attention given to a careful physical examination of the bones (infants with osteomyelitis may exhibit pseudoparalysis) and to the laboratory examination and culture of urine obtained by sterile suprapubic aspiration or urethral catheterization. Late-onset sepsis may be caused by the same pathogens as early-onset sepsis, but infants exhibiting sepsis late in the neonatal period also may have infections caused by the pathogens usually found in older infants (*H. influenzae*, *S. pneumoniae*, and *Neisseria meningitidis*). In addition, viral agents (HSV, cytomegalovirus, or enteroviruses) may manifest with a late-onset, sepsis-like picture.

Because of the increased rate of resistance of *H. influenzae* and pneumococcus to ampicillin, some centers begin treatment with ampicillin and a third-generation cephalosporin (and vancomycin if meningitis is present) when sepsis occurs in the last week of the first month of life. The treatment of late-onset neonatal sepsis and meningitis is the same as that for early-onset sepsis.

CHAPTER 66
Congenital Infections

An infection acquired transplacentally during gestation is a congenital infection. Numerous pathogens that produce mild or subclinical disease in older infants and children can cause severe disease in neonates who acquire such infections prenatally or perinatally. Sepsis, meningitis, pneumonia, and other infections caused by numerous perinatally acquired pathogens are the cause of significant neonatal morbidity and mortality. Congenital infections include a well-known group of fungal, bacterial, and viral pathogens: toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus, congenital syphilis, parvovirus, human immunodeficiency virus (HIV), hepatitis B, Zika virus, *Neisseria gonorrhoeae*, *Chlamydia*, and *Mycobacterium tuberculosis.*

Many of the clinical manifestations of congenital infections are similar, including intrauterine growth restriction, nonimmune hydrops, anemia, thrombocytopenia, jaundice, hepatosplenomegaly, chorioretinitis, and congenital malformations. Some unique manifestations and epidemiological characteristics of these infections are listed in Table 66.1. Evaluation of patients thought to have a congenital infection should include attempts to isolate the organism by culture (for rubella, CMV, HSV, gonorrhea, and *M. tuberculosis*), to identify

TABLE 66.1 Perinatal Congenital Infections (TORCH)

AGENT	MATERNAL EPIDEMIOLOGY	NEONATAL FEATURES
Toxoplasma gondii	Heterophil-negative mononucleosis Exposure to cats or raw meat or immunosuppression High-risk exposure at 10-24-wk gestation	Hydrocephalus, abnormal spinal fluid, intracranial calcifications, chorioretinitis, jaundice, hepatosplenomegaly, fever Many infants asymptomatic at birth Treatment: pyrimethamine plus sulfadiazine
Rubella virus	Unimmunized seronegative mother; fever ± rash Detectable defects with infection: by 8 wk, 85% 9-12 wk, 50% 13-20 wk, 16% Virus may be present in infant's throat for 1 yr Prevention: vaccine	Intrauterine growth restriction, microcephaly, microphthalmia, cataracts, glaucoma, "salt and pepper" chorioretinitis, hepatosplenomegaly, jaundice, PDA, deafness, blueberry muffin rash, anemia, thrombocytopenia, leukopenia, metaphyseal lucencies, B-cell and T-cell deficiency Infant may be asymptomatic at birth
CMV	Sexually transmitted disease: primary genital infection may be asymptomatic Heterophil-negative mononucleosis; infant may have viruria for 1-6 yr	Sepsis, intrauterine growth restriction, chorioretinitis, microcephaly, periventricular calcifications, blueberry muffin rash, anemia, thrombocytopenia, neutropenia, hepatosplenomegaly, jaundice, deafness, pneumonia Many asymptomatic at birth Prevention: CMV-negative blood products Possible treatment: ganciclovir
Herpes simplex type 2 or 1 virus	Sexually transmitted disease: primary genital infection may be asymptomatic; intrauterine infection rare, acquisition at time of birth more common	Intrauterine infection: chorioretinitis, skin lesions, microcephaly Postnatal: encephalitis, localized or disseminated disease, skin vesicles, keratoconjunctivitis Treatment: acyclovir
Varicella-zoster virus	Intrauterine infection with chickenpox Infant develops severe neonatal varicella with maternal illness 5 days before or 2 days after delivery	Microphthalmia, cataracts, chorioretinitis, cutaneous and bony aplasia/hypoplasia/atrophy, cutaneous scars Zoster as in older child Prevention of neonatal condition with VZIG Treatment of ill neonate: acyclovir
Treponema pallidum (syphilis)	Sexually transmitted infection Maternal primary asymptomatic: painless "hidden" chancre Penicillin, not erythromycin, prevents fetal infection	Presentation at birth as nonimmune hydrops, prematurity, anemia, neutropenia, thrombocytopenia, pneumonia, hepatosplenomegaly Late neonatal as snuffles (rhinitis), rash, hepatosplenomegaly, condylomata lata, metaphysitis, cerebrospinal fluid pleocytosis, keratitis, periosteal new bone, lymphocytosis, hepatitis Late onset: teeth, eye, bone, skin, central nervous system, ear Treatment: penicillin
Parvovirus	Etiology of fifth disease; fever, rash, arthralgia in adults	Nonimmune hydrops, fetal anemia Treatment: in utero transfusion
HIV	AIDS; most mothers are asymptomatic and HIV positive; high-risk history; prostitute, drug abuse, married to bisexual, or hemophiliac	AIDS symptoms develop between 3 and 6 mo of age in 10-25%; failure to thrive, recurrent infection, hepatosplenomegaly, neurological abnormalities Management: trimethoprim/sulfamethoxazole, AZT, other antiretroviral agents Prevention: prenatal, intrapartum, postpartum AZT; avoid breast feeding
Hepatitis B virus	Vertical transmission common; may result in cirrhosis, hepatocellular carcinoma	Acute neonatal hepatitis; many become asymptomatic carriers Prevention: HBIG, vaccine
Neisseria gonorrhoeae	Sexually transmitted infection, infant acquires at birth Treatment: cefotaxime, ceftriaxone	Gonococcal ophthalmia, sepsis, meningitis Prevention: silver nitrate, erythromycin eye drops Treatment: ceftriaxone
Chlamydia trachomatis	Sexually transmitted infection, infant acquires at birth Treatment: oral erythromycin	Conjunctivitis, pneumonia Prevention: erythromycin eye drops Treatment: oral erythromycin
Mycobacterium tuberculosis	Positive PPD skin test, recent converter, positive chest radiograph, positive family member Treatment: INH and rifampin ± ethambutol	Congenital rare septic pneumonia; acquired primary pulmonary TB; asymptomatic, follow PPD Prevention: INH, BCG, separation Treatment: INH, rifampin, pyrazinamide
Trypanosoma cruzi (Chagas disease)	Central South American native, immigrant, travel Chronic disease in mother	Failure to thrive, heart failure, achalasia Treatment: nifurtimox
Zika virus	see text	see text

AZT, Zidovudine (azidothymidine); *BCG*, bacille Calmette-Guerin; *CMV*, cytomegalovirus; *HBIG*, hepatitis B immune globulin; *INH*, isoniazid; *PDA*, patent ductus arteriosus; *PPD*, purified protein derivative; *TB*, tuberculosis; *VZIG*, varicella-zoster immune globulin.

the antigen of the pathogen (for hepatitis B and *Chlamydia trachomatis*), to identify the pathogen's genome with polymerase chain reaction (PCR), and to identify specific fetal production of antibodies (immunoglobulin M [IgM] or increasing titer of IgG for *Toxoplasma*, syphilis, parvovirus, HIV, or *Borrelia*).

Treatment is not always available, specific, or effective. Nonetheless, some encouraging results have been reported for preventing the disease and for specifically treating the infant when the correct diagnosis is made (see Table 66.1).

TOXOPLASMOSIS

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Abnormal Head Size, Shape, and Fontanels
Visual Impairment and Leukocoria
Petechiae/Purpura

Vertical transmission of *Toxoplasma gondii* occurs by transplacental transfer of the organism from the mother to the fetus after an acute maternal infection. Fetal infection rarely can occur after reactivation of disease in an immunocompromised pregnant mother. Transmission from an acutely infected mother to her fetus occurs in about 30-40% of cases, but the rate varies directly with gestational age. Transmission rates and the timing of fetal infection correlate directly with placental blood flow; the risk of infection increases throughout gestation to 90% or greater near term, and the time interval between maternal and fetal infection decreases.

The severity of fetal disease varies inversely with the gestational age at which maternal infection occurs. Most infants have subclinical infection with no overt disease at birth; however, specific ophthalmologic and central nervous system (CNS) evaluations may reveal abnormalities. The classic findings of hydrocephalus, chorioretinitis, and intracerebral calcifications suggest the diagnosis of congenital toxoplasmosis. Affected infants tend to be small for gestational age, develop early-onset jaundice, have hepatosplenomegaly, and present with a generalized maculopapular rash. Seizures are common, and skull films may reveal diffuse cortical calcifications in contrast to the periventricular pattern observed with CMV. These infants are at increased risk for long-term neurological and neurodevelopmental complications.

Serological tests are the primary means of diagnosis. IgG-specific antibodies achieve a peak concentration 1-2 months after infection and remain positive indefinitely. For infants with seroconversion or a fourfold increase in IgG titers, specific IgM antibody determinations should be performed to confirm disease. Especially for congenital infections, measurement of IgA and IgE antibodies can be useful to confirm the disease. Thorough ophthalmologic, auditory, and neurological evaluations (head computed tomography and cerebrospinal fluid [CSF] examination) are indicated.

For symptomatic and asymptomatic congenital infections, initial therapy should include pyrimethamine (supplemented with folic acid) combined with sulfadiazine. Duration of therapy is often prolonged, even up to 1 year. Optimal dosages of medications and duration of therapy should be determined in consultation with appropriate specialists.

RUBELLA

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Abnormal Head Size, Shape, and Fontanelles
Visual Impairment and Leukocoria
Heart Murmurs
Hearing Loss

With the widespread use of vaccination, congenital rubella is rare in developed countries. Acquired in utero during early gestation, rubella can cause severe neonatal consequences. The occurrence of congenital defects approaches 85% if infection is acquired during the first 4 weeks of gestation; close to 40% spontaneously abort or are stillborn. If infection occurs during weeks 13-16, 35% of infants can have abnormalities. Infection after 4 months' gestation does not seem to cause disease.

The most common characteristic abnormalities associated with congenital rubella include ophthalmologic (cataracts, retinopathy, and glaucoma), cardiac (patent ductus arteriosus and peripheral pulmonary artery stenosis), auditory (sensorineural hearing loss), and neurological (behavioral disorders, meningoencephalitis, and developmental delay) conditions. In addition, infants can present with growth retardation, hepatosplenomegaly, early-onset jaundice, thrombocytopenia, radiolucent bone disease, and purpuric skin lesions ("blueberry muffin" appearance from dermal erythropoiesis).

Detection of rubella-specific IgM antibody usually indicates recent infection. Measurement of rubella-specific IgG over several months can be confirmatory. Rubella virus can be isolated from blood, urine, CSF, and throat swab specimens. Infants with congenital rubella are chronically and persistently infected and tend to shed live virus in urine, stools, and respiratory secretions for 1 year. Infants should be isolated while in the hospital and kept away from susceptible pregnant women when sent home.

CYTOMEGALOVIRUS

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Visual Impairment and Leukocoria
Hepatomegaly
Hearing Loss
Petechiae/Purpura

CMV is the most common congenital infection and the leading cause of sensorineural hearing loss, mental retardation, retinal disease, and cerebral palsy. Congenital CMV occurs in about 0.5-1.5% of births. When primary infection occurs in mothers during a pregnancy, the virus is transmitted to the fetus in approximately 35% of cases. Rates of CMV infection are three to seven times greater in infants born to adolescent mothers compared to others. The risk of transmission of CMV to the fetus is independent of gestational age at the time of maternal infection. The earlier in gestation that the primary maternal infection occurs, the more symptomatic the infant

will be at birth. The most common sources of CMV for primary infections occurring in mothers during pregnancy are sexual contacts and contact with young children. It is well known that CMV can be transmitted to the fetus even when maternal infection occurred long before conception. This transmission can occur as the result of virus reactivation, chronic infection, or reinfection with a new strain.

More than 90% of infants who have congenital CMV infection exhibit no clinical evidence of disease at birth. Approximately 10% of infected infants are small for gestational age and have symptoms at birth. Findings include microcephaly, thrombocytopenia, hepatosplenomegaly, hepatitis, intracranial calcifications, chorioretinitis, and hearing abnormalities. Some infants can present with a blueberry muffin appearance as the result of dermal erythropoiesis. Skull films may reveal periventricular calcifications. An additional 10% of infected infants may not present until later in infancy or early childhood, when they are found to have sensorineural hearing loss and developmental delays. Mortality is 10-15% in symptomatic newborns. Perinatal CMV infection acquired during birth or from mother's milk is not associated with newborn illness or CNS sequelae.

Congenital CMV infection is diagnosed by detection of virus in the urine or saliva. Detection is often accomplished by traditional virus culture methods but can take several weeks to obtain a result. Rapid culture methods using centrifugation to enhance infectivity and monoclonal antibody to detect early antigens in infected tissue culture can give results in 24 hours. PCR also can be used to detect small amounts of CMV DNA in the urine. Detection of CMV within the first 3 weeks after birth is considered proof of congenital CMV infection.

Trial studies in severely symptomatic newborns of the antiviral agent ganciclovir have shown a lack of progression of hearing loss.

HERPES SIMPLEX VIRUS

HSV-2 accounts for 90% of primary genital herpes. About 70-85% of neonatal herpes simplex infections are caused by HSV-2. Most commonly, neonatal infections are acquired from the mother shortly before (ascending infection) or during passage through the birth canal at delivery. The incidence of neonatal HSV is estimated to range from 1 in 3,000 to 1 in 20,000 live births. Infants with HSV infections are more likely to be born prematurely (40% of affected infants are <36 weeks' gestation). The risk of infection at delivery in an infant born vaginally to a mother with primary genital herpes is about 33-50%. The risk to an infant born to a mother with a reactivated infection is less than 5%. More than 75% of infants who acquire HSV infection are born to mothers who have no previous history or clinical findings consistent with HSV infection.

Most infants are normal at birth, and symptoms of infection develop at 5-10 days of life. Symptoms of neonatal HSV infection include disseminated disease involving multiple organ systems, most notably the liver and lungs; localized infection to the CNS; or localized infection to the skin, eyes, and mouth. Symptoms may overlap, and in many cases of disseminated disease, skin lesions are a late finding. Disseminated infection should be considered in any infant with symptoms of sepsis, liver dysfunction, and negative bacteriological cultures. HSV infection also should be suspected in any neonate who presents with fever, irritability, abnormal CSF findings, and seizures. Initial symptoms can occur anytime between birth and 4 weeks of age, although disseminated disease usually occurs during the first week of life. HSV infections are often severe, and a delay in treatment can result in significant morbidity and mortality.

For the diagnosis of neonatal HSV infection, specimens for culture should be obtained from any skin vesicle, nasopharynx, eyes, urine, blood, CSF, stool, or rectum. Positive cultures obtained from these sites more than 48 hours after birth indicate intrapartum exposure. PCR is a sensitive method for detecting HSV DNA in blood, skin lesions, and CSF.

Parenteral acyclovir is the treatment of choice for neonatal HSV infections. Acyclovir should be administered to all infants suspected to have infection or diagnosed with HSV. The most benign outcome with regard to morbidity and mortality is observed in infants with disease limited to the skin, eyes, and mouth.

CONGENITAL SYPHILIS

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Rhinorrhea
Abnormal Head Size, Shape, and Fontanels
Red Eye
Hoarseness
Hepatomegaly
Hearing Loss
Lymphadenopathy

Congenital syphilis most commonly results from transplacental infection of the fetus, although the fetus can acquire infection by contact with a chancre at birth. In addition, hematogenous infection can occur throughout pregnancy. The longer the time elapsed between the mother's infection and pregnancy, the less likely she is to transmit the disease to the fetus.

Intrauterine infection can result in stillbirth, hydrops fetalis, or prematurity. Clinical symptoms vary but include hepatosplenomegaly, snuffles, lymphadenopathy, mucocutaneous lesions, osteochondritis, rash, hemolytic anemia, and thrombocytopenia. Untreated infants, regardless of whether they manifest symptoms at birth, may develop late symptoms, which usually appear after 2 years of age and involve the CNS, bones, joints, teeth, eyes, and skin. Some manifestations of disease may not become apparent until many years after birth, such as interstitial keratitis, eighth cranial nerve deafness, Hutchinson teeth, bowing of the shins, frontal bossing, mulberry molars, saddle nose, rhagades, and Clutton joints. The combination of interstitial keratitis, eighth cranial nerve deafness, and Hutchinson teeth is commonly referred to as the *Hutchinson triad* (see Table 66.1).

Many infants are asymptomatic at the time of diagnosis. If untreated, most infants develop symptoms within the first 5 weeks of life. The most striking lesions affect the mucocutaneous tissues and bones. Early signs of infection may be poor feeding and snuffles (syphilitic rhinitis). Snuffles are more severe and persistent than the common cold and are often bloody. A maculopapular desquamative rash develops over the palms and soles and around the mouth and anus. The rash may progress to become vesicular with bullae. Severely ill infants may be born with hydrops and have profound anemia. Severe consolidated pneumonia may be present at birth, and there may

be laboratory findings consistent with a glomerulonephritis. CSF evaluation may reveal a pleocytosis and elevated protein. More than 90% of symptomatic infants exhibit radiographic abnormalities of the long bones consistent with osteochondritis and perichondritis.

No newborn should be discharged from the hospital without knowledge or determination of the mother's serological status for syphilis. All infants born to seropositive mothers require a careful examination and a quantitative nontreponemal syphilis test. Dark-field examination of direct fluorescent antibody staining of organisms obtained by scraping a skin or mucous membrane lesion is the quickest and most direct method of diagnosis. More commonly, serological testing is used. The nontreponemal reaginic antibody assays—the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin—are helpful as indicators of disease. The test performed on the infant should be the same as that performed on the mother to enable comparison of results. An infant should be evaluated further if the maternal titer has increased fourfold, if the infant's titer is fourfold greater than the mother's titer, if the infant is symptomatic, or if the mother has inadequately treated syphilis. A mother infected later in pregnancy may deliver an infant who is incubating active disease. The mother and infant may have negative serological testing at birth. When clinical or serological tests suggest congenital syphilis, CSF should be examined microscopically, and a CSF VDRL test should be performed. An increased CSF white blood cell count and protein concentration suggests neurosyphilis; a positive CSF VDRL is diagnostic.

Parenteral penicillin is the preferred drug of choice for treatment of syphilis. Penicillin G for 10-14 days is the only documented effective therapy for infants who have congenital syphilis and neurosyphilis. Infants should have repeat nontreponemal antibody titers repeated at 3, 6, and 12 months to document falling titers. Infants with neurosyphilis must be followed carefully with serological testing and CSF determinations every 6 months for at least 3 years or until CSF findings are normal.

HUMAN IMMUNODEFICIENCY VIRUS

See Chapter 125.

HEPATITIS B

See Chapter 113.

NEISSERIA GONORRHOEAE

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Hepatomegaly

N. gonorrhoeae infection in a newborn usually involves the eyes (ophthalmia neonatorum). Other sites of infection include scalp abscesses (often associated with fetal monitoring with scalp electrodes), vaginitis, and disseminated disease with bacteremia, arthritis, or meningitis. Transmission to the infant usually occurs during passage through the birth canal when mucous membranes come in contact with infected secretions.

Infection usually is present within the first 5 days of life and is characterized initially by a clear, watery discharge, which rapidly becomes purulent. There is marked conjunctival hyperemia and chemosis. Infection tends to be bilateral; however, one eye may be clinically worse than the other. Untreated infections can spread to the cornea (keratitis) and anterior chamber of the eye. This extension can result in corneal perforation and blindness.

Recommended treatment for isolated infection, such as ophthalmia neonatorum, is one intramuscular dose of ceftriaxone. Infants with gonococcal ophthalmia should receive eye irrigations with saline solution at frequent intervals before discharge. Topical antibiotic therapy alone is inadequate and is unnecessary when recommended systemic antimicrobial therapy is given. Infants with gonococcal ophthalmia should be hospitalized and evaluated for disseminated disease (sepsis, arthritis, meningitis). Disseminated disease should be treated with antimicrobial therapy (ceftriaxone or cefotaxime) for 7 days. Cefotaxime can be used in infants with hyperbilirubinemia. If documented, infants with meningitis should be treated for 10-14 days.

Tests for concomitant infection with *C. trachomatis*, congenital syphilis, and HIV should be performed. Results of the maternal test for hepatitis B surface antigen should be confirmed. Topical prophylaxis with silver nitrate, erythromycin, or tetracycline is recommended for all newborns for the prevention of gonococcal ophthalmia.

CHLAMYDIA

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Hepatomegaly

C. trachomatis is the most common reportable sexually transmitted infection, with a high rate of infection among sexually active adolescents and young adults. Prevalence of the organism in pregnant women ranges from 6% to 12% and can be 40% in adolescents. *Chlamydia* can be transmitted from the genital tract of an infected mother to her newborn. Acquisition occurs in about 50% of infants born vaginally to infected mothers. Transmission also has been reported in some infants delivered by cesarean section with intact membranes. In infected infants, the risk of conjunctivitis is 25-50%, and the risk of pneumonia is 5-20%. The nasopharynx is the most commonly infected anatomical site.

Neonatal chlamydial conjunctivitis is characterized by ocular congestion, edema, and discharge developing 5-14 days to several weeks after birth and lasting for 1-2 weeks. Clinical manifestations vary from mild conjunctivitis to intense inflammation and swelling. Both eyes are almost always involved; however, one eye may appear to be more swollen and infected than the other. The cornea is rarely involved, and preauricular adenopathy is rare.

Pneumonia in a young infant can occur between 2 and 19 weeks of age and is characterized by an afebrile illness with a repetitive staccato cough, tachypnea, and rales. Wheezing is uncommon. Hyperinflation with diffuse infiltrates can be seen on chest radiograph. Nasal stuffiness and otitis media can occur.

Diagnosis can be made by scraping the conjunctiva and culturing the material. Giemsa staining of the conjunctival

scrapings revealing the presence of blue-stained intracytoplasmic inclusions within the epithelial cells is diagnostic. PCR is also available. Infants with conjunctivitis and pneumonia are treated with oral erythromycin for 14 days. Topical treatment of conjunctivitis is ineffective and unnecessary. The recommended topical prophylaxis with silver nitrate, erythromycin, or tetracycline for all newborns for the prevention of gonococcal ophthalmia does not prevent neonatal chlamydial conjunctivitis.

MYCOBACTERIUM TUBERCULOSIS

See Chapter 124.

ZIKA VIRUS

Zika virus is an arthropod-borne flavivirus carried and transmitted by mosquitoes, and is associated with severe congenital anomalies. Zika virus is a neurotropic virus that particularly targets progenitor cells. Zika virus causes a maternal infection leading to a placental infection and injury to the fetus. The infection is transmitted to the fetal brain where it kills neuronal progenitor cells disrupting neuronal proliferation, migration, and differentiation. In utero infections can be transmitted to the fetus at any time during the pregnancy and result in severe brain abnormalities (i.e., microcephaly, cerebellar hypoplasia, ventriculomegaly, lissencephaly) and craniofacial malformations. Additionally, the virus can result in pulmonary hypoplasia and multiple congenital contractures.

Suggested Readings

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PEARLS FOR PRACTITIONERS

CHAPTER 58

Assessment of the Mother, Fetus, and Newborn

- High-risk pregnancies include those with intrauterine growth restriction (IUGR), maternal hypertension or diabetes, autoimmune diseases (systemic lupus erythematosus [SLE]), and those with prior intrauterine fetal demise or neonatal deaths.
- Additional high-risk pregnancies include those with oligo- or polyhydramnios, multiple gestation, or macrosomic fetuses.
- Polyhydramnios is associated with fetal central nervous system (CNS) anomalies as well as high gastrointestinal obstruction.
- Low birthweight is defined by birthweight <2,500 g.
- Vitamin K must be given to all newborns to prevent hemorrhagic disease of the newborn.
- The Apgar examination performed at 1 and 5 minutes assesses fetal to neonatal transition and identifies infants in need of resuscitation.
- Hair tufts over the lumbosacral area suggest a neural tube anomaly.
- Leukokoria may be due to cataracts, ocular tumor, chorioretinitis, retinopathy of prematurity, or persistent hyperplastic primary vitreous.
- Shock in the delivery room is often due to blood loss such as fetal to maternal hemorrhage or internal bleeding (liver, spleen).
- Erb-Duchenne palsy involves the 5th and 6th cervical nerves.
- Early neonatal hypocalcemia may be due to maternal hyperparathyroidism, or neonatal DiGeorge syndrome; it is also seen in infants of diabetic mothers, preterm infants, or following birth asphyxia.
- About 10% of neonates will require some form of intervention and/or resuscitation in the delivery room.
- Since most medical centers now use Erythromycin eye ointment following delivery, any eye redness or purulent discharge needs immediate attention and potential treatment.
- The biophysical profile, which includes fetal movement, fetal breathing, fetal tone, amniotic fluid volume, and fetal heart rate reactivity, is often used to assess fetal well-being. A score of <6 out of 10 indicates possible fetal compromise and may necessitate delivery of the infant.
- Pulse oximetry screening (preductal and postductal) should be performed on all infants before discharge from the hospital. A difference of >3% is suggestive of cyanotic heart disease.
- Hearing loss is a most common congenital condition in the United States; each infant should be screened for hearing loss prior to being discharged from the hospital.
- Failure of a term infant to pass urine in the first 24 hours or meconium in the first 48 hours warrant further evaluation.
- Rule of 2s and congenital heart failure: Heart failure at 2 days is most likely caused by transposition of the great arteries (as the patent ductus arteriosus [PDA] closes), at 2 weeks, coarctation of the aorta, and at 2 months, ventricular septal defect.

- Transposition of the great arteries is the most common cyanotic heart disease to present in the neonatal period, whereas tetralogy of Fallot will most commonly present outside the neonatal period.
- Tetralogy of Fallot is the most common congenital cyanotic heart disease to present in the pediatric population.

CHAPTER 59

Maternal Diseases Affecting the Newborn

- Maternal diabetes mellitus represents a high risk for teratogenic changes in the fetus (i.e., congenital heart disease, caudal regression).
- For the fetus, insulin is the primary growth hormone; in situations where fetal insulin levels are increased, the fetus can be overgrown (macrosomic, large for gestational age).
- Infants of diabetic mothers are at risk for birth trauma, hypoglycemia, hypocalcemia, hyperbilirubinemia (increased red cell mass), cardiac disease, and caudal regression.
- All pregnant mothers should be screened for HIV. In addition, serologies for the following should be known at the time of birth: complete blood type; immunity for rubella, syphilis, and chlamydia status; gonorrhea and group B streptococcus cultures (usually obtained at ~35 weeks' gestation); and hepatitis B titers.
- Autoimmune diseases of the mother may affect the fetus by placental transfer of IgG autoantibodies such as seen in maternal immune thrombocytopenia, SLE, hyperthyroidism, or myasthenia gravis.

CHAPTER 60

Diseases of the Fetus

- Causes of IUGR include poor maternal nutrition, maternal hypertension, fetal anomalies or infection, and twin-twin transfusion syndrome.
- The quadruple test and testing fetal DNA in the maternal circulation screen for chromosomal disorders.
- Hepatosplenomegaly, jaundice, dermatitis, chorioretinitis, and micro- or hydrocephaly in an infant with IUGR suggests an intrauterine infection.
- Organ anomalies such as congenital heart disease, oral clefts, and limb anomalies suggest a congenital malformation syndrome.
- Hydrops fetalis is often due to fetal anemia secondary to immune hemolysis or decreased red cell production.
- Nonimmune hydrops has many etiologies including infection, malignancy, autoinflammatory diseases, and complex congenital anomalies.

CHAPTER 61

Respiratory Diseases of the Newborn

- Respiratory distress may manifest by cyanosis, sternal and intercostal retractions, nasal flaring, and expiratory grunting.
- Common causes of respiratory distress include infection, respiratory distress syndrome (RDS; hyaline membrane disease), and congenital anomalies of the airway, lung, or diaphragm.
- Maternal betamethasone therapy reduces the risk of RDS in at-risk premature infants.
- A patent ductus arteriosus may present with a widened pulse pressure, worsening hypoxia and hypercarbia, and signs of heart failure with a new cardiac murmur.
- Bronchopulmonary dysplasia may develop in infants with severe ventilator treated RDS and manifests as persistent ventilator and oxygen requirements and chronic changes on chest x-ray.
- Primary pulmonary hypertension of the newborn (PPHN) often accompanies birth asphyxia, meconium aspiration syndrome, pulmonary hypoplasia, and a congenital diaphragmatic hernia.
- PPHN is managed by oxygen and ventilation therapy; if these are unsuccessful, patients may be treated with inhaled nitric oxide and then extracorporeal membrane oxygenation (ECMO).

CHAPTER 62

Anemia and Hyperbilirubinemia

- Neonatal anemia is often due to immune mediated hemolysis, red cell membrane defects, or red cell enzyme deficiencies. Rarely is it due to decrease production as seen in Blackfan-Diamond syndrome.
- Prevention of hemolytic disease of the newborn due to Rh factor incompatibility is possible by administering RhoGAM to the Rh-negative mother during gestation and within 3 days after the delivery of the Rh-positive infant.
- Fetal to maternal hemorrhage may produce fetal anemia and may be detected by the Kleihauer-Betke test.
- Physiological jaundice is an indirect hyperbilirubinemia peaking on day 3 of life in term babies; the peak may be later in premature infants.
- Breast milk jaundice is an indirect hyperbilirubinemia that occurs 1-2 weeks after birth; its cause is unknown.
- Visible jaundice in the first day of life and any direct hyperbilirubinemia are due to potentially serious pathological processes and require immediate evaluation.

CHAPTER 63

Necrotizing Enterocolitis

- Necrotizing enterocolitis (NEC) manifests with a sepsis-like presentation and with abdominal distention and tenderness.
- Abdominal x-rays in NEC demonstrate pneumatosis intestinalis, portal-hepatic gas, pneumoperitoneum, or intestinal distention.
- Significant bilious emesis is considered a neonatal emergency and deserves further evaluation with an upper gastrointestinal tract series to rule out malrotation and midgut volvulus.

CHAPTER 64

Hypoxic-Ischemic Encephalopathy, Intracranial Hemorrhage, and Seizures

- Seizures in a neonate within the first 24 hours of birth are most likely secondary to birth asphyxia or hypoxia during labor and delivery.
- Therapeutic hypothermia has been shown to reduce the risk of neurodevelopmental disability following moderate to severe in utero hypoxia or ischemia; the outcome is best if hypothermia can be started before 6 hours of age.

CHAPTER 65

Sepsis and Meningitis

- Maternal chorioamnionitis puts the fetus at the greatest risk for a poor pregnancy and delivery outcome.
- Fever in the neonatal period should be considered as caused by significant bacterial infections and herpes virus infection.
- The most common organisms causing early onset neonatal sepsis include group B streptococcus and *Escherichia coli*; a synergistic combination of ampicillin and an aminoglycoside (usually gentamicin) is appropriate initial therapy for early-onset sepsis.
- Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multi-resistant organisms. This program is of utmost importance in the NICU where the results of antibiotic resistance can be followed and treatment protocols can be modified as needed based on resistance patterns.

CHAPTER 66

Congenital Infections

- "Blueberry muffin" appearance is most commonly seen in neonates with congenital rubella or cytomegalovirus infection. A biopsy of a blueberry muffin lesion will reveal dermal hematopoiesis. The "skin" is the first organ system to produce red cells.