Length of gestation tends to be inversely related to the number of fetuses. The mean age at delivery for singletons is 38.8 weeks, for twins 35.3 weeks, for triplets 32.2 weeks, and for quadruplets 29.9 weeks. The prematurity rate in multiple gestations is 5–10 times that of singletons, with 50% of twins and 90% of triplets born before 37 weeks. There is an increased incidence of cerebral palsy in multiple births, more so with monochorial than dichorial infants. Prematurity is the main cause of increased mortality and morbidity in twins, although in the case of monochorial twins, intravascular exchange through placental anastomoses, particularly after the death of one twin, also increases the risk substantially.

C. Obstetric Complications

Polyhydramnios, pregnancy-induced hypertension, premature rupture of membranes, abnormal fetal presentations, and prolapsed umbilical cord occur more frequently in women with multiple fetuses. Multiple pregnancy should always be identified prenatally with ultrasound examinations; doing so allows the obstetrician and pediatrician or neonatologist to plan management jointly. Because neonatal complications are usually related to prematurity, prolongation of pregnancy significantly reduces neonatal morbidity.


NEONATAL INTENSIVE CARE

PERINATAL RESUSCITATION

Perinatal resuscitation refers to the steps taken by the obstetrician to support the infant during labor and delivery and the resuscitative steps taken by the pediatrician after delivery. Intrapartum support includes maintaining maternal blood pressure, maternal oxygen therapy, positioning the mother to improve placental perfusion, readjusting oxytocin infusions or administering a tocolytic if appropriate, amnioinfusion, minimizing trauma to the infant, obtaining all necessary cord blood samples, and completing an examination of the placenta. The pediatrician or neonatologist focuses on temperature support, initiation and maintenance of effective ventilation, maintenance of perfusion and hydration, and glucose regulation.

A number of conditions associated with pregnancy, labor, and delivery place the infant at risk for birth asphyxia: (1) maternal diseases such as diabetes, pregnancy-induced hypertension, heart and renal disease, and collagen-vascular disease; (2) fetal conditions such as prematurity, multiple births, growth restriction, and fetal anomalies; and (3) labor and delivery conditions, including fetal distress with or without meconium in the amniotic fluid, and administration of anesthetics and opioid analgesics.

Physiology of Birth Asphyxia

Birth asphyxia can be the result of (1) acute interruption of umbilical blood flow (eg, prolapsed cord with cord compression), (2) premature placental separation, (3) maternal hypotension or hypoxia, (4) chronic placental insufficiency, and (5) failure to perform resuscitation properly.

The neonatal response to asphyxia follows a predictable pattern (Figure 2–6). The initial response to hypoxia is an increase in respiratory rate and a rise in heart rate and blood pressure. Respirations then cease (primary apnea) as heart rate and blood pressure begin to fall. The initial period of apnea lasts 30–60 seconds. Gasping respirations (3–6 per minute) then begin, while heart rate and blood pressure gradually decline. Secondary or terminal apnea then ensues, with further decline in heart rate and blood pressure. The longer the duration of secondary apnea, the greater is the risk for organ injury. A cardinal feature of the defense against hypoxia is the underperfusion of certain tissue beds (eg, skin, muscle, kidneys, and GI tract), which allows maintenance of perfusion to core organs (ie, heart, brain, and adrenals).

Figure 2–6.
Schematic depiction of changes in rhesus monkeys during asphyxia and on resuscitation by positive-pressure ventilation. The risk for permanent brain damage increases the longer effective resuscitation is delayed. (Adapted and reproduced, with permission, from Dawes GS: *Fetal and Neonatal Physiology*. Year Book; 1968.)

Response to resuscitation also follows a predictable pattern. During the period of primary apnea, almost any physical stimulus causes the infant to initiate respirations. Infants in secondary apnea require positive pressure ventilation (PPV). The first sign of recovery is an increase in heart rate, followed by an increase in blood pressure with improved perfusion. The time required for rhythmic, spontaneous respirations to occur is related to the duration of the secondary apnea. As a rough rule, for each minute past the last gasp, 2 minutes of PPV is required before gasping begins, and 4 minutes is required to reach rhythmic breathing. Not until sometime later do spinal and corneal reflexes return. Muscle tone gradually improves over the course of several hours.

**Delivery Room Management**

When perinatal depression is anticipated, a resuscitation team of at least two persons should be present, one to manage the airway and one to monitor the heartbeat and provide assistance. The necessary equipment and drugs are listed in Table 2–15.

<table>
<thead>
<tr>
<th>Clinical Needs</th>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulation</td>
<td>Radiant heat source with platform, mattress covered with warm sterile blankets, servocontrol heating, temperature probe, gallon size food-grade plastic bag or plastic wrap and an exothermic blanket (preterm)</td>
</tr>
<tr>
<td>Airway management</td>
<td><strong>Suction</strong>: bulb suction, mechanical suction with sterile catheters (6F, 8F, 10F), meconium aspirator</td>
</tr>
<tr>
<td></td>
<td><strong>Ventilation</strong>: manual infant resuscitation bag connected to manometer or with a pressure-release valve, or T-piece resuscitator, capable of delivering 100% oxygen; appropriate masks for term and preterm infants, oral airways, stethoscope, <strong>oxygen blender, pulse oximeter</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Intubation</strong>: neonatal laryngoscope with No. 0 and No. 1 blades; endotracheal tubes (2.5, 3.0, 3.5 mm outer diameter with stylet); extra bulbs and batteries for laryngoscope; scissors, adhesive tape, gloves, end-tidal CO₂ detection device</td>
</tr>
<tr>
<td>Gastric decompression</td>
<td>Nasogastric tube: 8F with 20-mL syringe</td>
</tr>
</tbody>
</table>

Table 2–15. Equipment for neonatal resuscitation.
Clinical Needs
Sterile umbilical catheterization tray, umbilical catheters (3.5F and 5F), normal saline, drug box with appropriate neonatal vials and dilutions, sterile syringes, needles, and alcohol sponges

Equipment
Transport
Warmed transport isolette with oxygen source

*aEpinephrine 1:10,000; 10% dextrose.


A. Steps in the Resuscitative Process

(Figure 2–7)

1. Dry the infant well, and place him or her under a radiant heat source. Do not allow the infant to become hyperthermic.

2. Position the infant to open the airway. Gently suction the mouth, then the nose.

3. Quickly assess the infant's condition. The best criteria are the infant's respiratory effort (apneic, gasping or, regular) and heart rate (> 100 or < 100 beats/min). A depressed heart rate—indicative of hypoxic myocardial depression—is the single most reliable indicator of the need for resuscitation.

4. Infants who are breathing and have heart rates more than 100 beats/min usually require no further intervention other than supplemental oxygen if persistently cyanotic. Infants with heart rates less than 100 beats/min and apnea or irregular respiratory efforts should be stimulated gently. The infant's back should be rubbed and/or heels flicked.

5. If the infant fails to respond to tactile stimulation within a few seconds, begin bag and mask ventilation, using a soft mask that seals well around the mouth and nose. For the initial inflations, pressures up to 30–40 cm H₂O may be necessary to overcome surface-active forces in the lungs. Adequacy of ventilation is assessed by observing expansion of the infant's chest accompanied by an improvement in heart rate, perfusion, and color. After the first few breaths, lower the peak pressure to 15–20 cm H₂O. The chest movement should resemble that of an easy breath rather than a deep sigh. The rate of bagging should be 40–60 breaths/min. An oximeter probe should be placed on the infant's right hand.

6. Most neonates can be resuscitated effectively with a bag and mask. If the infant does not respond to bag and mask ventilation, reposition the head (slight extension), reapply the mask to achieve a good seal, consider suctioning the mouth and the oropharynx, and try ventilating with the mouth open. An increase in peak pressure should also be attempted, but if the infant does not respond within 30 seconds, intubation is appropriate.

Failure to respond to intubation and ventilation can result from (1) mechanical difficulties (Table 2–16), (2) profound asphyxia with myocardial depression, and (3) inadequate circulating blood volume.

Quickly rule out the mechanical causes listed in Table 2–16. Check to ensure that the endotracheal tube passes through the vocal cords. A CO₂ detector placed between the endotracheal tube and the bag can be helpful as a rapid confirmation of proper tube position in the airway. Occlusion of the tube should be suspected when there is resistance to bagging and no chest wall movement. Very few neonates (approximately 0.1%) require either cardiac compressions or drugs during resuscitation. Almost all newborns respond to ventilation if done effectively. All resuscitations in term infants should begin using room air. Oxygen concentration can be increased using an oxygen blender during positive pressure ventilation to achieve oxygen saturation targets (Figure 2–7). It is not expected for the preductal (right hand) oxygen saturation to reach 90% until 10 minutes of age. The use of 100% oxygen may increase the risk of postresuscitative oxidative injury without any improvement in efficacy.

7. If mechanical causes are ruled out and the heart rate remains less than 60 beats/min after intubation and effective PPV for 30 seconds, cardiac compressions should be initiated. Chest compressions should be synchronized with ventilation at a 3:1 ratio (90 compressions and 30 breaths/min).

8. If drugs are needed, the drug and dose of choice is epinephrine 1:10,000 solution (0.1–0.3 mL/kg) given via an umbilical venous line. If volume loss is suspected, 10 mL/kg of normal saline should be administered through an umbilical vein line.
Table 2–16. Mechanical causes of failed resuscitation.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment failure</td>
<td>Malfunctioning bag, oxygen not connected or running</td>
</tr>
<tr>
<td>Endotracheal tube malposition</td>
<td>Esophagus, right main stem bronchus</td>
</tr>
<tr>
<td>Occluded endotracheal tube</td>
<td></td>
</tr>
<tr>
<td>Insufficient inflation pressure to expand lungs</td>
<td></td>
</tr>
<tr>
<td>Space-occupying lesions in the thorax</td>
<td>Pneumothorax, pleural effusions, diaphragmatic hernia</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td>Extreme prematurity, oligohydramnios</td>
</tr>
</tbody>
</table>


Figure 2–7.


**B. Continued Resuscitative Measures**

The appropriateness of continued resuscitative efforts should be reevaluated in infants who do not respond to initial measures. In current practice, resuscitative efforts are made even in apparent stillbirths (ie, infants whose Apgar score at 1 minute is 0–1). Modern resuscitative techniques have led to improved survival in such infants, with 60% of survivors...
showing normal development. Although it is clear that resuscitation of these infants should be performed, subsequent continued support depends on the response to resuscitation. If the Apgar score does not improve markedly in the first 10 minutes of life, the mortality rate and the incidence of severe developmental handicaps among survivors are high.

C. Special Considerations

1. Preterm infants

A. Minimizing heat loss improves survival. Prewarmed towels should be available. The environmental temperature of the delivery suite should be raised to more than 25°C (especially for infants weighing < 1500 g). An occlusive plastic skin cover with an opening to slip over the infant's head and an exothermic blanket should be used to minimize heat loss in the extremely low-birth-weight (< 1000 g) infant.

B. The lungs of preterm infants are especially prone to injury from PPV due to volutrauma. For this reason, if possible, the infant's respiratory efforts should be supported with continuous positive airway pressure (CPAP) rather than PPV. If PPV is needed, a T-piece resuscitation device should be used to allow precise and consistent regulation of pressure delivery. Resuscitation in the preterm should begin with a blended oxygen concentration of 30%–40% with titration to achieve target oxygen saturations (Figure 2–7).

C. In the infant of extremely low gestational age (< 27 weeks), immediate intubation for administration of surfactant can be considered.

D. Volume expanders should be infused slowly to minimize rapid swings in blood pressure.

2. Narcotic depression

In the case of opioid administration to the mother within 4 hours of delivery, institute resuscitation as described earlier. When the baby is stable with good heart rate, color, and perfusion, but still has poor respiratory effort, a trial of naloxone (0.1 mg/kg IV or IM) may be indicated. Naloxone should not be administered in place of PPV. Naloxone should not be used in the infant of an opioid-addicted mother because it will precipitate withdrawal. Respiratory depression may recur over the next hours, requiring redosing of the antagonist.

3. Meconium-stained amniotic fluid

A. The obstetrician performs routine suctioning of the mouth and nose after birth.

B. If the infant is active and breathing, requiring no resuscitation, the airway need not be inspected—only further suctioning of the mouth and nasopharynx as required.

C. The airway of any depressed infant requiring ventilation must be checked and cleared (by passage of a tube below the vocal cords) before PPV is instituted. Special adapters are available for use with regulated wall suction to allow suction to be applied directly to the endotracheal tube.

D. Because most severe cases of meconium aspiration syndrome with pulmonary hypertension likely have their origin in utero, resuscitative efforts should not be excessively delayed with attempts to clear the airway of meconium.

4. Universal precautions

In the delivery suite, universal precautions should always be observed.

Treatment of the Asphyxiated Infant

Asphyxia is manifested by multiorgan dysfunction, seizures, neonatal encephalopathy, and metabolic acidemia. The infant with significant perinatal hypoxia and ischemia is at risk for dysfunction of multiple end organs (Table 2–17). The organ of greatest concern is the brain.

Table 2–17. Signs and symptoms caused by asphyxia.
Neonatal encephalopathy, seizures
Respiratory distress due to aspiration or secondary surfactant deficiency, pulmonary hemorrhage
Persistent pulmonary hypertension
Hypotension due to myocardial dysfunction
Transient tricuspid valve insufficiency
Anuria or oliguria due to acute tubular necrosis
Feeding intolerance; necrotizing enterocolitis
Elevated aminotransferases due to liver injury
Adrenal insufficiency due to hemorrhage
Disseminated intravascular coagulation
Hypocalcemia
Hypoglycemia
Persistent metabolic acidemia
Hyperkalemia

The features of neonatal encephalopathy are decreased level of consciousness, poor tone, decreased spontaneous movement, periodic breathing or apnea, and seizures. Brainstem signs (oculomotor and pupillary disturbances, absent gag reflex) may also be present. The severity and duration of clinical signs correlate with the severity of the insult. Other evaluations helpful in assessing the severity in the full-term infant include a full lead or amplitude integrated single lead electroencephalogram (EEG) and MRI. A markedly abnormal EEG with voltage suppression and slowing evolving into a burst-suppression pattern is associated with severe clinical symptoms. MRI may show perfusion defects and areas of ischemic injury on diffusion weighted imaging.

Management is directed at supportive care and treatment of specific abnormalities. Fluids should be restricted initially to 60–80 mL/kg/d; oxygenation should be maintained with mechanical ventilation if necessary; blood pressure should be supported with judicious volume expansion (if hypovolemic) and pressors; and serum glucose concentrations should be maintained in the normal range of 45–100 mg/dL. Hypocalcemia, coagulation abnormalities, and metabolic acidemia should be corrected and seizures treated with IV phenobarbital (20 mg/kg as loading dose, with total initial 24-hour dosing up to 40 mg/kg). Other anticonvulsants should be reserved for refractory seizures. Hypothermia, either selective head cooling with mild systemic hypothermia or whole body cooling, initiated within 6 hours of birth in infants 36 weeks gestation or greater, has been shown to improve outcome at 18-month and 6- to 8-year follow-up of infants with moderate to severe neurologic symptoms and an abnormal amplitude-integrated EEG.

Birth Asphyxia: Long-Term Outcome

Fetal heart rate tracings, cord pH, and 1-minute Apgar scores are imprecise predictors of long-term outcome. Apgar scores of 0–3 at 5 minutes in full-term infants are associated with an increased risk of death in the first year of life and an 8% risk of cerebral palsy among survivors. The risks of mortality and morbidity increase with more prolonged depression of the Apgar score. The single best predictor of outcome is the severity of clinical neonatal encephalopathy (severe symptomatology including coma carries a 75% chance of death and a 100% rate of neurologic sequelae among survivors). The major sequela of neonatal encephalopathy is cerebral palsy with or without mental retardation and epilepsy. Other prognostic features are prolonged seizures refractory to therapy, markedly abnormal EEG, and MRI scan with evidence of major ischemic injury. Other clinical features required to support perinatal hypoxia as the cause of cerebral palsy include the presence of fetal distress prior to birth, a low arterial cord pH of less than 7.00, evidence of other end-organ dysfunction, and absence of a congenital brain malformation.


THE PRETERM INFANT

Premature infants comprise the majority of high-risk newborns. The preterm infant faces a variety of physiologic handicaps:

1. The ability to coordinate sucking, swallowing, and breathing is not achieved until 34–36 weeks' gestation. Therefore, enteral feedings must be provided by gavage. Further, preterm infants often have an immature gag reflex, which increases the risk of aspiration of feedings.

2. Lack of body fat stores causes decreased ability to maintain body temperature, and may predispose to hypoglycemia.

3. Pulmonary immaturity–surfactant deficiency is associated with structural immaturity in infants younger than 26 weeks' gestation. This condition is exacerbated by the combination of noncompliant lungs and an extremely compliant chest wall, causing inefficient respiratory mechanics.

4. Immature respiratory control leads to apnea and bradycardia.

5. Persistent patency of the ductus arteriosus compromises pulmonary gas exchange because of overperfusion and edema of the lungs.

6. Immature cerebral vasculature and structure predisposes to subependymal and intraventricular hemorrhage, and periventricular leukomalacia.

7. Impaired substrate absorption by the GI tract compromises nutritional management.

8. Immature renal function (including both filtration and tubular functions) complicates fluid and electrolyte management.

9. Increased susceptibility to infection.

10. Immaturity of metabolic processes predisposes to hypoglycemia and hypocalcemia.
1. Delivery Room Care

See section on Perinatal Resuscitation, earlier.

2. Care in the Nursery

A. Thermoregulation

Maintaining stable body temperature is a function of heat production and conservation balanced against heat loss. Heat production in response to cold stress occurs through voluntary muscle activity, involuntary muscle activity (shivering), and thermogenesis not caused by shivering. Newborns produce heat mainly through the last of these three mechanisms. This metabolic heat production depends on the quantity of brown fat, which is very limited in the preterm infant. Heat loss to the environment can occur through: (1) radiation—transfer of heat from a warmer to a cooler object not in contact; (2) convection—transfer of heat to the surrounding gaseous environment, influenced by air movement and temperature; (3) conduction—transfer of heat to a cooler object in contact; and (4) evaporation—cooling secondary to water loss through the skin. Heat loss in the preterm newborn is accelerated because of a high ratio of surface area to body mass, reduced insulation by subcutaneous tissue, and water loss through the immature skin.

The thermal environment of the preterm neonate must be regulated carefully. The infant can be kept warm in an isolette, in which the air is heated and convective heat loss is minimized. The infant can also be kept warm on an open bed with a radiant heat source. Although evaporative and convective heat losses are greater with radiant warmers, this system allows better access to an ill neonate. Ideally, the infant should be kept in a neutral thermal environment (Figure 2–8). The neutral thermal environment allows the infant to maintain a stable core body temperature with a minimum of metabolic heat production through oxygen consumption. The neutral thermal environment depends on the infant’s size, gestational age, and postnatal age. The neutral thermal environment (for either isolette or radiant warmer care) can be obtained by maintaining an abdominal skin temperature of 36.5°C. Generally, when infants reach 1700–1800 g, they are able to maintain temperature while bundled in an open crib.

B. Monitoring the High-Risk Infant

At a minimum, equipment to monitor heart rate, respirations, and blood pressure should be available. Oxygen saturation is assessed continuously using pulse oximetry, correlated with arterial oxygen tension (Pao₂) as needed. Transcutaneous Po₂ and Pco₂ can also be used to assess oxygenation and ventilation in sicker infants. Arterial blood gases, electrolytes, glucose, calcium, bilirubin, and other chemistries must be measured on small volumes of blood. Early in the care of a sick preterm infant, the most efficient way to sample blood for tests as well as to provide fluids and monitor blood pressure is through an umbilical arterial line. Once the infant is stable and the need for frequent blood samples is reduced (usually 4–7 days), the
umbilical line should be removed. All indwelling lines are associated with morbidity from thrombosis or embolism, infection, and bleeding.

C. Fluid and Electrolyte Therapy

Fluid requirements in preterm infants are a function of (1) insensible losses (skin and respiratory tract), (2) urine output, (3) stool output (< 5% of total), and (4) other losses, such as nasogastric losses. In most circumstances, the fluid requirement is determined largely by insensible losses plus urine losses. The major contribution to insensible water loss is evaporative skin loss. The rate of water loss is a function of gestational age (body weight, skin thickness, and maturity), environment (losses are greater under a radiant warmer than in an isolette), and the use of phototherapy. Respiratory losses are minimal when humidified oxygen is used. The renal contribution to water requirement is influenced by the limited ability of the preterm neonate either to concentrate the urine and conserve water, or to excrete a water load.

Electrolyte requirements are minimal for the first 24–48 hours until there is significant urinary excretion. Basal requirements thereafter are as follows: sodium, 3 mEq/kg/d; potassium, 2 mEq/kg/d; chloride, 2–3 mEq/kg/d; and bicarbonate, 2–3 mEq/kg/d. In the infant younger than 30 weeks' gestation, sodium and bicarbonate losses in the urine are often elevated, thereby increasing the infant's requirements.

Initial fluid management after birth varies with the infant's size and gestation. Infants of more than 1200 g should start at 80–100 mL/kg/d of D_{10}W. Those weighing less should start at 100–120 mL/kg/d of either D_{10}W or D_{5}W (infants < 800 g and born before 26 weeks' gestation often become hyperglycemic on D_{10}W at these infusion rates). The most critical issue in fluid management is monitoring. Monitoring body weight, urine output, fluid and electrolyte intake, serum and urine electrolytes, and glucose allows fairly precise determination of the infant's water, glucose, and electrolyte needs. Parenteral nutrition should be started early, preferably on the first day, and continued until an adequate enteral intake is achieved.

D. Nutritional Support

The average caloric requirement for the growing premature infant is 120 kcal/kg/d. Desired weight gain is 15–20 g/kg/d for infants younger than 35 weeks, and 15 g/kg/d for those older than 35 weeks; linear and head circumference growth should average 1 cm/wk. Infants initially require IV glucose infusion to maintain blood glucose concentration in the range of 60–100 mg/dL. Infusions of 5–7 mg/kg/min (approximately 80–100 mL/kg/d of D_{10}W) are usually needed. Aggressive nutritional support in the very low-birth-weight infant should be started as soon as possible after birth, with parenteral alimentation solutions containing 3–4 g/kg/d of amino acids, given either peripherally or centrally via an umbilical vein line or percutaneous catheter (Table 2–18). Small-volume trophic feeds with breast milk or 20 kcal/oz premature formula should be started by gavage at 10% or less of the infant's nutritional needs (< 10 mL/kg/d) as soon as possible, generally within the first few days after birth. After several days of trophic feeds the infant can be slowly advanced to full caloric needs over 5–7 days. Even extremely small feedings can enhance intestinal readiness to accept larger feeding volumes. Intermittent bolus feedings are preferred because these appear to stimulate the release of gut-related hormones and may accelerate maturation of the GI tract, although in the extremely low-birth-weight infant (< 1000 g) or the postsurgical neonate, continuous-drip feeds are sometimes better tolerated. A more rapid advancement schedule is used for infants weighing more than 1500 g, and the slowest schedule for those weighing less than 1000 g.

Table 2–18. Use of parenteral alimentation solutions.

<table>
<thead>
<tr>
<th>Volume (mL/kg/d)</th>
<th>Carbohydrate (g/dL)</th>
<th>Protein (g/kg)</th>
<th>Lipid (g/kg)</th>
<th>Calories (kcal/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral: Short-term (7–10 d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting solution</td>
<td>100–150</td>
<td>D_{10}W</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Target solution</td>
<td>150</td>
<td>D_{12.5}W</td>
<td>3–4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Central: Long-term (&gt; 10 d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting solution</td>
<td>100–150</td>
<td>D_{10}W</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Target solution</td>
<td>130</td>
<td>D_{12.5}–D_{15}W</td>
<td>3–4</td>
<td>3</td>
</tr>
</tbody>
</table>

**Notes:**

1. Advance dextrose in central hyperalimentation as tolerated per day as needed to achieve appropriate weight gain, as long as blood glucose remains normal, keeping glucose as 40%–60% of total calories administered.

2. Advance lipids by 0.5–1.0 g/kg/d as long as triglycerides are normal. Use 20% concentration.
3. Total water should be 100–150 mL/kg/d, depending on the child's fluid needs.

**Monitoring:**

1. Blood glucose two or three times a day when changing dextrose concentration, then daily.
2. Electrolytes daily, then twice a week when the child is receiving a stable solution.
3. Every 1–2 weeks: blood urea nitrogen and serum creatinine; total protein and serum albumin; serum calcium, phosphate, magnesium, direct bilirubin, and CBC with platelet counts.
4. Triglyceride level after 24 h at 2 g/kg/d and 24 h at 3 g/kg/d, then every other week.

In general, long-term nutritional support for infants of very low birth weight consists either of breast milk supplemented to increase protein, caloric density, and mineral content, or infant formulas modified for preterm infants. In these formulas, protein concentrations (approximately 2 g/dL) and caloric concentrations (approximately 24 kcal/oz) are relatively high. In addition, premature formulas contain some medium-chain triglycerides—which do not require bile for absorption—as an energy source. Increased calcium and phosphorus are provided to enhance bone mineralization. Formulas for both full-term and premature infants are enriched with long-chain polyunsaturated fatty acids in the hope of enhancing brain and retinal development. The infant should gradually be offered feedings of higher caloric density after a substantial volume (100–120 mL/kg/d) of 20 kcal/oz breast milk or formula is tolerated. Success of feedings is assessed by timely passage of feeds out of the stomach without emesis or large residual volumes, an abdominal examination free of distention, and a normal stool pattern.

When the preterm infant approaches term, the nutritional source for the bottle-fed infant can be changed to a transitional formula (22 kcal/oz) until age 6–9 months. Additional iron supplementation (2–4 mg/kg/d) is recommended for premature infants, beginning at 2 weeks to 2 months of age, depending on gestational age and number of previous transfusions. Infants who are treated with erythropoietin (epoetin alfa) for prevention or treatment of anemia of prematurity require a higher dosage of 6 mg/kg/d. Iron overload is a possibility in multiply-transfused sick preterm infants; such infants should be evaluated with serum ferritin levels prior to beginning iron supplementation.


3. **Apnea in the Preterm Infant**

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**

- Respiratory pause of sufficient duration to result in cyanosis or bradycardia.
- Most common in infants born before 34 weeks' gestation; onset before 2 weeks of age.
- Methylxanthines (eg, caffeine) provide effective treatment.

**General Considerations**

Apnea is defined as a respiratory pause lasting more than 20 seconds—or any pause accompanied by cyanosis and bradycardia. Shorter respiratory pauses associated with cyanosis or bradycardia also qualify as significant apnea, whereas periodic breathing, which is common in full-term and preterm infants, is defined as regularly recurring ventilatory cycles interrupted by short pauses not associated with bradycardia or color change. By definition, apnea of prematurity is not associated with a predisposing factor, and is a diagnosis of exclusion. A variety of processes may precipitate apnea (Table 2–19) and should be considered before a diagnosis of apnea of prematurity is established.

Table 2–19. Causes of apnea in the preterm infant.

http://accesspediatrics.mhmedical.com/content.aspx?bookid=1016&sectioni...
• Temperature instability—both cold and heat stress
• Response to passage of a feeding tube
• Gastroesophageal reflux
• Hypoxemia
  ◦ Pulmonary parenchymal disease
  ◦ Patent ductus arteriosus
  ◦ Anemia
• Infection
  ◦ Sepsis (viral or bacterial)
  ◦ Necrotizing enterocolitis
• Metabolic causes
  ◦ Hypoglycemia
• Intracranial hemorrhage
• Posthemorrhagic hydrocephalus
• Seizures
• Drugs (eg, morphine)
• Apnea of prematurity

Apnea of prematurity is the most frequent cause of apnea. Most apnea of prematurity is mixed apnea characterized by a centrally (brainstem) mediated respiratory pause preceded or followed by airway obstruction. Less common is pure central or pure obstructive apnea. Apnea of prematurity is the result of immaturity of both the central respiratory regulatory centers and protective mechanisms that aid in maintaining airway patency.

Clinical Findings

Onset is typically during the first 2 weeks of life. The frequency of spells gradually increases with time. Pathologic apnea should be suspected if spells are sudden in onset, unusually frequent, or very severe. Apnea at birth or on the first day of life is unusual but can occur in the nonventilated preterm infant. In the full-term or late preterm infant, presentation at birth suggests neuromuscular abnormalities of an acute (asphyxia, birth trauma, or infection) or chronic (eg, congenital hypotonia or structural CNS lesion) nature.

All infants—regardless of the severity and frequency of apnea—require a minimum screening evaluation, including a general assessment of well-being (eg, tolerance of feedings, stable temperature, normal physical examination), a check of the association of spells with feeding, measurement of PaO₂ or SaO₂, blood glucose, hematocrit, and a review of the drug history. Infants with severe apnea of sudden onset require more extensive evaluation for primary causes, especially infection. Other specific tests are dictated by relevant signs, for example, evaluation for necrotizing enterocolitis (NEC) in an infant with apnea and abdominal distention or feeding intolerance.

Treatment

Any underlying cause should be treated. If the apnea is due simply to prematurity, symptomatic treatment is dictated by the frequency and severity of apneic spells. Spells frequent enough to interfere with other aspects of care (eg, feeding), or severe enough to cause cyanosis or bradycardia necessitating significant intervention or bag and mask ventilation require treatment. Caffeine citrate (20 mg/kg as loading dose and then 5–10 mg/kg/d) is the drug of choice. Side effects of caffeine are generally mild, and include tachycardia and occasional feeding intolerance. The dose used should be the smallest dose...
necessary to decrease the frequency of apnea and eliminate severe spells. Target drug level, if monitored, is usually 10–20 mcg/mL. Nasal continuous positive airway pressure (CPAP) or high flow nasal cannula, by treating the obstructive component of apnea, is effective in some infants. Intubation and ventilation can eliminate apneic spells but carry the risks associated with mechanical ventilation. Although many preterm infants are treated medically for possible reflux-associated apnea, there is little evidence to support this intervention. If suspected, a trial of continuous drip gastric or transpyloric feedings can be helpful as a diagnostic and therapeutic intervention.

Prognosis

In most premature infants, apneic and bradycardiac spells cease by 34–36 weeks postmenstrual age. Spells that require intervention cease prior to self-resolving episodes. In infants born at less than 28 weeks' gestation, episodes may continue past term. Apneic and bradycardiac episodes in the nursery are not predictors of later SIDS, although the incidence of SIDS is slightly increased in preterm infants. Thus, home monitoring in infants who experienced apnea in the nursery is rarely indicated.

4. Hyaline Membrane Disease

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Tachypnea, cyanosis, and expiratory grunting.
- Poor air movement despite increased work of breathing.
- Chest radiograph showing hypoexpansion and air bronchograms.

General Considerations

The most common cause of respiratory distress in the preterm infant is hyaline membrane disease. The incidence increases from 5% of infants born at 35–36 weeks' gestation to more than 50% of infants born at 26–28 weeks' gestation. This condition is caused by a deficiency of surfactant production as well as surfactant inactivation by protein leak into airspaces. Surfactant decreases surface tension in the alveolus, allowing the alveolus to remain partly expanded and maintain a functional residual capacity during expiration. The absence or inactivation of surfactant results in poor lung compliance and atelectasis. The infant must expend a great deal of effort to expand the lungs with each breath, and respiratory failure ensues (Figure 2–9).


Clinical Findings

Infants with hyaline membrane disease show all the clinical signs of respiratory distress. On auscultation, air movement is diminished despite vigorous respiratory effort. The chest radiograph demonstrates diffuse bilateral atelectasis, causing a ground-glass appearance. Major airways are highlighted by the atelectatic air sacs, creating air bronchograms. In the unintubated child, doming of the diaphragm and hypoinflation occur.
Treatment

Supplemental oxygen, nasal CPAP, early intubation for surfactant administration and ventilation, and close physiologic monitoring (eg, placement of umbilical artery and vein lines) are the initial interventions required. A ventilator that can deliver breaths synchronized with the infant's respiratory efforts (synchronized intermittent mandatory ventilation) and accurately deliver a preset tidal volume (5–6 mL/kg) should be used. Alternatively, pressure limited ventilation with measurement of exhaled tidal volumes can be used. High-frequency ventilators are available for rescue of infants doing poorly on conventional ventilation or who have air leak problems.

Surfactant replacement is used both in the delivery room as prophylaxis for infants born before 27 weeks' gestation and with established hyaline membrane disease as rescue, preferably within 2–4 hours of birth. Surfactant therapy decreases both the mortality rate in preterm infants and air leak complications of the disease. During the acute course, ventilator settings and oxygen requirements are significantly lower in surfactant-treated infants than in controls. The dose of the bovine-derived beractant (Survanta) is 4 mL/kg, the calf lung surfactant extract (Infasurf) is 3 mL/kg, and the porcine-derived poractant (Curosurf) is 1.25–2.5 mL/kg, given intratracheally. Repeat dosing is indicated in infants who remain on the ventilator in more than 30%–40% oxygen. A total of two to three doses given 8–12 hours apart may be administered. Endogenous surfactant production begins within 48 hours after delivery in most infants. As the disease evolves, proteins that inhibit surfactant function leak into the air spaces, making surfactant replacement less effective. In stable infants, a trial of nasal CPAP at 5–6 cm H₂O pressure can be attempted prior to intubation and surfactant administration. For those who require mechanical ventilation, extubation to nasal CPAP should be done as early as possible to minimize lung injury and evolution of chronic lung disease. Nasal intermittent positive pressure ventilation (NIPPV) is another modality that may be attempted for ventilatory support of the VLBW infant, with potential for less morbidity. Antenatal administration of corticosteroids to the mother is an important strategy to accelerate lung maturation. Infants whose mothers were given corticosteroids more than 24 hours prior to preterm birth are less likely to have respiratory distress syndrome and have a lower mortality rate.

5. Chronic Lung Disease in the Premature Infant

General Considerations

Chronic lung disease, defined as respiratory symptoms, oxygen requirement, and chest radiograph abnormalities at 36 weeks postconception, occurs in about 20% of preterm infants ventilated for surfactant deficiency. The incidence is higher at lower gestational ages and in infants exposed to chorioamnionitis prior to birth. The development of chronic lung disease is a function of lung immaturity at birth, inflammation, and exposure to high oxygen concentrations and ventilator volutrauma. Surfactant-replacement therapy or early nasal CPAP has diminished the severity of chronic lung disease. The mortality rate from chronic lung disease is very low, but there is still significant morbidity secondary to reactive airway symptoms and hospital readmissions during the first 2 years of life for intercurrent respiratory infection.

Treatment

Long-term supplemental oxygen, mechanical ventilation, and nasal CPAP are the primary therapies for chronic lung disease of the premature. Diuretics (furosemide, 1–2 mg/kg/d, or hydrochlorothiazide-spiroanolactone, 1–2 mg/kg/d), inhaled β₂-adrenergics, inhaled corticosteroids (fluticasone or budesonide), and systemic corticosteroids (dexamethasone [0.2 mg/kg/d], prednisone [1–2 mg/kg/d]) or hydrocortisone [4–5 mg/kg/d]) are used as adjunctive therapy. The use of systemic corticosteroids remains controversial. Although a decrease in lung inflammation can aid infants in weaning from ventilator support, there are data associating dexamethasone use in the first week of life with an increased incidence of cerebral palsy. This risk must be balanced against the higher risk of neurodevelopmental handicap in infants with severe chronic lung disease. There is likely a point in the course of these infants at which the benefit of using systemic corticosteroids for the shortest amount of time at the lowest dose possible outweighs the risk of continued mechanical ventilation. After hospital discharge, some of these infants will require oxygen at home. This can be monitored by pulse oximetry with a target Sao₂ of 94%–96%. Some will continue to manifest pulmonary symptomatology into adolescence.

6. Patent Ductus Arteriosus

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Hyperdynamic precordium.
- Widened pulse pressure.
- Hypotension.
- Presence of a systolic heart murmur in many cases.

General Considerations

Clinically significant patent ductus arteriosus usually presents on days 3–7 as the respiratory distress from hyaline membrane disease is improving. Presentation can be on days 1 or 2, especially in infants born before 28 weeks' gestation and in those who have received surfactant-replacement therapy. The signs include a hyperdynamic precordium, increased peripheral pulses, and a widened pulse pressure with or without a systolic machinery type heart murmur. Early presentations are sometimes manifested by systemic hypotension without a murmur or hyperdynamic circulation. These signs are often accompanied by an increased need for respiratory support and metabolic acidemia. The presence of patent ductus arteriosus is confirmed by echocardiography.

Treatment

Treatment of patent ductus arteriosus is by medical or surgical ligation. A clinically significant ductus can be closed with indomethacin (0.2 mg/kg IV q12h for three doses) in about two-thirds of cases. If the ductus reopens or fails to close completely, a second course of drug may be used or surgical ligation can be considered if the infant remains symptomatic. In addition, in the extremely low-birth-weight infant (< 1000 g) who is at very high risk of developing a symptomatic ductus, a prophylactic strategy of indomethacin (0.1 mg/kg q24h for 3–5 days) beginning on the first day of life may be used, with the possible additional benefit of decreasing the incidence of severe IVH, although there is no evidence of an effect on mortality or neurodevelopment. The most common side effect of indomethacin is transient oliguria, which can be managed by fluid restriction until urine output improves. Indomethacin should not be used if the infant is hyperkalemic, if the creatinine is higher than 2 mg/dL, or if the platelet count is less than 50,000/mL. There is an increased incidence of intestinal perforation if indomethacin is used concomitantly with hydrocortisone in extremely low-birth-weight infants (9% vs 2% for either drug alone). Ibuprofen lysine can be used as an alternative to indomethacin given every 24 hours as an initial dose of 10 mg/kg and then 5 mg/kg for two doses. Oliguria is less severe and less frequent than with indomethacin.

7. Necrotizing Enterocolitis

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Feeding intolerance with gastric residuals or vomiting.
- Bloody stools.
- Abdominal distention and tenderness.
- Pneumatosis intestinalis on abdominal radiograph.

General Considerations

NEC is the most common acquired GI emergency in the newborn. It is most common in preterm infants, with an incidence of 6% in infants less than 1500 g. In full-term infants, it occurs in association with polycythemia, congenital heart disease, and birth asphyxia. The pathogenesis of NEC is multifactorial. Ischemia, immaturity, microbial dysbiosis (proliferation of pathogenic bacteria with less colonization with beneficial or commensal bacteria), and genetics are all thought to play a role. In up to 20% of affected infants, the only risk factor is prematurity. IUGR infants with a history of absent or reversed end-diastolic flow in the umbilical artery prior to delivery have abnormalities of splanchnic flow after delivery and have an increased risk of NEC.

Clinical Findings

The most common presenting sign is abdominal distention. Other signs are vomiting, increased gastric residuals, hemopositive stools, abdominal tenderness, temperature instability, increased apnea and bradycardia, decreased urine output, and poor perfusion. There may be an increased white blood cell count with an increased band count or, as the disease progresses, absolute neutropenia. Thrombocytopenia often occurs along with stress-induced hyperglycemia and metabolic acidosis. Diagnosis is confirmed by the presence of pneumatosis intestinalis (air in the bowel wall) or biliary tract air on a plain abdominal radiograph. There is a spectrum of disease, and milder cases may exhibit only distention of bowel loops with bowel wall edema.

Treatment

A. Medical Treatment

NEC is managed by making the infant NPO, nasogastric decompression of the gut, maintenance of oxygenation, mechanical ventilation if necessary, and IV fluids to replace third-space GI losses. Enough fluid should be given to restore good urine output. Other measures include broad-spectrum antibiotics (usually ampicillin, a third-generation cephalosporin or an aminoglycoside, and possibly additional anaerobic coverage), close monitoring of vital signs, and serial physical examinations and laboratory studies (blood gases, white blood cell count, platelet count, and radiographs). Although there are no proven strategies to prevent NEC, use of trophic feedings, breast milk, and cautious advancement of feeds, as well as probiotic agents, may provide some protection, even though the optimal formulation and dose of probiotics for prevention are as yet unknown.

B. Surgical Treatment

Indications for surgery are evidence of perforation (free air present on a left lateral decubitus or cross-table lateral film), a fixed dilated loop of bowel on serial radiographs, abdominal wall cellulitis, or deterioration despite maximal medical support. All of these signs are indicative of necrotic bowel. In the operating room, necrotic bowel is removed and ostomies are created, although occasionally a primary end-to-end anastomosis may be performed. In extremely low-birth-weight infants, the initial surgical management may simply be the placement of peritoneal drains. Reanastomosis in infants with ostomies is performed after the disease resolves and the infant is bigger (usually > 2 kg and after 4–6 weeks).
**Course & Prognosis**

Infants treated medically or surgically should not be refed until the disease is resolved (normal abdominal examination and resolution of pneumatosis), usually after 7–10 days. Nutritional support during this time should be provided by total parenteral nutrition.

Death occurs in 10% of cases. Surgery is needed in fewer than 25% of cases. Long-term prognosis is determined by the amount of intestine lost. Infants with short bowel require long-term support with IV nutrition (see Chapter 21). Late strictures—about 3–6 weeks after initial diagnosis—occur in 8% of patients whether treated medically or surgically, and generally require operative management. Infants with surgically managed NEC have an increased risk of poor neurodevelopmental outcome.


**8. Anemia in the Premature Infant**

**General Considerations**

In the premature infant, the hemoglobin concentration reaches its nadir at about 8–12 weeks and is 2–3 g/dL lower than that of the full-term infant. The lower nadir in premature infants appears to be the result of decreased erythropoietin response to the low red cell mass. Symptoms of anemia include poor feeding, lethargy, increased heart rate, poor weight gain, and perhaps periodic breathing.

**Treatment**

Transfusion is not indicated in an asymptomatic infant simply because of a low hematocrit. Most infants become symptomatic if the hematocrit drops below 20%. Infants on ventilators and supplemental oxygen are usually maintained with hematocrits above 25%–30%. Alternatively, infants can be treated with erythropoietin (350 U/kg/d for 7–10 days for hematocrits < 28%). The therapeutic goal is to minimize blood draws and use conservative guidelines for transfusion. Delayed cord clamping 1–2 minutes after birth, if possible, can significantly decrease the need for future transfusion. Early use of erythropoietin may increase the rate and severity of retinopathy of prematurity and should be used judiciously.


**9. Intraventricular Hemorrhage**

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**
• Large bleeds cause hypotension, metabolic acidosis, and altered neurologic status; smaller bleeds can be asymptomatic.

• Routine cranial ultrasound scanning is essential for diagnosis in infants born before 32 weeks' gestation.

General Considerations

Periventricular–intraventricular hemorrhage occurs almost exclusively in premature infants. The incidence is 15%–25% in infants born before 31 weeks' gestation and weighing less than 1500 g. The highest incidence occurs in infants of the lowest gestational age (< 26 weeks). Bleeding most commonly occurs in the subependymal germinal matrix (a region of undifferentiated cells adjacent to or lining the lateral ventricles). Bleeding can extend into the ventricular cavity. The proposed pathogenesis of bleeding is presented in Figure 2–10. The critical event is ischemia with reperfusion injury to the capillaries in the germinal matrix in the immediate perinatal period. The actual amount of bleeding is influenced by a variety of factors that affect the pressure gradient across the injured capillary wall, such as venous congestion or increased arterial inflow. This pathogenetic scheme applies also to intraparenchymal bleeding (venous infarction in a region rendered ischemic) and to periventricular leukomalacia (ischemic white matter injury in a watershed region of arterial supply). CNS complications in preterm infants are more frequent in infants exposed to intrauterine and postnatal infection, implying also the involvement of inflammatory mediators in the pathogenesis of brain injury.

Figure 2–10.

Pathogenesis of periventricular and intraventricular hemorrhage.

Clinical Findings

Up to 50% of hemorrhages occur before 24 hours of age, and virtually all occur by the fourth day. The clinical syndrome ranges from rapid deterioration (coma, hypoventilation, decerebrate posturing, fixed pupils, bulging anterior fontanelle, hypotension, acidosis, or acute drop in hematocrit) to a more gradual deterioration with more subtle neurologic changes. In some cases, infants manifest no physiologic or neurologic signs.

The diagnosis can be confirmed by ultrasound scan. Routine scanning should be done at 7–10 days in all infants born before 29 weeks' gestation. Hemorrhages are graded as follows: grade I, germinal matrix hemorrhage only; grade II, intraventricular bleeding without ventricular enlargement; grade III, intraventricular bleeding with ventricular enlargement; or grade IV, any intraparenchymal bleeding. The amount of bleeding is minor (grade I or II) in the majority of infants who bleed. Follow-up ultrasound examinations are scheduled based on the results of the initial scan. Infants with no bleeding or germinal matrix hemorrhage require only a single follow-up scan at age 4–6 weeks to look for periventricular leukomalacia (PVL). An infant with blood in the ventricular system is at risk for posthemorrhagic ventriculomegaly. This is usually the result of impaired absorption of cerebrospinal fluid (CSF) but can also occur secondary to obstructive phenomena. An initial follow-up scan should be done 1–2 weeks after the initial scan. Infants with intraventricular bleeding and ventricular
enlargement should be followed every 7–10 days until ventricular enlargement stabilizes or decreases. Infants born at 29–32 weeks' gestational age need only a single late scan done at 4–6 weeks of age to look for PVL or ventriculomegaly.

**Treatment**

During acute hemorrhage, supportive treatment (restoration of volume and hematocrit, oxygenation, and ventilation) should be provided to avoid further cerebral ischemia. Progressive posthemorrhagic hydrocephalus is treated initially with a subgaleal shunt. When the infant is large enough, this can be converted to a ventriculoperitoneal shunt.

Although the incidence and severity of intracranial bleeding in premature infants have decreased, strategies to prevent this complication are still needed. Maternal antenatal corticosteroids appear to decrease the risk of intracranial bleeding, and phenobarbital may have a role in the mother who has not been prepared with steroids and is delivering before 28 weeks' gestation. Magnesium sulfate administered to the mother appears to reduce the rate of cerebral palsy, although not the rate of IVH per se.

**Prognosis**

No deaths occur as a result of grade I and grade II hemorrhages. Grade III and grade IV hemorrhages carry a mortality rate of 10%–20%. Posthemorrhagic ventricular enlargement is rarely seen with grade I hemorrhages but is seen in 54%–87% of grade II–IV hemorrhages. Very few of these infants will require a ventriculoperitoneal shunt. Long-term neurologic sequelae are seen slightly more frequently in infants with grade I and grade II hemorrhages than in preterm infants without bleeding. In infants with grade III and grade IV hemorrhages, severe sequelae occur in 20%–25% of cases, mild sequelae in 35% of cases, but no sequelae in 40% of cases. Severe periventricular leukomalacia, large parenchymal bleeds, especially if bilateral, and progressive hydrocephalus increase the risk of neurologic sequelae. It is important to note that extremely low-birth-weight infants without major ultrasound findings also remain at increased risk for both cerebral palsy and cognitive delays. Recent reports using quantitative MRI scans demonstrate that subtle gray and white matter findings not seen with ultrasound are prevalent in preterm survivors and are predictive of neurodevelopmental handicap. This is especially true in infants born weighing less than 1000 g and before 28 weeks' gestation.


**10. Retinopathy of Prematurity**

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**

- Risk of severe retinopathy is greatest in the most immature infants.
- Diagnosis depends on screening eye examinations in at-risk preterm infants.
- Examination evaluates stage of abnormal retinal vascular development, extent of retinal detachment, and distribution and amount of retina involved.

Retinopathy of prematurity occurs only in the incompletely vascularized premature retina. The incidence of retinopathy in infants weighing less than 1250 g is 66%, but only 6% have retinopathy severe enough to warrant intervention. The incidence is highest in infants of the lowest gestational age. The condition appears to be triggered by an initial injury to the developing retinal vessels and low levels of insulin-like growth factor-1. After the initial injury, normal vessel development may follow or abnormal vascularization may occur due to excessive vascular endothelial growth factor (VEGF), with ridge formation on the retina. Lability in oxygen levels with periods of hypoxia/hyperoxia likely potentiate this progression. The
frequency of retinopathy progressing to the need for treatment can be diminished by careful monitoring of the infant's
oxygen saturation levels. The process can regress at this point or may continue, with growth of fibrovascular tissue into the
vitreous associated with inflammation, scarring, and retinal folds or detachment. The disease is graded by stages of
abnormal vascular development and retinal detachment (I–V), by the zone of the eye involved (1–3, with zone 1 being the
posterior region around the macula), and by the amount of the retina involved, in "clock hours" (eg, a detachment in the
upper, outer quadrant of the left eye would be defined as affecting the left retina from 12 to 3 o'clock).

Initial eye examination should be performed at 31 weeks postmenstrual age or at 4 weeks of age, whichever is earlier, in
infants born at 30 weeks' gestation or 1500 g or less, as well as in infants up to 32 weeks' gestation with an unstable clinical
course. Follow-up occurs at 1- to 3-week intervals, depending on the findings, until the retina is fully vascularized. Laser
therapy is used in infants with progressive disease at risk for retinal detachment. Although this treatment does not always
prevent retinal detachment, it reduces the incidence of poor outcomes based on visual acuity and retinal anatomy. A new
investigational form of therapy is intravitreal bevacizumab, an anti-VEGF monoclonal antibody, which may prove to be
superior to laser therapy for severe Zone I retinopathy of prematurity.

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11. Discharge & Follow-Up of the Premature Infant

A. Hospital Discharge

Criteria for discharge of the premature infant include maintaining normal temperature in an open crib, adequate oral intake,
acceptable weight gain, and absence of apnea and bradycardia spells requiring intervention. Infants going home on
supplemental oxygen should not desaturate below 80% in room air or should demonstrate the ability to arouse in response to
hypoxia. Factors such as support for the mother at home and the stability of the family situation play a role in the timing of
discharge. Home nursing visits and early physician follow-up can be used to hasten discharge. Additionally, the American
Academy of Pediatrics recommends that preterm infants have a period of observation in an infant car seat, preferably their
own, before hospital discharge, with careful positioning to mimic optimal restraint as would occur in the car, to see that they
do not have obstructive apnea or desaturation for periods up to 90–120 minutes.

B. Follow-Up

With advances in obstetric and maternal care, survival of infants born after 28 weeks' gestation or weighing as little as 1000
g at birth is now better than 90%. Mortality increases at lower birth weights and gestational ages (Figure 2–11).

Figure 2-11.

**Mortality rates before discharge by 100-g birth weight subgroups in 2007.** (Reproduced, with permission, from the
Vermont Oxford Network, 2008.)
These high rates of survival come with some morbidity. Major neurologic sequelae, including cerebral palsy, cognitive delay, and hydrocephalus, occur in 10%–25% of survivors of birth weight less than 1500 g. The rate of these sequelae tends to be higher in infants with lower birth weights. Infants with birth weights less than 1000 g also have an increased rate of lesser disabilities, including learning, behavioral, and psychiatric problems. Risk factors for neurologic sequelae include seizures, grade III or IV intracranial hemorrhage, periventricular leukomalacia, ventricular dilation, white matter abnormalities on term-equivalent MRI examinations, severe IUGR, poor early head growth, need for mechanical ventilation, chronic lung disease, bacterial and candidal sepsis, NEC, and low socioeconomic class. Maternal fever and chorioamnionitis are associated with an increased risk of cerebral palsy. Other morbidities include chronic lung disease and reactive airway disease, resulting in increased severity of respiratory infections and hospital readmissions in the first 2 years; retinopathy of prematurity with associated loss of visual acuity and strabismus; hearing loss; and growth failure. All of these issues require close multidisciplinary outpatient follow-up. Infants with residual lung disease are candidates for monthly palivizumab (Synagis) injections during their first winter after hospital discharge to prevent infection with respiratory syncytial virus. Routine immunizations should be given at the appropriate chronologic age and should not be age-corrected for prematurity.

THE LATE PRETERM INFANT

The rate of preterm births in the United States has increased by more than 30% in the past 30 years, so that preterm infants now comprise 12.8% of all births. Late preterm births, those from 34 0/7 to 36 6/7 weeks' gestation (Figure 2–12), have increased the most, and now account for over 70% of all preterm births. While births less than 34 weeks' gestation have increased by 10% since 1990, late preterm births have increased by 25%. This is in part due to changes in obstetric practice with an increase in inductions of labor (up from 9.5% in 1990 to 22.5% today), and an increase in cesarean sections (currently more than 30% of all births), as well as a rise in multiple births. While many late preterm births are unavoidable and/or medically indicated, perhaps 1 in 5 late preterm births could be prevented by implementing well-conceived delivery guidelines that would be safe for both the mother and her fetus.

Figure 2–12.


Compared with term infants, late preterm infants have higher prevalence of acute neonatal problems including respiratory distress, temperature instability, hypoglycemia, kernicterus, apnea, seizures, feeding problems, and rehospitalization after hospital discharge. The respiratory issues are caused by delayed clearance of lung fluid or surfactant deficiency, or both, and can progress to respiratory failure requiring mechanical ventilation and even ECMO support. Feeding issues are caused by immature coordination of suck and swallow, which can interfere with bottle feeding and cause failure to establish successful breast feeding, putting the infant at risk for excessive weight loss and dehydration. These infants are nearly five times as likely as full-term infants to require either supplemental IV fluids, or gavage feedings. Related both to feeding issues and immaturity, late preterm infants have at least four times the risk of developing a bilirubin level above 20 mg/dL when compared with infants born after 40 completed weeks. As a consequence, late preterm gestation is a major risk factor for excessive hyperbilirubinemia and kernicterus. Rehospitalizations due to jaundice, proven or suspected infection, feeding difficulties, and failure to thrive are much more common than in term infants. Long-term development may also be adversely affected, with some large population-based studies showing a higher incidence of cerebral palsy, developmental delay, and behavioral and emotional disturbances compared with term infants.

Late preterm infants, even if similar in size to their term counterparts, should be considered preterm rather than near term, and require close in-hospital monitoring after birth for complications. Although they may feed reasonably well for the first day or two, they often fail to increase feeding volume and become more sleepy and less interested in feeding as they lose weight and become jaundiced, especially if younger than 36 weeks. Discharge of these newborns should be delayed until they have demonstrated reliable and appropriately increasing intake and absence of other issues such as hypothermia, hypoglycemia, significant jaundice, or apnea. If nursing, use of a breast pump to ensure adequate emptying of the breast and milk supply should also be instituted, along with supplementation of the infant's breast feeding with expressed milk by bottle or gavage. It is better to ensure adequate feeding and mature behaviors for an extra day or two in the hospital than to have a readmission for "lethargy and poor feeding, possible sepsis" after premature discharge. Following nursery discharge, close outpatient follow-up is indicated, generally within 48–72 hours, to ensure continued adequate intake and weight gain.
CARDIAC PROBLEMS IN THE NEWBORN INFANT

STRUCTURAL HEART DISEASE

1. Cyanotic Presentations

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Cyanosis, initially without associated respiratory distress.
- Failure to increase Pao$_2$ with supplemental oxygen.
- Chest radiograph with decreased lung markings suggests right heart obstruction, while increased lung markings suggest transposition or pulmonary venous obstruction.

General Considerations

The causes of cyanotic heart disease in the newborn are transposition of the great vessels, total anomalous pulmonary venous return, truncus arteriosus (some types), tricuspid atresia, and pulmonary atresia or critical pulmonary stenosis. Most can be diagnosed antenatally by ultrasound.

Clinical Findings

Infants with these disorders present with early cyanosis. The hallmark of many of these lesions is cyanosis without associated respiratory distress. In most of these infants, tachypnea develops over time either because of increased pulmonary blood flow or secondary to metabolic acidemia from progressive hypoxemia. Diagnostic aids include comparing the blood gas or oxygen saturation in room air to that in 100% Fio$_2$. Failure of Pao$_2$ or Sao$_2$ to increase suggests cyanotic heart disease. Note: A Pao$_2$, if feasible, is the preferred measure. Saturation in the newborn may be misleadingly high despite pathologically low Pao$_2$ due to the left-shifted oxyhemoglobin dissociation curve seen with fetal hemoglobin. Other useful aids are chest radiography, electrocardiography, and echocardiography.

Transposition of the great vessels is the most common form of cyanotic heart disease presenting in the newborn. Examination generally reveals a systolic murmur and single S$_2$. Chest radiograph shows a generous heart size and a narrow mediastinum with normal or increased lung markings. There is little change in Pao$_2$ or Sao$_2$ with supplemental oxygen. Total anomalous pulmonary venous return, in which venous return is obstructed, presents early with severe cyanosis and respiratory failure because of severe pulmonary edema. The chest radiograph typically shows a small to normal heart size with marked pulmonary edema. Infants with right heart obstruction (pulmonary and tricuspid atresia, critical pulmonary stenosis, and some forms of truncus arteriosus) have decreased lung markings on chest radiographs and, depending on the
severity of hypoxia, may develop metabolic acidemia. Those lesions with an underdeveloped right heart will have left-sided predominance on electrocardiography. Although tetralogy of Fallot is the most common form of cyanotic heart disease, the obstruction at the pulmonary valve is often not severe enough to result in cyanosis in the newborn. In all cases, diagnosis can be confirmed by echocardiography.

2. Acyanotic Presentations

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**

- Most newborns with symptomatic acyanotic heart disease have left-sided outflow obstruction.
- Differentially diminished pulses (coarctation) or decreased pulses throughout (aortic atresia).
- Metabolic acidemia.
- Chest radiograph showing large heart and pulmonary edema.

**General Considerations**

Newborn infants who present with serious acyanotic heart disease usually have congestive heart failure secondary to left-sided outflow tract obstruction. Infants with left-to-right shunt lesions (eg, ventricular septal defect) may have murmurs in the newborn period, but clinical symptoms do not occur until pulmonary vascular resistance drops enough to cause significant shunting and subsequent congestive heart failure (usually at 3–4 weeks of age).

**Clinical Findings**

Infants with left-sided outflow obstruction generally do well for several days until the ductus arteriosus—the source of all or some of the systemic flow—narrows. Tachypnea, tachycardia, congestive heart failure, and metabolic acidosis develop. On examination, all of these infants have abnormalities of the pulses. In aortic atresia (hypoplastic left heart syndrome) and stenosis, pulses are all diminished, whereas in coarctation syndromes, differential pulses (diminished or absent in the lower extremities) are evident, and $\text{SPO}_2$ may be lower in the legs than in the right upper extremity. Chest radiographic films in these infants show a large heart and pulmonary edema. Diagnosis is confirmed with echocardiography.

3. Treatment of Cyanotic & Acyanotic Lesions

Early stabilization includes supportive therapy as needed (eg, IV glucose, oxygen, ventilation for respiratory failure, and pressor support). Specific therapy includes infusions of prostaglandin $E_1$ (0.0125–0.025 mcg/kg/min) to maintain ductal patency. In some cyanotic lesions (eg, pulmonary atresia, tricuspid atresia, and critical pulmonary stenosis) in which lung blood flow is ductus-dependent, this improves pulmonary blood flow and $\text{Pao}_2$ by allowing shunting through the ductus to the pulmonary artery. In left-sided outflow tract obstruction, systemic blood flow is ductus-dependent; prostaglandins improve systemic perfusion and resolve the acidosis. Further specific management—including palliative surgical and cardiac catheterization procedures—is discussed in Chapter 20. Neurodevelopmental outcome with congenital heart disease depends on the lesion, associated defects and syndromes, severity of neonatal presentation, and complications related to palliative and corrective surgery.

**PERSISTENT PULMONARY HYPERTENSION**

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**

- Onset of symptoms on day 1 of life.
- Hypoxia with poor response to high concentrations of inspired oxygen.
- Right-to-left shunts through the foramen ovale, ductus arteriosus, or both.
- Most often associated with parenchymal lung disease.

**General Considerations**

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Persistent pulmonary hypertension of the newborn (PPHN) results when the normal decrease in pulmonary vascular resistance after birth does not occur. Most affected infants are full term or postterm, and many have experienced perinatal asphyxia. Other clinical associations include hypothermia, meconium aspiration syndrome, hyaline membrane disease, polycythemia, neonatal sepsis, chronic intrauterine hypoxia, and pulmonary hypoplasia.

There are three underlying pathophysiologic mechanisms of PPHN: (1) vasoconstriction due to perinatal hypoxia related to an acute event such as sepsis or asphyxia; (2) prenatal increase in pulmonary vascular smooth muscle development, often associated with meconium aspiration syndrome; and (3) decreased cross-sectional area of the pulmonary vascular bed associated with lung hypoplasia (eg, diaphragmatic hernia).

**Clinical Findings**

Clinically, the syndrome is characterized by onset on the first day of life, usually from birth. Respiratory distress is prominent, and Pao$_2$ is usually poorly responsive to high concentrations of inspired oxygen. Many infants have associated myocardial depression with systemic hypotension. Echocardiography reveals right-to-left shunting at the level of the ductus arteriosus or foramen ovale, or both. The chest radiograph may show lung infiltrates related to associated pulmonary pathology (eg, meconium aspiration and hyaline membrane disease). If the majority of right-to-left shunting is at the ductal level, pre- and postductal differences in Pao$_2$ and Sao$_2$ will be observed.

**Treatment**

Therapy for PPHN involves treatment of other postasphyxia problems such as seizures, renal failure, hypoglycemia, and infection. Specific therapy is aimed at both increasing systemic arterial pressure and decreasing pulmonary arterial pressure to reverse the right-to-left shunting through fetal pathways. First-line therapy includes oxygen and ventilation (to reduce pulmonary vascular resistance) and crystalloid infusions (10 mL/kg, up to 30 mL/kg) to improve systemic pressure. Ideally, systolic pressure should be greater than 50–60 mm Hg. With compromised cardiac function, systemic pressors can be used as second-line therapy (eg, dopamine, 5–20 mcg/kg/min; epinephrine 0.01–0.1 mcg/kg/min; or both). Metabolic acidemia should be corrected because acidemia exacerbates pulmonary vasoconstriction. Pulmonary vasodilation can be enhanced using inhaled nitric oxide, which is identical or very similar to endogenous endothelium-derived relaxing factor, at doses of 5–20 ppm. High-frequency oscillatory ventilation has proved effective in many of these infants, particularly those with severe associated lung disease, by improving lung expansion and recruitment. In cases in which conventional therapy is failing (poor oxygenation despite maximum support) extracorporeal membrane oxygenation (ECMO) is used. The lungs are essentially at rest during ECMO, and with resolution of pulmonary hypertension infants are weaned from ECMO back to ventilator therapy. Approximately 10%–15% of survivors of PPHN have significant neurologic sequelae, with cerebral palsy or cognitive delays. Other sequelae such as chronic lung disease, sensorineural hearing loss, and feeding problems have also been reported.

**ARRHYTHMIAS**

Irregularly irregular heart rates, commonly associated with premature atrial contractions and less commonly with premature ventricular contractions, are common in the first days of life in well newborns. These arrhythmias are benign. Clinically significant bradyarrhythmias are seen in association with congenital heart block. Heart block can be seen in an otherwise structurally normal heart (associated with maternal lupus) or with structural cardiac abnormalities. In the absence of fetal hydrops, the bradycardhythmia is often well tolerated. Cardiac pacing may be required if there are symptoms of inadequate cardiac output.

Tachyarrhythmias can be either wide complex (ventricular tachycardia) or narrow complex (supraventricular tachycardia) on ECG. Supraventricular tachycardia is the most common neonatal tachyarrhythmia and may be a sign of structural heart disease, myocarditis, left atrial enlargement, and aberrant conduction pathways, or may be an isolated event. Acute treatment is ice to the face to induce a vagal response, and if unsuccessful, IV adenosine (50 mcg/kg). If there is no response, the dose can be increased every 2 minutes by 50 mcg/kg to a maximum dose of 250 mcg/kg. Long-term prophylactic antiarrhythmic therapy is generally indicated; cardiology consultation is suggested. Cardioversion is rarely needed for supraventricular tachycardia but is needed acutely for hemodynamically unstable ventricular tachycardia.

GASTROINTESTINAL & ABDOMINAL SURGICAL CONDITIONS IN THE NEWBORN INFANT

(See also Chapter 21)

ESOPHAGEAL ATRESIA & TRACHEOESOPHAGEAL FISTULA

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Polyhydramnios.
- Excessive drooling and secretions; choking with attempted feeding.
- Unable to pass an orogastric tube to the stomach.

General Considerations

Esophageal atresia is characterized by a blind esophageal pouch with or without a fistulous connection between the proximal or distal esophagus (or both) and the airway. In 85% of infants, the fistula is between the distal esophagus and the airway. Polyhydramnios is common because of high GI obstruction. Incidence is approximately 1 in 3000 births.

Clinical Findings

Infants present in the first hours of life with copious secretions, choking, cyanosis, and respiratory distress. Diagnosis is confirmed with chest radiograph after careful placement of a nasogastric (NG) tube to the point at which resistance is met. The tube will be seen radiographically in the blind pouch. If a tracheoesophageal fistula is present to the distal esophagus, gas will be present in the bowel. In esophageal atresia without tracheoesophageal fistula, there is no gas in the bowel.

Treatment

The NG tube in the proximal pouch should be placed on low intermittent suction to drain secretions and prevent aspiration. The head of the bed should be elevated to prevent reflux of gastric contents through the distal fistula into the lungs. IV glucose and fluids should be provided and oxygen administered as needed. Definitive treatment is surgical, and the technique used depends on the distance between the segments of esophagus. If the distance is not too great, the fistula can be ligated and the ends of the esophagus anastomosed. If the ends of the esophagus cannot be brought together, the initial surgery is fistula ligation and a feeding gastrostomy. Echocardiography should be performed prior to surgery to rule out a right-sided aortic arch (for which a left-sided thoracotomy would be preferred).

Prognosis

Prognosis is determined primarily by the presence or absence of associated anomalies, particularly cardiac, and low birth weight. Mortality is highest when the infant is less than 2000 g and has a serious associated cardiac defect. Vertebral, anal, cardiac, renal, and limb anomalies are the most likely to be observed (VACTERL association). Evaluation for associated anomalies should be initiated early.


INTESTINAL OBSTRUCTION

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Infants with high intestinal obstruction present soon after birth with emesis.
- Bilious emesis suggests intestinal malrotation with midgut volvulus until proved otherwise.
• Low intestinal obstruction is characterized by abdominal distention and late onset of emesis, often with delayed or absent stooling.

General Considerations

A history of polyhydramnios is common, and the fluid, if bile-stained, can easily be confused with thin meconium staining. The higher the location of the obstruction in the intestine, the earlier the infant will develop vomiting and the less prominent the abdominal distention will be. Lower intestinal obstruction presents with abdominal distention and later onset of emesis. Most obstructions are bowel atresias, believed to be caused by an ischemic event during development. Approximately 30% of cases of duodenal atresia are associated with Down syndrome. Meconium ileus is a distal small bowel obstruction caused by the viscous meconium produced in-utero by infants with pancreatic insufficiency secondary to cystic fibrosis. Hirschsprung disease is caused by a failure of neuronal migration to the myenteric plexus of the distal bowel. The distal bowel lacks ganglion cells, causing a lack of peristalsis in that region with a functional obstruction.

Malrotation with midgut volvulus is a surgical emergency that appears in the first days to weeks as bilious vomiting without distention or tenderness. If malrotation is not treated promptly, torsion of the intestine around the superior mesenteric artery will lead to necrosis of the entire small bowel. For this reason, bilious vomiting in the neonate always demands immediate attention and evaluation.

Clinical Findings

Diagnosis of intestinal obstructions depends on plain abdominal radiographs with either upper GI series (high obstruction suspected) or contrast enema (lower obstruction apparent) to define the area of obstruction. Table 2–20 summarizes the findings expected.

Table 2–20. Intestinal obstruction.

<table>
<thead>
<tr>
<th>Site of Obstruction</th>
<th>Clinical Findings</th>
<th>Plain Radiographs</th>
<th>Contrast Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal atresia</td>
<td>Down syndrome (30%–50%); early vomiting, sometimes bilious</td>
<td>&quot;Double bubble&quot; (dilated stomach and proximal duodenum, no air distal)</td>
<td>Not needed</td>
</tr>
<tr>
<td>Malrotation and volvulus</td>
<td>Bilious vomiting with onset anytime in the first few weeks</td>
<td>Dilated stomach and proximal duodenum; paucity of air distally (may be normal gas pattern)</td>
<td>UGI shows displaced duodenojejunal junction with &quot;corkscrew&quot; deformity of twisted bowel</td>
</tr>
<tr>
<td>Jejunoileal atresia, meconium ileus</td>
<td>Bilious gastric contents &gt; 25 mL at birth; progressive distention and bilious vomiting</td>
<td>Multiple dilated loops of bowel; intra-abdominal calcifications if in-utero perforation occurred (meconium peritonitis)</td>
<td>Barium or osmotic contrast enema shows microcolon; contrast refluxed into distal ileum may demonstrate and relieve meconium obstruction (successful in about 50% of cases)</td>
</tr>
<tr>
<td>Meconium plug syndrome; Hirschsprung disease</td>
<td>Distention, delayed stooling (&gt; 24 h)</td>
<td>Diffuse bowel distention</td>
<td>Barium or osmotic contrast enema outlines and relieves plug; may show transition zone in Hirschsprung disease; delayed emptying (&gt; 24 h) suggests Hirschsprung disease</td>
</tr>
</tbody>
</table>

UGI, upper gastrointestinal contrast study.

Infants with meconium ileus are suspected to have cystic fibrosis, although infants with pancolonic Hirschsprung disease, colon pseudo-obstruction syndrome, or colonic dysgenesis or atresia may also present with meconium impacted in the distal ileum. Definitive diagnosis of cystic fibrosis is by the sweat chloride test (Na⁺ and Cl⁻ concentration > 60 mEq/L) or by genetic testing. Approximately 10%–20% of infants with cystic fibrosis have meconium ileus. Infants with cystic fibrosis and meconium ileus generally have a normal immunoreactive trypsinogen on their newborn screen because of the associated severe exocrine pancreatic insufficiency in utero.

Intestinal perforation in-utero results in meconium peritonitis with residual intra-abdominal calcifications. Many perforations are completely healed at birth. If the infant has no signs of obstruction or ongoing perforation, no immediate evaluation is needed. A sweat test to rule out cystic fibrosis should be done at a later date.
Low intestinal obstruction may present with delayed stooling (> 24 hours in term infants is abnormal) with mild distention. Radiographic findings of gaseous distention should prompt contrast enema to diagnose (and treat) meconium plug syndrome. If no plug is found, the diagnosis may be small left colon syndrome (occurring in IDM's) or Hirschsprung disease. Rectal biopsy will be required to clarify these two diagnoses. Imperforate anus is generally apparent on physical examination, although a rectovaginal fistula with a mildly abnormal-appearing anus can occasionally be confused with normal. High imperforate anus in males may be associated with rectourethral or rectovesical fistula, with meconium "pearls" seen along the median raphe of the scrotum, and meconium being passed via the urethra.

**Treatment**

NG suction to decompress the bowel, IV glucose, fluid and electrolyte replacement, and respiratory support as necessary should be instituted. Antibiotics are usually indicated due to the bowel distention and possibility of translocation of bacteria. The definitive treatment for these conditions (with the exception of meconium plug syndrome, small left colon syndrome, and some cases of meconium ileus) is surgical.

**Prognosis**

Up to 10% of infants with meconium plug syndrome are subsequently found to have cystic fibrosis or Hirschsprung disease. For this reason, it is appropriate to obtain a sweat chloride test and rectal biopsy in all of these infants before discharge, especially the infant with meconium plug syndrome who is still symptomatic after contrast enema.

In duodenal atresia associated with Down syndrome, the prognosis depends on associated anomalies (eg, heart defects) and the severity of prestenotic duodenal dilation and subsequent duodenal dysmotility. Otherwise, these conditions usually carry an excellent prognosis after surgical repair.

**ABDOMINAL WALL DEFECTS**

1. **Omphalocele**

Omphalocele is a membrane-covered herniation of abdominal contents into the base of the umbilical cord; the incidence is 2 per 10,000 live births (0.02%). Over 50% of cases have either an abnormal karyotype or an associated syndrome. The sac may contain liver and spleen as well as intestine. Prognosis varies with the size of the lesion, with the presence of pulmonary hypoplasia and respiratory insufficiency, and with the presence of associated abnormalities.

At delivery, the omphalocele is covered with a sterile dressing soaked with warm saline to prevent fluid loss. NG decompression is performed, and IV fluids, glucose, and antibiotics are given. If the contents of the omphalocele fit into the abdomen and can be covered with skin, muscle, or both, primary surgical closure is done. If not, staged closure is performed, with placement of a Gore-Tex patch over the exposed contents, and gradual coverage of the patch by skin over days to weeks. A large ventral hernia is left, which is repaired in the future.

2. **Gastroschisis**

In gastroschisis, the uncovered intestine extrudes through a small abdominal wall defect to the right of the umbilical cord. There is no membrane or sac and no liver or spleen outside the abdomen. Gastroschisis is associated with intestinal atresia in approximately 10%–20% of infants, and with intrauterine growth restriction (IUGR). The evisceration is thought to be related to abnormal involution of the right umbilical vein or a vascular accident involving the omphalomesenteric artery, although the exact cause is unknown. The prevalence of gastroschisis has been increasing worldwide over the past 20 years, from 0.03% to 0.1%. Environmental factors, including use of illicit drugs such as methamphetamine and cocaine, and cyclooxygenase inhibitors such as aspirin and ibuprofen taken during pregnancy, may be involved. Young maternal age is also strongly linked to the occurrence of gastroschisis.

Therapy initially involves placing the bowel or the lower half of the infant into a silastic bowel bag to decrease fluid and electrolyte losses as well as to conserve heat. IV fluids, antibiotics, and low intermittent gastric suction are required. The infant is placed right side down to preserve bowel perfusion. Subsequent therapy involves replacement of the bowel into the abdominal cavity. This is done as a single primary procedure if the amount of bowel to be replaced is small. If the amount of bowel is large or if the bowel is very dilated, staged closure with placement of a silastic silo and gradual reduction of the bowel into the underdeveloped abdominal cavity over several days is preferred. Postoperatively, third-space fluid losses may be extensive; fluid and electrolyte therapy, therefore, must be monitored carefully. Bowel motility, especially
duodenal, may be slow to return if the bowel was dilated, thickened, matted together, and covered with a fibrinous "peel" at
delivery. Prolonged intravenous nutrition is often required, but long-term outcome is very good.

[PubMed: 22682386].
Juhasz-Bossi,  GR. Fetal and neonatal outcome in patients with anterior abdominal wall defects (gastroschisis and
[PubMed: 22085153].

DIAPHRAGMATIC HERNIA

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

• Respiratory distress from birth.
• Poor breath sounds; flat or scaphoid abdomen.
• Bowel loops seen in the chest with mediastinal shift to opposite side on chest radiograph.

This congenital malformation consists of herniation of abdominal organs into the hemithorax (usually left-sided) through a
posterolateral defect in the diaphragm. The incidence overall is 1 in 2500 births. It is often diagnosed antenatally by
ultrasound, and, if so, delivery should occur at a perinatal center. If undiagnosed, it should be suspected in any infant with
severe respiratory distress, poor breath sounds, and a scaphoid abdomen. The rapidity and severity of presentation depend
on several factors: the degree of pulmonary hypoplasia resulting from lung compression by the intrathoracic abdominal
contents in utero; degree of associated pulmonary hypertension; and associated anomalies, especially chromosomal
abnormalities and congenital cardiac defects. Affected infants are prone to development of pneumothorax during attempts at
ventilation of the hypoplastic lungs.

Treatment includes intubation, gentle mechanical ventilation, and decompression of the GI tract with an NG tube. An IV
infusion of glucose and fluid should be started. A chest radiograph confirms the diagnosis. Surgery to reduce the abdominal
contents from the thorax and close the diaphragmatic defect is delayed until after the infant is stabilized and pulmonary
hypertension and compliance have improved, usually after 24–48 hours. Both pre- and postoperatively, pulmonary
hypertension may require therapy with high-frequency oscillatory ventilation, inhaled nitric oxide, or ECMO. The survival
rate for infants with this condition is improving, and now approaches 80%. Use of a gentle ventilation style and permissive
hypercarbia is recommended to avoid barotrauma and further lung injury. Many of these infants have ongoing problems
with severe gastroesophageal reflux, and are at risk for neurodevelopmental problems, behavior problems, hearing loss, and
poor growth.

[PubMed: 23395144]
treatment protocol. Fetal Diagn Ther 2011;29:55
[PubMed: 21325859].

GASTROINTESTINAL BLEEDING

Upper Gastrointestinal Bleeding

Upper GI bleeding sometimes occurs in the newborn nursery, but is rarely severe. Old blood ("coffee-grounds" material) in
the stomach of the newborn may be either swallowed maternal blood or infant blood from gastritis or stress ulcer. Bright red
blood from the stomach is most likely from acute bleeding due to gastritis. Treatment generally consists of gastric lavage to
obtain a sample for Apt testing or blood typing to determine if it is mother's or baby's blood, and antacid medication. If the
volume of bleeding is large, intensive monitoring, fluid and blood replacement, and endoscopy are indicated. Coagulation
studies should also be sent, and vitamin K administration confirmed or repeated.
**Lower Gastrointestinal Bleeding**

Rectal bleeding in the newborn is less common than upper GI bleeding and is associated with infections (e.g., *Salmonella* acquired from the mother perinatally), milk protein intolerance (blood streaks with diarrhea), or, in ill infants, NEC. An abdominal radiograph should be obtained to rule out pneumatosis intestinalis or other abnormalities in gas pattern suggesting inflammation, infection, or obstruction. If the radiograph is negative and the examination is benign, a protein hydrolysate or elemental formula should be tried. The nursing mother should be instructed to avoid all cow milk protein products in her diet. If the amount of rectal bleeding is large or persistent, endoscopy may be needed.


**GASTROESOPHAGEAL REFLUX**

Physiologic regurgitation is common in infants. Reflux is pathologic and should be treated when it results in failure to thrive owing to excessive regurgitation, poor intake due to dysphagia and irritability, apnea or cyanotic episodes, or chronic respiratory symptoms of wheezing and recurrent pneumonias. Diagnosis is clinical, with confirmation by pH probe and impedance study. Barium radiography is helpful to rule out anatomic abnormalities causing delayed gastric emptying, but is not diagnostic of pathologic reflux.

Most antireflux therapies have not been studied systematically in infants, especially in premature infants, and there is little correlation between clinical symptoms and documented gastroesophageal reflux events when studied. Treatment modalities have included thickened feeds for those with frequent regurgitation and poor weight gain, and positioning in a prone or left side down position for 1 hour after a feeding, although this may increase risk for SIDS. Gastric acid suppressants such as *ranitidine* (2 mg/kg bid) or *lansoprazole* (1.5 mg/kg/d) can also be used, especially if there is associated irritability; however, these may be associated with an increased incidence of NEC and invasive infections in the young and/or premature infant. Prokinetic agents such as *erythromycin* or *metoclopramide* are of little benefit and have significant side effects. Because most infants improve by 12–15 months of age, surgery is reserved for the most severe cases.


**INFECTIONS IN THE NEWBORN INFANT**

There are three major routes of perinatal infection: (1) blood-borne transplacental infection of the fetus (e.g., cytomegalovirus [CMV], rubella, and syphilis); (2) ascending infection with disruption of the barrier provided by the amniotic membranes (e.g., bacterial infections after 12–18 hours of ruptured membranes); and (3) infection on passage through an infected birth canal or exposure to infected blood at delivery (e.g., herpes simplex, hepatitis B, HIV, and bacterial infections).

Susceptibility of the newborn infant to infection is related to immaturity of the immune system at birth. This feature applies particularly to the preterm neonate. Passive protection against some organisms is provided by transfer of IgG across the placenta, particularly during the third trimester of pregnancy. Preterm infants, especially those born before 30 weeks' gestation, do not have the full amount of passively acquired antibody.

**BACTERIAL INFECTIONS**

1. Bacterial Sepsis

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES
Most infants with early-onset sepsis present at < 24 hours of age.

Respiratory distress is the most common presenting symptom.

Hypotension, acidemia, and neutropenia are associated clinical findings.

The presentation of late-onset sepsis is more subtle.

General Considerations

The incidence of early-onset (< 3 days) neonatal bacterial infection is 1–2 in 1000 live births. If rupture of the membranes occurs more than 24 hours prior to delivery, the infection rate increases to 1 in 100 live births. If early rupture of membranes with chorioamnionitis occurs, the infection rate increases further to 1 in 10 live births. Regardless of membrane rupture, infection rates are five times higher in preterm than in full-term infants.

Clinical Findings

Early-onset bacterial infections appear most commonly on day 1 of life, the majority by 12 hours of age. Respiratory distress due to pneumonia is the most common presenting sign. Other features include unexplained low Apgar scores without fetal distress, poor perfusion, and hypotension. Late-onset bacterial infection (> 3 days of age) presents in a more subtle manner, with poor feeding, lethargy, hypotonia, temperature instability, altered perfusion, new or increased oxygen requirement, and apnea. Late-onset bacterial sepsis is more often associated with meningitis or other localized infections.

Low total white blood cell count, absolute neutropenia (< 1000/mL), and elevated ratio of immature to mature neutrophils all suggest neonatal bacterial infection. Thrombocytopenia is another common feature. Other laboratory signs are hypoglycemia or hyperglycemia with no change in glucose administration, unexplained metabolic acidosis, and elevated C-reactive protein and procalcitonin. In early-onset bacterial infection, pneumonia is invariably present; chest radiography shows infiltrates, but these infiltrates cannot be distinguished from those resulting from other causes of neonatal lung disease. Presence of a pleural effusion makes a diagnosis of pneumonia more likely. Definitive diagnosis is made by positive cultures from blood, CSF, or other body fluids.

Early-onset infection is most often caused by group B β-hemolytic streptococci (GBS) and gram-negative enteric pathogens (most commonly E coli). Other organisms to consider are non-typeable Haemophilus influenzae, enterococcus, Staphylococcus aureus, other streptococci and Listeria monocytogenes. Late-onset sepsis is caused by coagulase-negative staphylococci (most common in infants with indwelling central venous lines), S aureus, GBS, enterococcus, and gram-negative organisms, in addition to Candida species (see Fungal Sepsis).

Treatment

A high index of suspicion is important in diagnosis and treatment of neonatal infection. Infants with risk factors (rupture of membranes > 18 hours, maternal chorioamnionitis, prematurity) need to be carefully observed for signs of infection. Evaluation with a CBC and differential, blood and cerebrospinal fluid cultures are indicated in infants with clinical signs of sepsis. Early-onset sepsis is usually caused by GBS or gram-negative enteric organisms; broad-spectrum coverage, therefore, should include ampicillin (100–150 mg/kg/d divided every 12 h) plus an aminoglycoside (3–4 mg/kg/dose every 24 hours based on gestational age at birth) or third-generation cephalosporin (cefotaxime 100 mg/kg/d divided every 12 h). Late-onset infections can also be caused by the same organisms, but coverage may need to be expanded to include staphylococci. In particular, the preterm infant with an indwelling line is at risk for infection with coagulase-negative staphylococci, for which vancomycin (10–15 mg/kg every 8–24 h based on gestational and postnatal age) is the drug of choice. Initial broad-spectrum coverage should also include a third-generation cephalosporin (cefotaxime or ceftazidime, if Pseudomonas aeruginosa is strongly suspected) or an aminoglycoside. To prevent the development of vancomycin-resistant organisms, vancomycin should be stopped as soon as cultures and sensitivities indicate that it is not needed. The evaluation for late onset symptoms should include cultures of blood, urine, and cerebrospinal fluid. The duration of treatment for proven sepsis is 10–14 days of IV antibiotics. In sick infants, the essentials of good supportive therapy should be provided: IV glucose and nutritional support, volume expansion and pressors as needed, and oxygen and ventilator support.

Prevention

Prevention of early onset neonatal GBS infection has been achieved with intrapartum administration of penicillin given more than 4 hours prior to delivery, with overall rates of infection now at 0.3–0.4 cases per 1000 live births. The current
Indications for intrapartum antimicrobial prophylaxis to prevent early-onset group B streptococcal (GBS) disease using a universal prenatal culture screening strategy at 35–37 weeks’ gestation for all pregnant women. (Reproduced, with permission, from the Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease. MMWR 2010;59:RR-10.)

![Figure 2–13](image_url)

Figure 2–13. Indications for intrapartum antimicrobial prophylaxis to prevent early-onset group B streptococcal (GBS) disease using a universal prenatal culture screening strategy at 35–37 weeks’ gestation for all pregnant women. (Reproduced, with permission, from the Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease. MMWR 2010;59:RR-10.)

<table>
<thead>
<tr>
<th>Intrapartum GBS prophylaxis indicated</th>
<th>Intrapartum GBS prophylaxis not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous infant with invasive GBS disease</td>
<td>+ Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
</tr>
<tr>
<td>GBS bacteriuria during any trimester of the current pregnancy</td>
<td>GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
</tr>
<tr>
<td>Positive GBS vaginal–rectal screening culture in late gestation during current pregnancy</td>
<td>Positive vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors</td>
</tr>
<tr>
<td>Unknown GBS status at the onset of labor or (culture not done, incomplete, or results unknown) and any of the following:</td>
<td>• Caesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age</td>
</tr>
<tr>
<td>Delivery at ≤37 weeks’ gestation</td>
<td></td>
</tr>
<tr>
<td>Aseptic membrane rupture ≥18 hours</td>
<td></td>
</tr>
<tr>
<td>Intrapartum temperature ≥100.4°F (≥38.0°C)</td>
<td></td>
</tr>
<tr>
<td>Intrapartum NAAT is positive for GBS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NAAT: Nucleic acid amplification tests

Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns. (Reproduced, with permission, from the Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease. MMWR 2010;59:RR-10.)
2. Meningitis

Any newborn with bacterial sepsis is at risk for meningitis. The incidence is low in infants presenting in the first day of life, and higher in infants with later-onset infection. The workup for any newborn with possible signs of CNS infection should include a lumbar puncture because blood cultures can be negative in neonates with meningitis. The presence of seizures should increase the suspicion for meningitis. Diagnosis is suggested by a CSF protein level higher than 150 mg/dL, glucose less than 30 mg/dL, leukocytes of more than 20/μL, and a positive Gram stain. The diagnosis is confirmed by culture. The most common organisms are GBS and gram-negative enteric bacteria. Although sepsis can be treated with antibiotics for 10–14 days, meningitis requires 14–21 days. Gram-negative infections, in particular, are difficult to eradicate, and may relapse. The mortality rate of neonatal meningitis is approximately 10%, with significant neurologic morbidity present in one-third of the survivors.

3. Pneumonia

The respiratory system can be infected in-utero, on passage through the birth canal, or postnatally. Early-onset neonatal infection is usually associated with pneumonia. Pneumonia should also be suspected in older neonates with a recent onset of tachypnea, retractions, and cyanosis. In infants already receiving respiratory support, an increase in the requirement for oxygen or ventilator support, perhaps with a change in the character of tracheal secretions, may indicate pneumonia. Not only common bacteria but also viruses (CMV, respiratory syncytial virus, adenovirus, influenza, herpes simplex, parainfluenza) and Chlamydia can cause pneumonia. In infants with preexisting respiratory disease, intercurrent pulmonary infections contribute to the development of chronic lung disease.
4. Urinary Tract Infection

Infection of the urine is uncommon in the first days of life. Urinary tract infection in the newborn can occur in association with genitourinary anomalies and is usually caused by gram-negative enteric pathogens, or enterococcus. Urine should always be evaluated as part of the workup for later-onset infection. Culture should be obtained either by suprapubic aspiration or bladder catheterization. Antibiotic IV therapy is continued for 3–5 days if the blood culture is negative and clinical signs resolve quickly, then completed with oral medications. Evaluation for genitourinary anomalies with an ultrasound examination and a voiding cystourethrogram should be done in most cases.

5. Omphalitis

A normal umbilical cord stump atrophies and separates at the skin level. A small amount of purulent material at the base of the cord is common and can be minimized by keeping the cord open to air and dry. The cord can become colonized with streptococci, staphylococci, or gram-negative organisms that can cause local infection. Infections are more common in cords manipulated for venous or arterial lines. Omphalitis is diagnosed when redness and edema develop in the soft tissues around the stump. Local and systemic cultures should be obtained. Treatment is with broad-spectrum IV antibiotics (usually nafcillin at 50–75 mg/kg/d divided every 8–12 h) or vancomycin and a third-generation cephalosporin. Complications are determined by the degree of infection of the cord vessels and include septic thrombophlebitis, hepatic abscess, necrotizing fasciitis, and portal vein thrombosis. Surgical consultation should be obtained because of the potential for necrotizing fasciitis. It is also prudent at this point to add anaerobic coverage with metronidazole (15 mg/kg/d divided every 12 h) as the infection may be polymicrobial.

6. Conjunctivitis

Neisseria gonorrhoeae may colonize an infant during passage through an infected birth canal. Gonococcal ophthalmitis presents at 3–7 days with copious purulent conjunctivitis. The diagnosis can be suspected when gram-negative intracellular diplococci are seen on a Gram-stained smear and confirmed by culture. Treatment for nondisseminated disease is with IV or IM ceftriaxone, 25–50 mg/kg (not to exceed 125 mg) given once. For disseminated disease (sepsis, arthritis, or meningitis) cefotaxime for 7–10 days is preferred. Prophylaxis at birth is with 0.5% erythromycin ointment. Infants born to mothers with known gonococcal disease should also receive a single dose of ceftriaxone.

Chlamydia trachomatis is another important cause of conjunctivitis, appearing at 5 days to several weeks of age with conjunctival congestion, edema, and minimal discharge. The organism is acquired at birth after passage through an infected birth canal. Acquisition occurs in 50% of infants born to infected women, with a 25%–50% risk of conjunctivitis. Prevalence in pregnancy is over 10% in some populations. Diagnosis is by isolation of the organism or by rapid antigen detection tests. Treatment is with oral erythromycin (30 mg/kg/d in divided doses q8–12h) for 14 days. Topical treatment alone will not eradicate nasopharyngeal carriage, leaving the infant at risk for the development of pneumonitis.

FUNGAL SEPSIS

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

• Risk factors include low birth weight, indwelling central lines, and multiple antibiotic exposures.

• Colonization with Candida species is common; systemic infection occurs in 5%–7% of infants.

• Presents with often subtle clinical deterioration, thrombocytopenia, and hyperglycemia.

With the survival of smaller, sicker infants, infection with Candida species has become more common. Infants of extremely low birth weight with central lines who have had repeated exposures to broad-spectrum antibiotics are at highest risk. For infants of birth weight less than 1500 g, colonization rates of 27%–64% have been demonstrated. Many of these infants develop cutaneous lesions, with the GI tract as the initial site of colonization. A much smaller percentage develops systemic disease. The infection is more common in the smallest and least mature infants; up to 20% in infants 24 weeks' gestation, and 7% overall in those < 1000 g.

Clinical features of fungal sepsis can be indistinguishable from those of late-onset bacterial sepsis but are often more subtle. Thrombocytopenia may be the earliest and only sign, and hyperglycemia is often present. Deep organ involvement (renal, eye, or endocarditis) is commonly associated with systemic candidiasis. Treatment is with intravenous fluconazole (12 mg/kg loading dose followed by 6 mg/kg daily) or an amphotericin B lipid complex (5 mg/kg given daily). Prophylaxis for infants at highest risk, for example, those with central venous lines and receiving parenteral nutrition, is recommended. Prophylaxis with fluconazole diminishes intestinal colonization with yeast and decreases the frequency of systemic disease, with an overall reduction in invasive candidal disease of 83%, from 9% to 1.6%, without significant adverse effects, or resistance to fluconazole. Nystatin prophylaxis may also be effective, but has been less rigorously tested.

More rarely, Malassezia furfur is also seen in infants with central lines receiving IV fat emulsion. To eradicate this organism, as well as Candida species, it is necessary to remove the indwelling line.

[PubMed: 20813274].
[PubMed: 23297182].

CONGENITAL INFECTIONS

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

• Can be acquired in utero, perinatally, and postnatally.

• Can be asymptomatic in the newborn period.

• Clinical symptom complexes include IUGR, chorioretinitis, cataracts, cholestatic jaundice, thrombocytopenia, skin rash, and brain calcifications.

• Diagnosis can be confirmed using polymerase chain reaction (PCR) testing, antigen and antibody studies, and culture.

1. Cytomegalovirus Infection

(See also Chapter 40)

Cytomegalovirus (CMV) is the most common virus transmitted in utero, affecting approximately 1% of all newborns. Symptomatic disease in the newborn period occurs in 10% of these congenitally infected infants, with a spectrum of findings including hepatosplenomegaly, petechiae and blueberry muffin spots, growth restriction, microcephaly, direct hyperbilirubinemia, thrombocytopenia, intracranial calcifications, and chorioretinitis. More than half of these infants will develop long-term sequelae, including sensorineural deafness in 20%–30%. Sensorineural hearing loss is common even in asymptomatic infants, leading to deafness in another 10%–15%. Transmission of CMV can occur during either primary or...
reactivated maternal infection; the risk of symptomatic neonatal disease is highest when the mother acquires a primary infection in the first half of pregnancy. Children, especially in the day care setting, are an important source of infection. Diagnosis in the neonate should be confirmed by culture of the virus from urine or with PCR testing of urine or saliva. Diagnosis can also be confirmed in utero from an amniocentesis specimen. Ganciclovir therapy (6 mg/kg IV q12h for 6 weeks) is recommended for neonates with symptomatic congenital infection affecting the central nervous system and may prevent progression of hearing loss and neuronal damage. Trials with longer course therapy and oral valganciclovir are in progress.

Infection can also be acquired around the time of delivery, and postnatally through blood transfusion or ingestion of CMV-infected breast milk. These infections generally cause no symptoms or sequelae although hepatitis, pneumonia, and neurologic illness may occur in compromised seronegative premature infants. Transfusion risk can be minimized by using frozen, washed red blood cells; leukodepleted blood; or CMV antibody-negative donors.

2. Rubella

(See also Chapter 40)

Congenital rubella infection occurs as a result of maternal rubella infection during pregnancy. The risk of fetal infection and congenital defects is as high as 80%–85% in mothers infected during the first trimester, but after 12 weeks' gestation, the risk of congenital malformation decreases markedly. Features of congenital rubella syndrome include microcephaly and encephalitis; cardiac defects (patent ductus arteriosus and pulmonary arterial stenosis and arterial hypoplasia); cataracts, retinopathy, and microphthalmia; growth restriction, hepatosplenomegaly, thrombocytopenia, and purpura; and deafness. Affected infants can be asymptomatic at birth but develop clinical sequelae during the first year of life as the viral infection is persistent due to an inadequate immune response. The diagnosis should be suspected in cases of a characteristic clinical illness in the mother (rash, adenopathy, and arthritis) confirmed by an increase in serum rubella-specific IgM or culture of pharyngeal secretions in the infant. Congenital rubella is now rare in industrialized countries because of widespread immunization, but is still possible due to the prevalence of unimmunized individuals in the population and widespread travel.

3. Varicella

Congenital varicella syndrome is rare (1%–2% after maternal varicella infection acquired during the first 20 weeks of pregnancy) and may include limb hypoplasia, cutaneous scars, microcephaly, cortical atrophy, chorioretinitis, and cataracts. Perinatal exposure (5 days before to 2 days after delivery) can cause severe to fatal disseminated varicella in the infant. If maternal varicella infection develops within this perinatal risk period, the newborn should receive varicella-zoster immune globulin. If varicella immune globulin is not available, IVIG can be used instead. If this has not been done, subsequent illness can be treated with IV acyclovir.

Hospitalized premature infants of at least 28 weeks' gestation whose mothers have no history of chickenpox—and all hospitalized infants younger than 28 weeks' gestational age—should receive varicella immune globulin following any postnatal exposure.

4. Toxoplasmosis

(See also Chapter 43)

Toxoplasmosis is caused by the protozoan Toxoplasma gondii. Maternal infection occurs in 0.1%–0.5% of pregnancies and is usually asymptomatic; it is estimated that between 1 in 1000 and 1 in 10,000 infants are infected, 70%–90% initially asymptomatic. These children may develop mental retardation, visual impairment and learning disabilities within months to years. The sources of infection include exposure to cat feces and ingestion of raw or undercooked meat. Although the risk of transmission increases to 90% near term, fetal damage is most likely to occur when maternal infection occurs in the second to sixth month of gestation.

Clinical findings may include growth restriction, chorioretinitis, seizures, jaundice, hydrocephalus, microcephaly, intracranial calcifications, hepatosplenomegaly, adenopathy, cataracts, maculopapular rash, thrombocytopenia, and pneumonia. The serologic diagnosis is based on a positive toxoplasma-specific IgA, IgE, or IgM in the first 6 months of life, a rise in serial IgG levels compared to the mother's, or a persistent IgG beyond 12 months. Infants with suspected infection should have eye and auditory examinations and a CT scan of the brain. Organism isolation from placenta or cord blood and PCR tests on amniotic fluid or CSF are also available for diagnosis.
Spiramycin (an investigational drug in the United States) treatment of primary maternal infection is used to try to reduce transmission to the fetus. Neonatal treatment using pyrimethamine and sulfadiazine with folic acid can improve long-term outcome.

5. Parvovirus B19 Infection

Parvovirus B19 is a small, nonenveloped, single-stranded DNA virus that causes erythema infectiosum (fifth disease) in children, with a peak incidence at ages 6–7 years. Transmission to the mother is primarily by respiratory secretions. The virus replicates initially in erythroid progenitor cells and induces cell-cycle arrest, resulting in severe anemia, myocarditis, nonimmune hydrops, or fetal death in approximately 3%–6% of fetuses infected during pregnancy. Resolution of the hydrops may occur in utero, either spontaneously or after fetal transfusion. Mothers who have been exposed may have specific serologic testing, and serial ultrasound, Doppler examinations, and percutaneous umbilical cord blood sampling of the fetus to assess for anemia. If the fetus survives, the long-term outcome is good with no late effects from the infection.

6. Congenital Syphilis

(See also Chapter 42)

Active primary and secondary maternal syphilis leads to transplacental passage of Treponema pallidum to the fetus in nearly 100% of affected pregnancies while latent maternal infection leads to transplacental infection of the fetus in 40% of cases, and late maternal infection in 10%. Fetal infection is rare before 18 weeks' gestation. Fetal infection can result in stillbirth or prematurity. Findings of early congenital syphilis (presentation before age 2 years) include mucocutaneous lesions, lymphadenopathy, hepatosplenomegaly, bony changes, and hydrops, although newborn infants are often asymptomatic. Late manifestations (after 2 years of age) in untreated infants involve the central nervous system, bones and joints, teeth, eyes and skin. An infant should be evaluated for congenital syphilis if he or she has proven or probable congenital syphilis, defined as a suggestive examination, serum quantitative nontreponemal titer more than fourfold the mother's, positive darkfield exam of body fluids, or birth to a mother with positive nontreponemal tests confirmed by a positive treponemal test but without documented adequate treatment (parenteral penicillin G), including the expected fourfold decrease in nontreponemal antibody titer. Infants of mothers treated less than 1 month before delivery also require evaluation. Evaluation should include physical examination; a quantitative nontreponemal serologic test for syphilis; CBC; CSF examination for cell count, protein, and Venereal Disease Research Laboratory (VDRL) testing; and long bone radiographs. Guidelines for evaluation and therapy are presented in Figure 2–15.

Figure 2–15.

Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis.
(Reproduced, with permission, from Pickering LK et al: Red Book 2012 Report of the Committee on Infectious Diseases, AAP, Elk Grove Village, Ill; 2012.)


PERINATALLY ACQUIRED INFECTIONS

1. Herpes Simplex
Herpes simplex virus (HSV) infection is usually acquired at birth during transit through an infected birth canal. The mother may have either primary or reactivated secondary infection. Primary maternal infection, because of the high titer of organisms and the absence of antibodies, poses the greatest risk to the infant. The risk of neonatal infection with vaginal delivery in this setting is 25%–60%. Seventy percent of mothers with primary herpes at the time of delivery are asymptomatic. The risk to an infant born to a mother with recurrent herpes simplex is much lower (<2%). Time of presentation of localized (skin, eye, or mouth) or disseminated disease (pneumonia, shock, or hepatitis) in the infant is usually 5–14 days of age. CNS disease usually presents later, at 14–28 days with lethargy, fever, and seizures. In rare cases, presentation is as early as day 1 of life, suggesting in-utero infection. In about 45% of patients, localized skin, eye, and mouth disease is the first indication of infection. Another 30% present with CNS disease, whereas the remaining 25% have disseminated or multiorgan disease indistinguishable from bacterial sepsis. Herpes infection should be considered in neonates with sepsis syndrome, negative bacteriologic culture results, and severe liver dysfunction or coagulopathy. HSV also should be considered as a causative agent in neonates with fever, irritability, and abnormal CSF findings, especially in the presence of seizures. Viral culture from vesicles, usually positive in 24–72 hours, makes the definitive diagnosis. HSV PCR can assist in diagnosis but may be falsely negative in the CSF early in the course. If a CSF PCR performed shortly after the onset of symptoms is negative, it should be repeated after several days if HSV disease is considered a strong possibility.

**Acyclovir** (60 mg/kg/d divided q8h) is the drug of choice for neonatal herpes infection. Localized disease is treated for 14 days, and a 21-day course is used for disseminated or CNS disease. A repeat spinal tap should be done at the end of treatment for CNS disease to be sure the PCR is negative prior to discontinuing therapy. Treatment improves survival of neonates with CNS and disseminated disease and prevents the spread of localized disease. Prevention is possible by not allowing delivery through an infected birth canal (eg, by cesarean section within 6 hours after rupture of the membranes in the presence of known infection). However, antepartum cervical cultures are poor predictors of the presence of virus at the time of delivery. Furthermore, given the low incidence of infection in the newborn from recurrent maternal infection, cesarean delivery is not indicated for asymptomatic mothers with a history of recurrent herpes. Cesarean deliveries are performed in mothers with active lesions (either primary or recurrent) at the time of delivery.

Infants born to mothers with a history of genital HSV infection but no active lesions at delivery can be observed closely after birth and do not need to be isolated. Cultures should be obtained and acyclovir treatment initiated only for clinical signs of herpes virus infection. In infants born to mothers with a history of genital HSV infection and active lesions at delivery—regardless of the route of delivery—cultures of the eye, oropharynx, nasopharynx, and rectum and blood HSV PCR should be performed 12–24 hours after delivery, and the infant should be in contact isolation or with the mother. If the infant is colonized (positive cultures or PCR) or if symptoms consistent with herpes infection develop, additional evaluation (CSF examination and HSV PCR and serum ALT) should be performed and treatment with acyclovir should be started (to be administered for 10 days if no other evidence of disease identified; treatment for 14–21 days if other evidence of disease identified). In infants born to mothers who lack a history of genital HSV but who have active lesions at time of delivery (vaginal or cesarean), infant specimens including HSV surface cultures, blood and CSF HSV PCR, CSF cell count, and serum ALT should be obtained and IV acyclovir (60 mg/kg/d) should be initiated. If feasible, typing of virus from maternal lesions and determination of maternal type-specific serology for HSV-1 and HSV-2 antibodies should be performed. If these studies indicate that maternal infection actually represents recurrent infection, acyclovir may be stopped if neonatal virology studies are negative; if neonatal virology studies are positive, treatment should be continued as for infected infants born to mothers with known history of recurrent infection. If maternal evaluation confirms that maternal infection is not due to recurrent genital HSV infection, acyclovir should be administered for 10 days even in infants with negative studies to decrease the risk of invasive infection. Infants with abnormal evaluations and/or who develop symptomatic disease should be treated for 14–21 days of IV acyclovir. A repeat spinal tap should be done at the end of treatment for CNS disease to be sure the PCR is negative prior to discontinuing therapy. The major problem facing perinatologists is the high percentage of asymptomatic primary maternal infection and, therefore, unrecognized, high-risk neonatal exposures.

The prognosis is good for localized skin and mucosal disease that does not progress, although skin recurrences are common. The mortality rate for disseminated herpes is high (approximately 30%) even with treatment, with significant morbidity among survivors of both disseminated (20%) and CNS (80%) infections despite treatment. Delay in initiation of acyclovir treatment is associated with worse long-term outcome in infants with HSV disease. Cutaneous recurrences are common following all types of neonatal HSV disease, and examination of the CSF should be considered with skin recurrences. Infants who had neonatal HSV disease should receive long term suppressive oral acyclovir for 6 months after completion of intravenous treatment.

**2. Hepatitis B & C**
Infants become infected with hepatitis B at the time of birth; intrauterine transmission is rare. Clinical illness is rare in the neonatal period, but infants born to positive mothers are at risk of becoming chronic hepatitis B surface antigen (HBsAg) carriers and developing chronic active hepatitis, and even hepatocellular carcinoma. The presence of HBsAg should be determined in all pregnant women. If the result is positive, the infant should receive hepatitis B immune globulin (HBIG) and hepatitis B vaccine as soon as possible after birth, followed by two subsequent vaccine doses at 1 and 6 months of age. If HBsAg has not been tested prior to birth in a mother at risk, the test should be run after delivery and hepatitis B vaccine given within 12 hours after birth. If the mother is subsequently found to be positive, HBIG should be given as soon as possible (preferably within 48 hours, but not later than 1 week after birth). Subsequent vaccine doses should be given at 1 and 6 months of age. In premature infants born to HBsAg-positive mothers, vaccine and HBIG should be given at birth, but a three-vaccine hepatitis B series should be given beginning at 1 month of age.

Perinatal transmission of hepatitis C occurs in about 5% of infants born to mothers who carry the virus; maternal coinfection with HIV increases the risk of transmission. At present, no prevention strategies exist. Serum antibody to hepatitis C and hepatitis C RNA have been detected in colostrum, but the risk of hepatitis C transmission is similar in breast-fed and bottle-fed infants. Up to 12 months of age, the only reliable screen for hepatitis C infection is PCR. After that time, the presence of hepatitis C antibodies in the infant strongly suggests that infection has occurred.

3. Enterovirus Infection

Enterovirus infections occur most frequently in the late summer and early fall. Infection is usually acquired in the perinatal period. There is often a history of maternal fever, diarrhea, and/or rash in the week prior to delivery. The illness appears in the infant in the first 2 weeks of life and is most commonly characterized by fever, lethargy, irritability, diarrhea, and/or rash. More severe forms occasionally occur, especially if infection occurs before 1 week of age, including meningoencephalitis, myocarditis, hepatitis, pneumonia, shock, and disseminated intravascular coagulation. Diagnosis is best confirmed by PCR.

No therapy has proven efficacy. The prognosis is good in most cases, except those with severe hepatitis, myocarditis, or disseminated disease, which carry high mortality rates.

4. HIV Infection

(See also Chapter 41)

HIV can be acquired in utero or at the time of delivery, or can be transmitted postpartum via breast milk. Testing for HIV should be performed in all pregnant women. Without treatment, transmission of virus occurs in 13%–39% of births to infected mothers, mostly at the time of delivery. Treating the mother with zidovudine therapy, starting as early as 14 weeks' gestation and intrapartum, and the infant for the first 6 weeks of life (zidovudine beginning within 12 hours of birth) decreases vertical transmission to 7%. Shorter courses of zidovudine and cesarean delivery before the onset of labor or rupture of membranes are also associated with decreased disease transmission. The combination of zidovudine treatment, elective cesarean delivery, and avoidance of breast feeding can lower transmission to 1%–2%. Treatment of the mother with highly active antiretroviral therapy during pregnancy coupled with intrapartum and neonatal prophylaxis further reduces the risk of ante- and intrapartum transmission to < 1%. Current guidelines for antiretroviral drugs in pregnant HIV-infected women are similar to those for nonpregnant patients (ie, highly active antiretroviral combination therapy). In newborns whose mothers did not receive highly active combination therapy, prophylaxis with a 2 or 3 drug regimen is superior to zidovudine alone for the prevention of intrapartum transmission. In cases of unknown HIV status at presentation in labor, rapid HIV testing and intrapartum treatment if positive should be offered. The risk of transmission is increased in mothers with advanced disease, high viral loads, low CD4 counts, and intrapartum events such as chorioamnionitis and prolonged membrane rupture that increase exposure of the fetus to maternal blood.

Newborns with congenitally acquired HIV are usually asymptomatic. Infants of HIV-infected women should be tested by HIV DNA (or RNA) PCR at less than 48 hours, at 2 weeks, at 1–2 months, and at 2–4 months. If an infant aged 4 months has a negative PCR result, infection can be reasonably excluded. HIV-positive mothers should be counseled not to breastfeed their infants if safe feeding alternatives are available.


HEMATOLOGIC DISORDERS IN THE NEWBORN INFANT

BLEEDING DISORDERS

Bleeding in the newborn infant may result from inherited clotting deficiencies (eg, factor VIII deficiency) or acquired disorders—hemorrhagic disease of the newborn (vitamin K deficiency), disseminated intravascular coagulation, liver failure, and isolated thrombocytopenia.

1. Vitamin K Deficiency Bleeding of the Newborn

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Frequently exclusively breast fed, otherwise clinically well infant.
- Bleeding from mucous membranes, GI tract, skin, or internal (intracranial).
- Prolonged prothrombin time (PT), relatively normal partial thromboplastin time (PTT), normal fibrinogen and platelet count.

Bleeding is caused by the deficiency of the vitamin K–dependent clotting factors (II, VII, IX, and X). Bleeding occurs in 0.25%–1.7% of newborns who do not receive vitamin K prophylaxis after birth, generally in the first 5 days to 2 weeks in an otherwise well infant. There is an increased risk in infants of mothers receiving therapy with anticonvulsants that interfere with vitamin K metabolism. Early vitamin K deficiency bleeding (0–2 weeks) can be prevented by either parenteral or oral vitamin K administration, whereas late disease (onset 2 weeks to 6 months) is most effectively prevented by administering parenteral vitamin K. Sites of ecchymoses and surface bleeding include the GI tract, umbilical cord, circumcision site, and nose, although devastating intracranial hemorrhage can occur. Bleeding from vitamin K deficiency is more likely to occur in exclusively breast-fed infants because of very low amounts of vitamin K in breast milk and slower and more restricted intestinal bacterial colonization. Differential diagnosis includes disseminated intravascular coagulation and hepatic failure (Table 2–21).

Table 2–21. Features of infants bleeding from vitamin K deficiency (VKDB), disseminated intravascular coagulation (DIC), or liver failure.

<table>
<thead>
<tr>
<th>VKDB</th>
<th>DIC</th>
<th>Liver Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Well infant; no prophylactic vitamin K
GI tract, umbilical cord, circumcision, nose
2–3 d to 2 wk
Normal
Prolonged
Normal or prolonged

Sick infant; hypoxia, sepsis, etc
Generalized
Any time
Decreased
Prolonged

Sick infant; hepatitis, inborn errors of metabolism, shock liver
Generalized
Any time
Normal or decreased
Prolonged

http://accesspediatrics.mhmedical.com/content.aspx?bookid=1016&sectionid=...
2. Thrombocytopenia

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**

- Generalized petechiae; oozing at cord or puncture sites.
- Thrombocytopenia, often marked (platelets < 10,000–20,000/mL).
- In an otherwise well infant, suspect isoimmune thrombocytopenia.
- In a sick or asphyxiated infant, suspect disseminated intravascular coagulation.

Infants with thrombocytopenia have generalized petechiae (not just on the presenting part) and platelet counts less than 150,000/mL (usually < 50,000/mL; may be < 10,000/mL). Neonatal thrombocytopenia can be isolated in a seemingly well infant or may occur in association with a deficiency of other clotting factors in a sick infant. The differential diagnosis for thrombocytopenia is presented in Table 2–22. Treatment of neonatal thrombocytopenia is transfusion of platelets (10 mL/kg of platelets increases the platelet count by approximately 70,000/mL). Indications for transfusion in the full-term infant are clinical bleeding or a total platelet count less than 10,000–20,000/mL. In the preterm infant at risk for intraventricular hemorrhage, transfusion is indicated for counts less than 40,000–50,000/mL.

Table 2–22. Differential diagnosis of neonatal thrombocytopenia.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune</td>
<td></td>
</tr>
<tr>
<td>Passively acquired antibody; idiopathic thrombocytopenic purpura, systemic lupus erythematosus, drug-induced</td>
<td>Proper history, maternal thrombocytopenia</td>
</tr>
<tr>
<td>Isoimmune sensitization to HPA-1a antigen</td>
<td>No rise in platelet count from random donor platelet transfusion. Positive antiplatelet antibodies in baby’s serum, sustained rise in platelets by transfusion of mother’s platelets</td>
</tr>
<tr>
<td>Infections</td>
<td>Sick infants with other signs consistent with infection</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Congenital viral infections</td>
<td></td>
</tr>
<tr>
<td>Syndromes</td>
<td></td>
</tr>
<tr>
<td>Absent radii</td>
<td>Congenital anomalies, associated pancytopenia</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td></td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>Sick infants, abnormalities of clotting factors</td>
</tr>
<tr>
<td>Giant hemangioma</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Hyperviscous infants, vascular catheters</td>
</tr>
<tr>
<td>High-risk infant with respiratory distress syndrome, pulmonary hypertension, etc</td>
<td>Isolated decrease in platelets is not uncommon in sick infants even in the absence of DIC (localized trapping)</td>
</tr>
<tr>
<td>HPA, human platelet antigen.</td>
<td></td>
</tr>
</tbody>
</table>

Isoimmune (alloimmune) thrombocytopenia is analogous to Rh-isoimmunization, with a human platelet antigen [HPA]-1a (in 80%) or HPA-5b (in 15%)—negative mother and an HPA-1a— or HPA-5b—positive fetus. Transplacental passage of IgG antibody leads to platelet destruction. If platelet transfusion is required for acute bleeding, washed maternal platelets may be the most readily available antigen-negative platelet source, because 98% of the general population will also be HPA-1a— or HPA-5b—negative.
HPA-5b–positive. Treatment with IVIG infusion, 1 g/kg/d for 2–3 days, until the platelet count has doubled or is over 50,000/mL, is potentially beneficial. Twenty to thirty percent of infants with isoimmune thrombocytopenia will experience intracranial hemorrhage, half of them before birth. Antenatal therapy of the mother with IVIG with or without steroids may reduce this risk.

Infants born to mothers with idiopathic thrombocytopenic purpura are at low risk for serious hemorrhage despite the thrombocytopenia, and treatment is usually unnecessary. If bleeding does occur, IVIG can be used.

ANEMIA

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Hematocrit < 40% at term birth.
- Acute blood loss—signs of hypovolemia, normal reticulocyte count.
- Chronic blood loss—pallor without hypovolemia, elevated reticulocyte count.
- Hemolytic anemia—accompanied by excessive hyperbilirubinemia.

The newborn infant with anemia from acute blood loss presents with signs of hypovolemia (tachycardia, poor perfusion, and hypotension), with an initially normal hematocrit that falls after volume replacement. Anemia from chronic blood loss is evidenced by hypovolemia with signs of hypovolemia, with an initially low hematocrit and reticulocytosis.

Anemia can be caused by hemorrhage, hemolysis, or failure to produce red blood cells. Anemia occurring in the first 24–48 hours of life is the result of hemorrhage or hemolysis. Hemorrhage can occur in utero (fetoplacental, fetomaternal, or twin-to-twin), perinatally (cord rupture, placenta previa, placental abruption, or incision through the placenta at cesarean section), or internally (intracranial hemorrhage, cephalohematoma, or ruptured liver or spleen). Hemolysis is caused by blood group incompatibilities, enzyme or membrane abnormalities, infection, and disseminated intravascular coagulation, and is accompanied by significant hyperbilirubinemia.

Initial evaluation should include a review of the perinatal history, assessment of the infant's volume status, and a complete physical examination. A Kleihauer-Betke test for fetal cells in the mother's circulation should be done. A CBC, blood smear, reticulocyte count, and direct and indirect Coombs tests should be performed. This simple evaluation should suggest a diagnosis in most infants. Most infants tolerate anemia quite well due to the increased oxygen availability in the extrauterine environment; however, treatment with erythropoietin or transfusion might be needed if the infant fails to thrive or develops signs of cardiopulmonary compromise. Additionally, if blood loss is the cause of the anemia, early supplementation with iron will be needed. It is important to remember that hemolysis related to blood group incompatibility can continue for weeks after birth. Serial hematocrits should be followed, because late transfusion may be needed.

POLYCYTHEMIA

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Hematocrit > 65% (venous) at term.
- Plethora, tachypnea, retractions.
- Hypoglycemia, irritability, lethargy, poor feeding.

Polycythemia in the newborn is manifested by plethora, cyanosis, respiratory distress with tachypnea and oxygen need, hypoglycemia, poor feeding, emesis, irritability, and lethargy. Hyperbilirubinemia is expected. The consequence of polycythemia is hyperviscosity with decreased perfusion of the capillary beds. Clinical symptomatology can affect several organ systems (Table 2–23). Renal vein, other deep vein, or artery thrombosis is a severe complication. Screening can be done by measuring a capillary (heelstick) hematocrit. If the value is greater than 68%, a peripheral venous hematocrit should be measured. Values greater than 65% should be considered consistent with hyperviscosity.

Table 2–23. Organ-related symptoms of hyperviscosity.

<table>
<thead>
<tr>
<th>Central nervous system</th>
<th>Irritability, jitteriness, seizures, lethargy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary</td>
<td>Respiratory distress secondary to congestive heart failure, or persistent pulmonary hypertension</td>
</tr>
</tbody>
</table>
Central nervous system
Gastrointestinal Irritability, jitteriness, seizures, lethargy
Renal Decreased urinary output, renal vein thrombosis
Metabolic Hypoglycemia
Hematologic Hyperbilirubinemia, thrombocytopenia

Elevated hematocrits occur in 2%–5% of live births. Delayed cord clamping is the most common cause of benign neonatal polycythemia. Although 50% of polycythemic infants are AGA, the prevalence of polycythemia is greater in the SGA and LGA populations. Other causes of increased hematocrit include (1) twin-twin transfusion, (2) maternal-fetal transfusion, and (3) chronic intrauterine hypoxia (SGA infants, and LGA infants of diabetic mothers).

Treatment is recommended for symptomatic infants. Treatment for asymptomatic infants based strictly on hematocrit is not indicated as there is no proven long term benefit. Treatment for symptomatic infants is isovolemic partial exchange transfusion with normal saline, effectively decreasing the hematocrit. The amount to exchange (in milliliters) is calculated using the following formula:

\[
\text{Number of milliliters to exchange} = \left( \frac{\text{PVH} - \text{DH}}{\text{PVH}} \right) \times \text{BV (mL/kg)} \times \text{Wt (kg)}
\]

where PVH is peripheral venous hematocrit, DH is desired hematocrit, BV is blood volume in mL/kg, and Wt is weight in kilograms.

Blood is withdrawn at a steady rate from an umbilical venous line while the replacement solution is infused at the same rate through a peripheral IV line over 15–30 minutes. The desired hematocrit value is 50%–55%; the assumed blood volume is 80 mL/kg.


**RENNAL DISORDERS IN THE NEWBORN INFANT**

(See also Chapter 24)

Renal function depends on postmenstrual age. The glomerular filtration rate is 20 mL/min/1.73 m\(^2\) in full-term neonates and 10–13 mL/min/1.73 m\(^2\) in infants born at 28–30 weeks' gestation. The speed of maturation after birth also depends on postmenstrual age. Creatinine can be used as a clinical marker of glomerular filtration rate. Values in the first month of life are shown in Table 2–24. Creatinine at birth reflects the maternal level and should decrease slowly over the first 3–4 weeks. An increasing serum creatinine is never normal.

Table 2-24. Normal values of serum creatinine (mg/dL).

<table>
<thead>
<tr>
<th>Gestational Age at Birth (wk)</th>
<th>Postnatal Age (d)</th>
<th>0–2</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28</td>
<td></td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>29–32</td>
<td></td>
<td>1.1</td>
<td>0.6</td>
</tr>
<tr>
<td>33–36</td>
<td></td>
<td>1.1</td>
<td>0.45</td>
</tr>
<tr>
<td>36–42</td>
<td></td>
<td>0.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The ability to concentrate urine and retain sodium also depends on gestational age. Infants born before 28–30 weeks' gestation are compromised in this respect and can easily become dehydrated and hyponatremic. Preterm infants also have an increased bicarbonate excretion and a low tubular maximum for glucose (approximately 120 mg/dL).

**RENAL FAILURE**

**ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES**

- **Clinical setting**—birth depression, hypovolemia, hypotension, shock.
- **Low or delayed urine output** (< 1 mL/kg/h).
- **Rising serum creatinine; hyperkalemia; metabolic acidosis; fluid overload.**

Renal failure is most commonly seen in the setting of birth asphyxia, hypovolemia, or shock from any cause. The normal rate of urine flow is 1–3 mL/kg/h. After a hypoxic or ischemic insult, acute tubular necrosis may ensue. Typically, 2–3 days of anuria or oliguria is associated with hematuria, proteinuria, and a rise in serum creatinine. The period of anuria or oliguria is followed by a period of polyuria and then gradual recovery. During the polyuric phase, excessive urine sodium and bicarbonate losses may be seen.

The initial management is restoration of the infant's intravascular volume status. Thereafter, restriction of fluids to insensible water loss (60 mL/kg/d) without added electrolytes, plus milliliter-for-milliliter urine replacement, should be instituted. Serum and urine electrolytes and body weights should be followed frequently. These measures should be continued through the polyuric phase. After urine output has been reestablished, urine replacement should be decreased to between 0.5 and 0.75 mL for each milliliter of urine output to see if the infant has regained normal function. If that is the case, the infant can be returned to maintenance fluids.

Finally, many of these infants experience fluid overload and should be allowed to lose enough water through urination to return to birth weight. Hyperkalemia, which may become life-threatening, may occur if urine output is low despite the lack of added IV potassium. If the serum potassium reaches 7 mEq/L, therapy should be started with glucose and insulin infusion, giving 1 unit of insulin for every 3 g of glucose administered, in addition to binding resins per rectum. Calcium chloride (20 mg/kg bolus), inhaled albuterol, and correction of metabolic acidosis with bicarbonate are also helpful in the acute management of arrhythmias resulting from hyperkalemia.

Peritoneal dialysis is occasionally needed for the management of neonatal acute renal failure and for removal of waste products and excess fluid. Hemodialysis, although possible, is difficult due to the small blood volume of the infant and problems with vascular access. Although most acute renal failure in the newborn resolves, ischemic injury severe enough to result in acute cortical necrosis and chronic renal failure can occur. Such infants are also at risk of developing hypertension.

**URINARY TRACT ANOMALIES**

Abdominal masses in the newborn are most frequently caused by renal enlargement. Most common is a multicystic or dysplastic kidney; congenital hydronephrosis is second in frequency. Chromosomal abnormalities and syndromes with multiple anomalies frequently include renal abnormalities. An ultrasound examination is the first step in diagnosis. In pregnancies complicated by oligohydramnios, renal agenesis or obstruction secondary to posterior urethral valves should be considered.

Only bilateral disease or disease in a solitary kidney is associated with oligohydramnios, significant morbidity, and death. Such infants will generally also have pulmonary hypoplasia, and present with pulmonary rather than renal insufficiency.

Ultrasonography identifies many infants with renal anomalies (most often hydronephrosis) prior to birth. Postnatal evaluation of infants with hydronephrosis should include renal ultrasound and a voiding cystourethrogram at about 1 week of age, depending on the severity of the antenatal findings. Earlier postnatal ultrasound might underestimate the severity of the hydronephrosis due to low glomerular filtration rates in the first days of life, although cases in which oligohydramnios or severe renal abnormality are suspected will be accurately diagnosed even on the first day of life. Until the presence and severity of vesicoureteral reflux is evaluated, some experts recommend antibiotic prophylaxis with low-dose penicillin or amoxicillin. However, the necessity for prophylaxis is a controversial issue.

**RENAL VEIN THROMBOSIS**
ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

• History of IDM, birth depression, dehydration.

• Hematuria, oliguria.

• Thrombocytopenia, polycythemia.

• Renal enlargement on examination.

Renal vein thrombosis occurs most often in dehydrated polycythemic newborns. At particular risk is the IDM with polycythemia. If fetal distress is superimposed on polycythemia and dehydration, prompt reduction in blood viscosity is indicated. Thrombosis is unilateral in 70%, usually begins in intrarenal venules, and can extend into larger veins and the vena cava. Hematuria, oliguria, thrombocytopenia, and possibly an enlarged kidney raise suspicion for this diagnosis. With bilateral renal vein thrombosis, anuria ensues. Diagnosis can be confirmed with an ultrasound examination that includes Doppler flow studies of the kidneys. Treatment involves correcting the predisposing condition; systemic heparinization or the use of thrombolytics for this condition is controversial. Prognosis for a full recovery is uncertain. Many infants will develop significant atrophy of the affected kidney, and some develop systemic hypertension. All require careful follow-up.


NEUROLOGIC PROBLEMS IN THE NEWBORN INFANT

SEIZURES

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

• Usual onset at 12–48 hours.

• Seizure types include subtle (characterized by variable findings), tonic, and multifocal clonic.

• Most common causes include hypoxic-ischemic encephalopathy, intracranial bleeds, and infection.

Newborns rarely have well-organized tonic-clonic seizures because of their incomplete cortical organization and a preponderance of inhibitory synapses. The most common type of seizure is characterized by a constellation of findings, including horizontal deviation of the eyes with or without jerking; eyelid blinking or fluttering; sucking, smacking, drooling, and other oral-buccal movements; swimming or bicycling movements; and apneic spells. Strictly tonic or multifocal clonic episodes are also seen.

Clinical Findings

The differential diagnosis of neonatal seizures is presented in Table 2–25. Most neonatal seizures occur between 12 and 48 hours of age. Later-onset seizures suggest meningitis, benign familial seizures, or hypocalcemia. Information regarding antenatal drug use, the presence of birth asphyxia or trauma, and family history (regarding inherited disorders) should be obtained. Physical examination focuses on neurologic features, other signs of drug withdrawal, concurrent signs of infection, dysmorphic features, and intrauterine growth. Screening workup should include blood glucose, ionized calcium, and electrolytes in all cases. Further workup depends on diagnoses suggested by the history and physical examination. In most cases, a lumbar puncture should be done. Hemorrhages, perinatal stroke, and structural disease of the CNS can be addressed with ultrasound, CT, and MRI scans. Metabolic workup should be pursued when appropriate. EEG should be
done; the presence of spike discharges must be noted and the background wave pattern evaluated. At times correlation between EEG changes and clinical seizure activity is absent making a prolonged EEG with video monitoring a useful tool.

Table 2–25. Differential diagnosis of neonatal seizures.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td>Most common cause (60%), onset in first 24 h</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Up to 15% of cases, periventricular/intraventricular hemorrhage, subdural or subarachnoid bleeding, stroke</td>
</tr>
<tr>
<td>Infection</td>
<td>12% of cases</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Small for gestational age, IDM</td>
</tr>
<tr>
<td>Hypocalcemia, hypomagnesemia</td>
<td>Infant of low birth weight, IDM</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Rare, seen with SIADH</td>
</tr>
<tr>
<td>Disorders of amino and organic acid metabolism, hyperammonemia</td>
<td>Associated acidosis, altered level of consciousness</td>
</tr>
<tr>
<td>Pyridoxine dependency</td>
<td>Seizures refractory to routine therapy; cessation of seizures after administration of pyridoxine</td>
</tr>
<tr>
<td>Developmental defects</td>
<td>Other anomalies, chromosomal syndromes</td>
</tr>
<tr>
<td>Drug withdrawal</td>
<td></td>
</tr>
<tr>
<td>No cause found</td>
<td>10% of cases</td>
</tr>
<tr>
<td>Benign familial neonatal seizures</td>
<td></td>
</tr>
</tbody>
</table>

IDM, infant of a diabetic mother; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Treatment

Adequate ventilation and perfusion should be ensured. Hypoglycemia should be treated immediately with a 2-mL/kg infusion of D$_{10}$W followed by 6 mg/kg/min of D$_{10}$W (100 mL/kg/d). Other treatments such as calcium or magnesium infusion and antibiotics are indicated to treat hypocalcemia, hypomagnesemia, and suspected infection. Electrolyte abnormalities should be corrected. Phenobarbital (20 mg/kg IV) should be administered to stop seizures. Supplemental doses of 5 mg/kg can be used if seizures persist, up to a total of 40 mg/kg. In most cases, phenobarbital controls seizures.

If seizures continue, therapy with fosphenytoin, levetiracetam, or lorazepam may be indicated. For refractory seizures, a trial of pyridoxine is indicated.

Prognosis

Outcome is related to the underlying cause of the seizure. The outcomes for hypoxic-ischemic encephalopathy and intraventricular hemorrhage have been discussed earlier in this chapter. In these settings, seizures that are difficult to control carry a poor prognosis for normal development. Seizures resulting from hypoglycemia, infection of the CNS, some inborn errors of metabolism, and developmental defects also have a high rate of poor outcome. Seizures caused by hypocalcemia or isolated subarachnoid hemorrhage generally resolve without sequelae.

HYPOTONIA

One should be alert to the diagnosis of congenital hypotonia when a mother has polyhydramnios and a history of poor fetal movement. The newborn may present with poor respiratory effort and birth asphyxia. For a discussion of causes and evaluation, see Chapter 25.

INTRACRANIAL HEMORRHAGE

1. Subdural Hemorrhage

Subdural hemorrhage is related to birth trauma; the bleeding is caused by tears in the veins that bridge the subdural space. Prospective studies relating incidence to specific obstetric complications are not available.
Most commonly, subdural bleeding is from ruptured superficial cerebral veins, with blood over the cerebral convexities. These hemorrhages can be asymptomatic or may cause seizures, with onset on days 2–3 of life, vomiting, irritability, and lethargy. Associated findings include retinal hemorrhages and a full fontanelle. The diagnosis is confirmed by CT scan.

Specific treatment entailing needle drainage of the subdural space is rarely necessary. Most infants survive; 75% are normal on follow-up.

1Intraventricular hemorrhage is discussed earlier, in the section on The Preterm Infant.

2. Primary Subarachnoid Hemorrhage

Primary subarachnoid hemorrhage is the most common type of neonatal intracranial hemorrhage. In the full-term infant, it can be related to trauma of delivery, whereas subarachnoid hemorrhage in the preterm infant can be seen in association with germinal matrix hemorrhage. Clinically, these hemorrhages can be asymptomatic or can present with seizures and irritability on day 2, or rarely, a massive hemorrhage with hemodynamic instability. The seizures associated with subarachnoid hemorrhage are very characteristic—usually brief, with a normal examination interictally. Diagnosis can be suspected on lumbar puncture and confirmed with CT scan. Long-term follow-up is uniformly good.

3. Neonatal Stroke

Focal cerebral ischemic injury can occur in the context of intraventricular hemorrhage in the premature infant and hypoxic-ischemic encephalopathy. Neonatal stroke has also been described in the context of underlying disorders of thrombolysis, maternal drug use (cocaine), a history of infertility, preeclampsia, prolonged membrane rupture, and chorioamnionitis. In some cases, the origin is unclear. The injury often occurs antenatally. The most common clinical presentation of an isolated cerebral infarct is with seizures, and diagnosis can be confirmed acutely with diffusion-weighted MRI scan. The most frequently described distribution is that of the middle cerebral artery.

Treatment is directed at controlling seizures. Use of anticoagulants and thrombolytics are controversial. Long-term outcome is variable, ranging from near-normal to hemiplegias and cognitive deficits.


METABOLIC DISORDERS IN THE NEWBORN INFANT

HYPERGLYCEMIA

Hyperglycemia may develop in preterm infants, particularly those of extremely low birth weight who are also SGA. Glucose concentrations may exceed 200–250 mg/dL, particularly in the first few days of life. This transient diabetes-like syndrome usually lasts approximately 1 week.

Management may include simply reducing glucose intake while continuing to supply IV amino acids to prevent protein catabolism with resultant gluconeogenesis and worsened hyperglycemia. Intravenous insulin infusions may be needed in infants who remain hyperglycemic despite glucose infusion rates of less than 5–6 mg/kg/min, but caution should be used as hypoglycemia is a frequent complication.

2Hypoglycemia is discussed earlier, in the section on Common Problems in the Term Newborn.

HYPOCALCEMIA

(See also Chapter 34)
ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Irritability, jitteriness, seizures.
- Normal blood glucose.
- Possible dysmorphic features, congenital heart disease (DiGeorge syndrome).

Calcium concentration in the immediate newborn period decreases in all infants. The concentration in fetal plasma is higher than that of the neonate or adult. Hypocalcemia is usually defined as a total serum concentration less than 7 mg/dL (equivalent to a calcium activity of 3.5 mEq/L), although the physiologically active fraction, ionized calcium, should be measured whenever possible, and is usually normal even when total calcium is as low as 6–7 mg/dL. An ionized calcium level above 0.9 mmol/L (1.8 mEq/L; 3.6 mg/dL) is not likely to be detrimental.

Clinical Findings

The clinical signs of hypocalcemia and hypocalcemic tetany include a high-pitched cry, jitteriness, tremulousness, and seizures.

Hypocalcemia tends to occur at two different times in the neonatal period. Early-onset hypocalcemia occurs in the first 2 days of life and has been associated with prematurity, maternal diabetes, asphyxia, and rarely, maternal hypoparathyroidism. Late-onset hypocalcemia occurs at approximately 7–10 days and is observed in infants receiving modified cow's milk rather than infant formula (high phosphorus intake), in infants with hypoparathyroidism (DiGeorge syndrome, 22q11 deletion), or in infants born to mothers with severe vitamin D deficiency. Hypomagnesemia should be sought and treated in cases of hypocalcemia that are resistant to treatment.

Treatment

A. Oral Calcium Therapy

The oral administration of calcium salts, often along with vitamin D, is the preferred method of treatment for chronic forms of hypocalcemia resulting from hypoparathyroidism. (See Chapter 34.)

B. Intravenous Calcium Therapy

IV calcium therapy is usually needed for infants with symptomatic hypocalcemia or an ionized calcium level below 0.9 mmol/L. A number of precautions must be observed when calcium is given intravenously. The infusion must be given slowly so that there is no sudden increase in calcium concentration of blood entering the right atrium, which could cause severe bradycardia and even cardiac arrest. Furthermore, the infusion must be observed carefully, because an IV infiltrate containing calcium can cause full-thickness skin necrosis requiring grafting. For these reasons, IV calcium therapy should be given judiciously and through a central venous line if possible. IV administration of 10% calcium gluconate is usually given as a bolus of 100–200 mg/kg (1–2 mL/kg) over approximately 10–20 minutes, followed by a continuous infusion (0.5 –1 g/kg/d) over 1–2 days, if central venous access is available. Ten percent calcium chloride (20 mg/kg or 0.2 mL/kg per dose) may result in a larger increment in ionized calcium and greater improvement in mean arterial blood pressure in sick hypocalcemic infants and thus may have a role in the newborn. Note: Calcium salts cannot be added to IV solutions that contain sodium bicarbonate because they precipitate as calcium carbonate.

Prognosis

The prognosis is good for neonatal seizures entirely caused by hypocalcemia that is promptly treated.

INBORN ERRORS OF METABOLISM

(See also Chapter 36)

ESSENTIALS OF DIAGNOSIS & TYPICAL FEATURES

- Altered level of consciousness (poor feeding, lethargy, seizures) in a previously well-appearing infant.
- Tachypnea without hypoxemia or distress.
- Hypoglycemia, respiratory alkalosis, metabolic acidosis.
- Recurrent "sepsis" without proven infection.

Each individual inborn error of metabolism is rare, but collectively they have an incidence of 1 in 1000 live births. Expanded newborn genetic screening undoubtedly aids in the diagnosis of these disorders; however, many infants will present prior to these results being available. These diagnoses should be entertained when infants who were initially well present with sepsis-like syndromes, recurrent hypoglycemia, neurologic syndromes (seizures or altered levels of consciousness), or unexplained acidosis (suggestive of organic acidemias).

In the immediate neonatal period, urea cycle disorders present as an altered level of consciousness (coma) secondary to hyperammonemia. A clinical clue that supports this diagnosis is hyperventilation with primary respiratory alkalosis, along with a low blood urea nitrogen. The other major diagnostic category to consider consists of infants with severe and unremitting acidemia secondary to organic acidemias.


QUALITY ASSESSMENT AND IMPROVEMENT IN THE NEWBORN NURSERY AND NICU

Quality improvement initiatives are a critical element to provide the best care possible for patients and their families. This involves recognition that there is a gap between care as it is and care as it could and should be. Clinical units either individually or as part of a consortium need to identify goals for improvement and carry out changes using a plan, do, study, act (PDSA) approach to rapid cycle improvements in care. This involves planning and enacting a change, studying and analyzing the data collected during the change and then acting to assess what changes are to be made for the next PDSA cycle. Individual units can benchmark their care through participation in multicenter databases such as the Vermont Oxford Network. Neonatal intensive care units from over 600 sites submit data on their care of infants born at less than 1500 g. An individual unit can track their outcomes compared to outcomes seen across the network. These data can form the framework for strategies to improve performance in areas in a unit that are below network standards. Examples of possible initiatives include lowering the incidence of central line-associated bacteremia, decreasing the incidence of ventilator-associated pneumonia or structured feeding protocols to decrease the incidence of necrotizing enterocolitis. There is currently a national collaborative through the Children's Hospitals Neonatal Consortium to reduce central line-associated blood stream infections in Children's hospitals neonatal intensive care units. This provides an example of a multicenter effort to determine best practices for line insertion and care.

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