15 Respiratory System

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Lung Development

The tracheobronchial airway system develops as a ventral outpouching of the primitive foregut, which leads to the formation of the embryonic lung bud. The lung bud subsequently divides and branches, penetrating the mesenchyma and progressing toward the periphery. Lung development is divided into five phases (*Table 15.1*). A variety of physical, hormonal, and other factors affect the pace of lung development and maturation. Normal lung growth and development requires adequate distending pressure of fetal lung fluid and normal fetal breathing movements – their absence leads to pulmonary hypoplasia. Lack of saccular development and surface area for gas exchange are the limiting factors for survival of infants born in the late cannalicular phase before 24 weeks of gestation.

Respiratory Physiology/Lung Mechanics/ Gas Exchange

Although basic principles of lung mechanics and gas exchange are similar to those of older children and adults, newborn infants present the clinician with a number of special challenges that are the consequence of their unique physiology and pathophysiology. This is especially true when they are born prematurely. The reader is referred to any of the major texts on respiratory physiology for in-depth coverage of the subject. The key concepts are briefly reviewed below.

Lung Mechanics

The lungs of preterm infants are relatively noncompliant (stiff), while the chest wall lacks rigidity. As a result of this disturbed balance between the tendency of the lungs to collapse due to elastic recoil and the rigidity of the chest wall that maintains lung expansion, the lungs come to rest at a lower functional residual capacity and the airways tend to close near the end of exhalation. Therefore, special attention needs to be paid to maintaining adequate lung volume during respiratory support of newborn infants. Differences between the shape of an adult versus newborn infant's chest put the infant at a mechanical disadvantage. The infant's thorax is more cylindrical than ellipsoid and the ribs are more horizontal, rather than oblique. Because of these anatomic differences, the intercostal muscles in infants have a shorter course and provide less mechanical advantage for elevating the ribs and increasing intrathoracic volume during inspiration. Because the insertion of the infant's diaphragm is more horizontal than in the adult, the lower ribs tend to move inward rather than upward during inspiration. The compliant chest wall exacerbates this inward deflection with inspiration. This results in inefficient respiratory effort, which may be manifested clinically by intercostal and substernal retractions associated with abdominal breathing, especially when lung compliance is decreased. Additionally, infants have low muscle mass and a low percentage of type 1 (slow twitch) muscle fibers compared to adults, making infants with respiratory distress prone to respiratory muscle fatigue and respiratory failure.

During expiration the main driving force is elastic recoil, which depends on the surface tension produced by the air–liquid interface, the elastic elements of lung tissue, and the bony development of the rib cage. Expiration is largely passive. Because the chest wall of premature infants is compliant, it offers little resistance against expansion upon inspiration and little opposition against collapse upon expiration.

The airways of the preterm infants are very small, resulting in relatively high airway resistance, especially as airway epithelium becomes injured during mechanical ventilation. Additionally, the small size of the trachea necessitates the use of narrow endotracheal tubes that add substantially to the airway resistance (recall that resistance to flow is inversely proportional to the fourth power of the radius). All of these factors confer a significant mechanical disadvantage to the respiratory mechanics of newborn and especially preterm infants, making them more vulnerable to fatigue and respiratory failure.

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Table 15.1
The phases of lung development. There is some overlap between the phases

Embryonic phase (weeks 3–6)	Development of proximal airways. The lung bud arises from the foregut 21–26 days after fertilization
Pseudoglandular phase (weeks 6–16)	Development of the first 20 generations of conducting airways. The first eight generations (the bronchi) ultimately acquire cartilaginous walls. Generations 9–20 are the nonrespiratory bronchioles. Lymph vessels and bronchial capillaries follow the airways as they grow and develop
Canalicular phase (weeks 16–26)	Respiratory bronchioles (generations 21–23) develop. The proportion of parenchymal connective tissue diminishes. Pulmonary capillaries develop
Terminal sac phase (weeks 26–36)	Rudimentary primary saccules subdivide by formation of secondary crests into smaller saccules and alveoli, greatly increasing the surface area for gas exchange. The interstitium continues to thin out, decreasing the distance for diffusion. Capillary invasion leads to an increase in alveolar–blood barrier surface area. The surfactant system develops and matures
Alveolar phase (week 36–3 years)	Saccules become alveoli due to thinning of the acinar walls and invagination of alveoli by pulmonary capillaries with secondary crest formation. The alveoli attain a polyhedral shape

Oxygenation

As in older patients, oxygenation is a function of the fraction of inspired oxygen and optimal ventilation/perfusion (V/Q) matching. Optimal V/Q ratio occurs at normal lung volume. Atelectasis results in intrapulmonary right-to-left shunting and V/Q mismatch with resulting hypoxemia. The condition can be corrected by increasing mean airway pressure (best accomplished by raising positive end-expiratory pressure = PEEP), until oxygenation improves. Overexpansion of the lungs also results in V/Q mismatch and additionally may increase pulmonary vascular resistance by compressing pulmonary capillaries and result in extrapulmonary right-to-left shunt. Both over- and under-expansion contribute to lung injury and should be avoided. Chest radiographs, though not a direct measure of lung volume, are helpful in assessing the appropriateness of lung expansion. It is important to recognize that several factors influence mean airway pressure (MAP), including positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), inspiratory:expiratory ratio, and, finally, the slope of the inspiratory waveform, which determines how rapidly the pressure limit is reached. Alteration of any of these variables will affect MAP and thus may alter lung expansion. Because, in addition to the effects of their excessively compliant chest wall, newborn infants commonly are surfactant deficient, special attention must be directed toward maintaining adequate lung expansion.

CO_2 Elimination

CO_2 elimination (ventilation) is relatively independent of oxygenation and requires a flux of fresh gas in and out of terminal respiratory units. With conventional respiratory rates, the gas moves by bulk flow or convection in the large and small airways with diffusion accounting for gas movement in the respiratory bronchioles and terminal air sacs. Bulk flow of gas is greatly influenced by the mechanical properties of the lungs: compliance, airway resistance, and time constants. Understanding the concept of time constants is important for optimal selection of respiratory rate, specifically inspiratory and expiratory time. Conceptually, time constants describe the length of time required for gas to get in and out of the lungs when a change in pressure is applied at the airway opening (three time constants are required to reach 95% equilibration of pressure). Mathematically, the following equation describes the phenomenon of time constants:

$$\text{Time constant(s)} = \text{airway resistance}\left(\text{cmH}_2\text{O} \times \text{L}^{-1} \times \text{s}\right) \times \text{lung compliance}\left(\text{L/cmH}_2\text{O}\right)$$

Because total compliance, not compliance/kg is used, time constants are also a function of subject size – as is intuitively obvious, the larger the lung is the longer it takes to get gas in and out.

The practical consequence of this relationship is that small infants with respiratory distress syndrome (i.e., low compliance, low resistance) have very short time constants and normally have rapid respiratory rates with little danger of air trapping, while larger infants with meconium aspiration or bronchopulmonary dysplasia (high airway

resistance) need slower respiratory rates and are more prone to air trapping, thus require longer expiratory times. Inspiratory times are normally shorter than expiratory times, because expiratory airway resistance is always higher, but should also be adjusted according to patient size and pathology. Typically, inspiratory to expiratory ratio of 1:2 is used, as this approximates normal breathing.

CO_2 elimination is determined by how effectively fresh gas is moved in and out of the terminal gas exchanging units. Total minute ventilation is the product of respiratory rate and tidal volume (V_T). Tidal volume is principally determined by lung compliance and pressure amplitude or ΔP (peak pressure – PEEP). In newborn respiratory support, pressure-limited ventilation has traditionally been used. In this mode, V_T is not set directly, but is a derived variable, which is indirectly controlled by adjusting ΔP and is affected by changes in lung compliance. An additional consideration is the fact that exhaled alveolar gas occupies the upper airway, endotracheal tube, and any additional apparatus such as a flow sensor at the end of each exhalation. Thus, with the next breath, at least a portion of this dead space gas flows back into the lungs, followed by fresh gas. Traditional physiology teaches that:

$$\text{Alveolar minute ventilation} = (\text{VT} - \text{dead space volume}) \times \text{respiratory rate}.$$

In practice, at the high flow rates seen in small infants with very short time constants, there appears to be considerable mixing of gases in the dead space volume, resulting in partial bypass of the anatomical and instrumental dead space.

Regulation of Respiration

Regulation of breathing is accomplished by a complex process involving the respiratory control center, peripheral and central sensors, and respiratory muscles. The respiratory control center consists of a group of neurons in the brainstem that receive and integrate the afferent information from the sensors and in turn send motor impulses to the respiratory muscles to regulate respiratory activity. The respiratory regulatory mechanism undergoes a significant maturation process during the neonatal period. The preterm infant's respiratory control center is immature, resulting in irregular respiratory pattern, periodic breathing, and apnea. Sleep states have the potential for profound influences on the control of respiration. In the older, awake individual, respiratory activity is under a significant degree of voluntary control. The degree to which this is true in the immediate neonatal period is unclear, but an infant's activity and emotional state clearly do influence the respiratory pattern.

A group of 150–200 neurons, known as the *pre-Botzinger complex* (PBC), located in the medullary region of the brainstem functions as the pacemaker for automatic respiratory activity. PBC neuron activity is modulated by afferent input from neurons located in the lower pons called the *apneustic center* (stimulatory effect) and inhibited by neurons in the upper pons, known as the *pneumotaxic center.* Thus, damage to various parts of the brain often manifests with abnormal respiratory pattern.

Central and peripheral chemoreceptors and a variety of mechanoreceptors provide feedback to the central respiratory controller. Central chemoreceptors located over a large area of the brain are bathed by the cerebrospinal fluid (CSF) and respond to changes in the H^+ concentration, i.e., pH. A decrease in pH concentration stimulates ventilatory activity, while an increase inhibits it. The CSF is separated from the blood by the blood-brain barrier, which is relatively impermeable to H^+ and HCO_3^- ions, but readily permeable to CO_2. A rise in $PaCO_2$ is quickly reflected in a similar rise in the CSF, resulting in a fall in CSF pH and stimulation of ventilation. It is important to understand that changes in $PaCO_2$ exert their influence on ventilation through changes in CSF pH. The CSF has much less CO_2 buffering capacity than blood because of a much lower protein concentration. This amplifies the response to CO_2, because the same change $PaCO_2$ in blood leads to a larger change in CSF pH. With a persistent elevation in $PaCO_2$, the pH of the CSF gradually normalizes as HCO_3^- equilibrates across the blood-brain barrier. Thus compensated respiratory acidosis is associated with a relatively normal CSF pH and therefore these infants do not increase their ventilatory response in response to these high levels of $PaCO_2$.

Peripheral chemoreceptors, located in carotid bodies just above the bifurcation of the common carotid arteries, and in the aortic bodies in the aortic arch primarily respond to changes in PaO_2 with hypoxia stimulating ventilation and hyperoxia having an inhibitory effect. Exposure to unnecessarily high FiO_2 may thus depress the respiratory response to CO_2, another of the many reasons to avoid hyperoxia. The carotid bodies also respond to pH irrespective of whether the acidosis is respiratory or metabolic. The effect of hypoxia and acidosis is synergistic, leading to a greater degree of stimulation by their combination than either one alone. Hypoxia is a more potent stimulus than alkalosis; therefore hypoxic respiratory drive usually leads to some degree of hyperventilation when hypoxemia persists.

Mechanical receptors provide additional input to the respiratory control center. *Stretch receptors* located within the airway smooth muscle are stimulated by lung inflation, decreasing the respiratory rate by inhibition of inspiratory muscle activity and an increase in expiratory time. This reflex is called the Hering–Breuer inflation reflex. Hering–Breuer deflation reflex stimulates inspiratory muscle activity in response to deflation of the lung. *Irritant receptors* in the airway mucous membranes are stimulated by particulate matter and other noxious stimuli, including cold air. So-called J receptors or juxta-capillary receptors located in the alveolar walls close to the pulmonary capillaries respond to pulmonary capillary engorgement, interstitial and alveolar wall edema by inducing shallow and rapid respirations and a sensation of dyspnea. *Muscle receptors* in the diaphragm and the intercostal muscles sense the degree of stretch of the muscle and control the strength of contraction. Activation of muscle receptors by excessive chest wall distortion occasioned by the very compliant rib cage may be partially responsible for the cessation of inspiration and apnea seen with airway obstruction in preterm infants. Important afferent input also originates in the upper airway and especially the laryngeal area. Superior laryngeal nerve afferents are connected to cardiac vagal neurons in nucleus ambiguus, or terminate in the nucleus of the solitary tract with inhibitory connections to phrenic motor neurons. Inhibition of phrenic and cardiac motor neurons with laryngeal stimulation is likely the mechanism of apnea and bradycardia associated with gastroesophageal reflux.

The response of the respiratory control center to chemoreceptor and mechanoreceptor input and the efficiency of the respiratory muscles are markedly altered in the preterm newborn infant, compared to older subjects. Unlike adults who have an immediate and sustained response to hypoxemia characterized by hyperventilation, the newborn exhibits a biphasic response. After an initial brief period of hyperventilation, the newborn exhibits hypoventilation and apnea in the face of sustained hypoxemia. The more premature the infant is, the more pronounced and earlier is the apneic response to hypoxemia. Neonates also have a decreased CO_2 responsiveness as measured by an increase in minute ventilation for a given increase in $PaCO_2$. This decreased chemoreceptor responsiveness and the paradoxical response to hypoxia is a key difference between the newborn and older subjects and a major contributor to their susceptibility to various forms of respiratory depression and apnea. Additionally, the inhibitory stimuli from the larynx of newborn infants appears to be more active than in older subjects and appears to play an important role in the genesis of neonatal apnea/bradycardia.

Sleep has a profound effect on respiratory control, decreasing central responsiveness to CO_2. Rapid eye movement (REM) sleep, the predominant sleep pattern in premature babies that accounts for more than 60% of the total, leads to suppression of postural muscle tone and lack of spontaneous movements. The depression of muscle tone during REM sleep has two important effects. Increased compliance of the chest wall leads to less efficient respiration and may lead to loss of lung volume (microatelectasis) with resulting hypoxemia. Relaxation of upper airway muscles cause airway obstruction and contribute to obstructive apnea.

Apnea of Prematurity

A striking feature of the resting breathing pattern of the premature newborn is its irregularity, characterized by large breath-to-breath variability accompanied by long stretches of periodic breathing and brief apnea. Clinically important apnea of prematurity is almost always associated with periodic breathing. Although the mechanisms have not been fully elucidated, it is likely that the periods of hyperpnea or hyperventilation decrease the $PaCO_2$ thus reducing the stimulus to breathe, resulting in apnea; the resulting hypoxemia may then further depress the respiratory center.

Apnea of prematurity (AOP) can be thought of as a developmental disorder that reflects physiological immaturity of respiratory control. AOP occurs in up to 85% of infants of less than 34 weeks' gestational age. AOP increases in frequency with decreasing maturity and resolves with increasing maturity. In $>$90% of infants, AOP resolves by 37 weeks postmenstrual age, but occasionally it may last until 40 weeks or beyond, especially in infants born at 24–26 weeks or those with chronic lung disease.

Clinically significant apnea is defined as cessation of breathing that lasts for at least 20 s. Shorter apneas, if associated with significant bradycardia or oxyhemoglobin desaturation, may also be considered clinically significant. Lack of airflow may occur despite continued respiratory effort in the presence of airway obstruction and may be the reason for the shorter "apneas" being associated with bradycardia and desaturation.

Brief episodes of bradycardia are common and typically not associated with desaturation.

Apnea is traditionally classified as central, obstructive, or mixed, based on the primary mechanism involved. These mechanisms can be distinguished by simultaneous measurement of chest wall movement by electrical

impedance, airflow by nasal thermistor, and heart rate by EKG. Central apnea is, as the name implies central in origin, characterized by cessation of respiratory effort and airflow and is related to immaturity of the respiratory control center. Obstructive apnea is characterized by cessation of airflow despite continued respiratory movement and is believed to be related to poor pharyngeal muscle tone, especially during REM sleep. The majority of apneas are mixed with central apnea preceded or followed by obstructive apnea. These events represent a continuum and are the result of a complex interaction of airway obstruction and central respiratory depression: central apnea leading to hypoxemia results in relaxation of the pharyngeal muscles and the resulting airway obstruction will prolong the duration of apnea. Airway obstruction in turn produces desaturation with resulting depression of central respiratory control. Most such events are self-limited and terminated eventually by arousal, but in some infants, active intervention is required when the normal arousal mechanisms fail and the infant enters a state of severe bradycardia and hypoxemia.

Treatment of apnea should be guided by an assessment of the predominant nature of the apneic events. Methylxanthines are a mainstay of therapy for central apnea. Caffeine has now been shown to be safe and in fact was associated with improved neurodevelopment and lower incidence of BPD. Adjunctive treatments include continuous positive airway pressure (CPAP), which helps maintain lung volume and counteract the REM sleep-related chest wall distortion issues, as well as reduce airway obstruction by providing distending pressure that helps maintain pharyngeal patency. Nasal cannula flow may serve the same function, though perhaps less effectively. Avoidance of hypoxemia is important in reducing central apnea, but possible benefit of higher oxygen saturation targets must be weighed against adverse consequences of oxygen exposure. Lower environmental temperature has been shown to reduce apnea in preterm infants. Although acid reflux is capable of triggering reflex apnea and bradycardia, there are no studies that have established a causative relationship between gastroesophageal reflux and apnea/bradycardia in the preterm infant and no studies that have demonstrated benefit of anti-reflux drugs.

Controversy persists regarding the question of whether the episodes of apnea/bradycardia/desaturation are associated with neurodevelopmental sequelae. Clearly, since most preterm infants experience a substantial number of such events, harm, if any, is minimal with the commonly seen brief episodes. However, alterations in cerebral oxygenation have been documented and there is substantial concern that more prolonged and profound episodes are likely to lead to some degree of cumulative harm. It is unclear whether the improved neurodevelopmental outcome seen in the caffeine-treated infants in the CAP trial reflects a decrease in such episodes or is due to the lower incidence of BPD; the frequency of apnea was not documented in that study.

Persistent apnea is often the last remaining condition that delays discharge. There is no uniform approach to judging an infant's readiness for discharge. Most clinicians rely on an apnea-free interval of 5–7 days as indicative of a safe discharge to home care without the need for home monitors. However, it has been demonstrated that only 33–50% of apnea or bradycardia events recorded by bedside pneumograms are documented by nursing staff, raising a question about the reliability of this approach. The alternative is to perform screening pneumogram recordings on all infants with history of apnea. This approach is also controversial, as most infants will continue to have some events well past the stage when clinical symptoms are apparent and these recordings have not been shown to have good predictive value. Because most apnea resolves prior to 37 weeks postmenstrual age, it is customary to discontinue methylxanthines when an infant reaches 34–36 weeks and observe. It must be understood that these are long-acting drugs that require several days to drop below therapeutic levels. If symptoms recur, pharmacotherapy is restarted and if effective, the infant may be discharged home with outpatient follow-up.

The Infant with Respiratory Distress

Respiratory distress is a common presenting sign in newborn infants with potentially life-threatening implications. In considering the approach to such infants, it is important to recognize that the underlying cause may not be limited to the respiratory tract. Respiratory distress may be a nonspecific manifestation of neurologic, cardiovascular, metabolic, hematologic, or neuromuscular disorders, as well as reflection of sepsis, drug withdrawal, and other conditions such as severe anemia (*Table 15.2*).

The diagnostic approach begins with obtaining a good medical history focusing on potential risk factors for any of the possible etiologies. Is the infant term, preterm or postmature? Was there any difficulty at birth? What was the route of delivery? When did the signs begin? Was the amniotic fluid stained with meconium or blood? Was it foul smelling? Maternal history may offer important clues to possible infection, maternal medical conditions, intrauterine medication exposure, or family history of heritable disorders. A thorough physical examination needs to focus

Table 15.2
Differential diagnosis of respiratory distress in newborn infants

Major category	Subcategory	Examples
Pulmonary	Airway	Laryngeal web, tracheomalacia, TE fistula, vascular ring
	Congenital	Hypoplasia, CDH, CCAM, sequestration, lobar emphysema
	Developmental	RDS, TTN, pulmonary insufficiency of prematurity
	Aspiration	Meconium, blood, amniotic fluid
	Miscellaneous	Pneumothorax, pulmonary hemorrhage, pleural effusion
Cardiac	Structural heart disease	Transposition, anomalous venous return, coarctation
	Pulmonary hypertension	Primary, secondary
	Myocardial dysfunction	Myocardiopathy, myocarditis, asphyxia
	Hypovolemia/shock	Hemorrhage, capillary leak, sepsis
	Congestive failure	PDA, VSD, A-V malformation, severe anemia
Infectious	Sepsis	Group B strep, *E. coli*
	Congenital pneumonia	Bacterial, viral, chlamydia
Metabolic	Hypoglycemia	Infant of a diabetic mother
	Severe acidosis	Lactic acidosis, inborn errors
	Polycythemia	
Neuromuscular	CNS depression	Anesthetic, narcotic analgesics, asphyxia
	Nerve injury	Phrenic nerve, laryngeal nerve
	Muscle weakness	Muscular dystrophy, MgSO4
	Anterior motor neuron	Werdnig Hoffman, spinal muscular atrophy
Skeletal	Asphyxiating thoracic dystrophy	Thanatophoric dwarfism
		Camptomelic dwarfism
	Rib fractures	Severe osteogenesis imperfecta

not only on the evaluation of breath sounds, but also the general appearance and activity of the infant, the nature of respiratory efforts, adequacy of the circulatory status, and coexisting physical findings in other organ systems. The history and physical exam will then guide the next steps in the evaluation, which will likely include a chest radiograph, evaluation for possible infection, a basic chemistry panel including glucose, plus additional studies based on clues from the H&P. Cardiology consultation may be appropriate if there is suspicion of cardiac anomaly based on clinical findings of a murmur, congestive failure, abnormal pulses, cyanosis out of proportion to the degree of distress, or abnormal cardiac shape on chest radiograph. Pulse oximetry now provides a quick assessment of the oxygenation status of the infant and will also detect a pre- and post-ductal saturation gradient that may be indicative of heart disease or persistent pulmonary hypertension.

While general supportive measures, including provision of supplemental oxygen when needed, thermal support, and provision of adequate fluid and calories, are common to all infants with respiratory distress, specific intervention depends on accurate diagnosis. In the majority of infants, the respiratory illness will be self-limited with full recovery, but management and outcome depend heavily on the underlying cause. The pulmonary causes of respiratory distress will be reviewed in the following paragraphs.

Specific Respiratory Disorders

Transient Tachypnea/Delayed Transition

Definition: Transient tachypnea of the newborn (TTN) is a usually benign condition associated with delayed clearance of lung fluid after birth.

Etiology/Pathogenesis: TTN typically occurs in term or late preterm infants and is greatly increased in infants born

by elective cesarean delivery. The process of lung fluid reabsorption normally begins prior to the onset of spontaneous labor and is greatly accelerated during labor. Infants who do not benefit from this normal process are at a distinct disadvantage and require a longer time to achieve adequate fluid clearance, because they have a substantially larger volume of fluid to clear and have not initiated this process in utero. The exact mechanism responsible for changing the lung epithelium from a Cl-secretory to a Na-reabsorption mode is the subject of intense study. Postnatally, lung fluid is taken up by the lung lymphatics and capillaries by a process mediated by the epithelial Na channels (ENaC). These mechanisms are less effective in the preterm infant and also vary among full-term infants, explaining the variation in the presence and extent of delayed fluid clearance.

Epidemiology: The true incidence of TTN is unknown as milder forms are often unreported. TTN account for a substantial number of admissions to NICUs, especially where the rate of cesarean section and late preterm delivery is high.

Clinical Manifestations: TTN presents with tachypnea, occasionally grunting respirations, and minimal retractions. The oxygen requirement, if any, is usually no more than 30%. The onset is shortly after birth and the signs resolve within a few hours to 2–3 days. Occasionally, TTN may be accompanied by persistent pulmonary hypertension (PPHN) with a high oxygen requirement out of proportion to the degree of lung disease and this can become a life-threatening illness, discussed further under PPHN.

Diagnosis: The presence of a compatible history, absence of infection, and a benign clinical course may be sufficient to establish the diagnosis. The chest radiograph may show hazy lung fields, but good lung expansion (as opposed to the loss of lung volume in respiratory distress syndrome), but more classically reveals streaky increased perihilar lung markings due to engorged lymphatics. The lung volume is normal or increased. Blood cultures, leukocyte counts, and other tests to rule out infection may be indicated.

Differential Diagnosis: TTN must be distinguished from respiratory distress syndrome (RDS), pneumonia, aspiration syndromes, and all the other common causes of respiratory distress.

Treatment: Treatment is supportive with provision of supplemental oxygen if hypoxemia is present, maintenance of temperature and provision of fluids/nutrition if the distress is severe enough to preclude oral feeding. There is no contraindication to breastfeeding of the tachypneic infant, as long as the distress is mild and the infant is not exhibiting desaturation during feeding. Nasogastric tube feeding is usually well tolerated. Continuous positive airway pressure is often used in these infants, but this practice is not evidence-based or physiologically sound, since the etiology of TTN is not specifically addressed by increased distending airway pressure. Antibiotics may be appropriate until infection has been ruled out.

Prognosis: The clinical course is usually benign and the signs resolve quickly. Duration and severity greater than described above should prompt a reevaluation of the diagnosis.

Prevention: Avoidance of elective cesarean delivery without labor would reduce the incidence dramatically. There are no other known prevention strategies.

Respiratory Distress Syndrome (RDS)

Definition: RDS is a specific disorder that occurs almost exclusively in preterm infants and is due to deficiency, inactivation, or dysfunction of pulmonary surfactant. It is not to be confused with "respiratory distress," which is merely a clinical sign. RDS is synonymous with the older term "hyaline membrane disease" (HMD).

Etiology: RDS results from functional deficiency of pulmonary surfactant, the surface tension lowering substance produced in type II pneumocytes.

Epidemiology: The incidence of RDS is inversely proportional to gestational age and is higher in male infants, those born by cesarean section, and in infants of mothers with diabetes. RDS is rare, but can occur in early-term infants and becomes progressively more common in late preterm, preterm and extremely preterm infants. Reported rates of RDS range from 80% in infants $<$26 weeks to 50% at 26–28 weeks, and under 30% at 30–32 weeks. RDS is the most common cause of respiratory failure in preterm infants. It is estimated that approximately 25,000 cases of RDS occur in the United States alone and it is known to occur in all races and regions of the world, though precise statistics are unavailable. Genetic variations underlying individual variation in susceptibility to RDS for individuals of the same gestational age are the subject of intense study.

Pathogenesis: Surfactant is a complex mixture of phospholipids and four types of surfactant-associated proteins. Surfactant lines the terminal air sacs and reversibly lowers the surface tension at the air–liquid interface, allowing alveoli of different sizes to coexist. In the absence of sufficient amount of functional surfactant, smaller alveoli, which require greater pressure to remain

open, will empty into larger alveoli, leading to diffuse microatelectasis. Atelectasis results in further surfactant inactivation, worsening lung compliance, increased pulmonary vascular resistance, increased ventilation/perfusion mismatch, and hypoxemia. Anatomical immaturity of the lung coexists with RDS in the very preterm infants and contributes to their respiratory insufficiency. Surfactant-associated protein B (SP-B) and to a lesser degree surfactant-associated protein C (SP-C) are necessary for adequate surfactant function. Rare mutations in SP-B and SP-C and ATP-binding cassette transporter *A3* (*ABCA3*) genes lead to severe, often fatal cases of RDS in term infants.

Clinical Manifestations: Infants with RDS present with tachypnea, cyanosis, grunting, subcostal and intercostal retractions, and nasal flaring. Oliguria with mild generalized edema may be present. Oxygen requirement may increase rapidly and is typically higher than that seen in infants with TTN. The natural course of the disease is worsening in the first 24 h, followed by stabilization and recovery by 72–96 h, usually heralded by spontaneous diuresis. In the modern era, this course is modified by therapeutic interventions.

Diagnosis: Typical clinical signs coupled with a characteristic appearance on chest radiograph of "ground glass" parenchymal opacification, air bronchograms, and decreased lung volume are sufficient to establish the diagnosis.

Differential Diagnosis: RDS must be distinguished from TTN, spontaneous pneumothorax, sepsis, and pneumonia. The clinical and radiographic presentation of RDS and group B streptococcus pneumonia are often indistinguishable. Other, less common etiologies listed previously should be considered when the clinical picture is atypical.

Treatment: Mild cases only require supplemental oxygen and supportive treatment as described above. Continuous positive airway pressure (CPAP) is helpful in preventing or reversing the diffuse microatelectasis and maintaining FRC. Surfactant replacement therapy has become standard of care in industrialized countries for infants who require mechanical ventilation and for those deemed at very high risk of RDS, namely, those below 27 weeks GA. More recently, it has been demonstrated that even very premature babies can be effectively treated with CPAP without surfactant replacement with similar results to those treated with mechanical ventilation and surfactant. This is particularly encouraging news for practitioners in resource-limited settings, as bubble CPAP can be delivered with very simple equipment. Surfactant replacement therapy, noninvasive respiratory support, and mechanical ventilation are covered in greater detail elsewhere in this Section.

Prognosis: Prognosis depends on gestational age and the presence of complications, many of which are a function of prematurity, rather than directly related to RDS, but all tend to occur more frequently in infants with RDS. Complete recovery is the rule in infants >30 weeks gestation with uncomplicated disease. In contrast, extremely preterm infants of 26 weeks or below often progress to bronchopulmonary dysplasia, discussed in more detail below. Mortality directly attributable to RDS is relatively low even in extremely low birth weight infants – more commonly, these infants succumb to sepsis, intraventricular hemorrhage, or pulmonary hemorrhage.

Prevention: Antenatal administration of betamethasone or dexamethasone at least 48 h prior to preterm birth dramatically lowers mortality and morbidity from RDS, as well as other complications of prematurity. Early application of CPAP in the delivery room and avoidance of excessive tidal volume with positive pressure ventilation can prevent inactivation of the marginal surfactant pool present in preterm newborns.

Meconium Aspiration Syndrome (MAS)

Definition: MAS refers to a clinical syndrome of respiratory distress associated with aspiration of meconium into the lungs before, during, or immediately after delivery.

Etiology: Fetal hypoxemia associated with placental insufficiency or limited fetal reserve leads to passage of meconium into the amniotic fluid prior to delivery. Subsequent gasping inspiratory effort caused by continued fetal distress leads to aspiration of meconium in utero. Rarely, aspiration of meconium present in the upper airway may occur after delivery. This only occurs in depressed infants, because vigorous infants are able to protect their airway against aspiration.

Epidemiology: Approximately 10–15% of all term deliveries have meconium stained amniotic fluid (MSAF). Passage of meconium is rare in preterm infants but occurs in as many as 33% of deliveries beyond 42 weeks gestation. Only about 5% of infants born through MSAF will have aspirated the material into their lungs and develop symptoms of MAS. A recent study from Australia and New Zealand reported an overall rate of MAS requiring mechanical ventilation of 0.43 per 1,000 live births.

Pathogenesis: Particulate meconium leads to partial or complete obstruction of the airways. Partial obstruction often results in hyperinflation, as air passes beyond the obstruction during inspiration when the airway dilates,

but it is trapped behind the obstruction on exhalation when the airway collapses around the obstruction, causing a ball-valve effect. Complete obstruction results in distal reabsorption and atelectasis. These events result in the typical radiographic picture of patchy atelectasis with areas of overexpansion. More dilute meconium that reaches the distal air spaces inactivates surfactant and leads to a picture similar to RDS with diffuse haziness and decreased lung volumes. Subsequently, the inflammatory response to the various components of meconium mediated by release of cytokines leads to alveolar and airway edema with release of protein-rich edema fluid further inactivating surfactant. Ventilator-induced lung injury may worsen the condition further, especially when aggressive hyperventilation is applied to treat PPHN, a practice no longer recommended.

Clinical Manifestations: Infants often appear dysmature with loose, peeling skin, greenish-yellow staining of the umbilical cord, nails, and skin. They present with tachypnea, nasal flaring, retractions, cyanosis, coarse rales, and rhonchi. There may be a barrel-shaped appearance of the chest related to air trapping or pneumomediastinum. Perinatal depression and PPHN often coexist as do complications of IUGR.

Diagnosis: The diagnosis is made in the presence of history of MSAF, respiratory distress, and radiographic changes. The radiographic appearance may be highly variable and changes over time. In the acute phase of MAS with particulate meconium, there is a typical patchy infiltrate with air trapping and increased lung volume, often accompanied by airleak. Where surfactant inactivation is the predominant pathophysiologic mechanism and in later stages of chemical pneumonitis, the chest radiograph may show homogeneous opacification with normal or low lung volume. Recovery of meconium from the trachea with suctioning confirms the diagnosis, but is not always present.

Differential Diagnosis: Because MSAF occurs in 10% of all deliveries, infants with other causes of respiratory distress may well have a history of MSAF. Most commonly, the dilemma is between MAS and TTN. The chest radiograph of an infant with TTN may be very suggestive of MAS; the differentiation rests on rapid clearance of the "infiltrate" in the infant with TTN, whereas meconium pneumonitis persists radiographically for many days. Other etiologies of respiratory distress, including infection, structural abnormalities of the lungs or airways, need to be considered.

Treatment: Supplemental oxygen, CPAP and mechanical ventilation may be required in that sequence if the severity of the illness is sufficient to require these steps. Avoidance of hypoxemia is important because of the propensity of these infants to develop PPHN. Hyperoxia does not offer any benefit over normoxia (PaO_2 50–70 mmHg); it may increase pulmonary artery vasoreactivity and blunt the response to inhaled nitric oxide if PPHN develops. Suctioning of the airway should be done judiciously, because each time the infant is suctioned, lung volume recruitment is lost. Saline lavage of the airways is ineffective and is not recommended. Surfactant replacement therapy is warranted because of the surfactant inactivation caused by meconium. Larger doses and repeated application may be necessary. Surfactant preparations that are more resistant to degradation by meconium may be preferred. Lung lavage with dilute surfactant may be effective, but is difficult to perform and not always well tolerated by the infant. Steroids may be effective in supressing the inflammatory and may reduce the severity of the disease process. However, their safety in this context has not been established. Antibiotics are indicated, typically for a 5–7-day course, because the aspirated material may have bacterial contamination and meconium may enhance bacterial growth. When mechanical ventilation is required, care must be taken to set an adequate inspiratory and expiratory time because infants with MAS have increased airway resistance and are thus prone to air trapping; therefore, rapid respiratory rates are to be avoided. Moderate PEEP of 4–7 cmH_2O is appropriate, despite evidence of overexpansion. This is because the distending expiratory pressure helps maintain airway diameter during expiration and decreases the ball-valve effect. When surfactant inactivation predominates and diffuse atelectasis is present, even higher PEEP of up to eight or more cmH_2O may be needed. High-frequency ventilation is widely used in infants with MAS with some objective evidence of benefit, but care must be taken to use lower frequencies to avoid air trapping. With very severe disease, especially when complicated by PPHN, rescue with extracorporeal life support (ECMO) may be required, where available – see Chap. 22, "ECMO".

Prognosis: With modern newborn intensive care, MAS is now rarely fatal, though it is occasionally associated with chronic lung disease. In a resource-limited setting MAS remains an important cause of morbidity and mortality. Associated PPHN increases mortality substantially.

Prevention: Avoidance of postmaturity is effective in reducing the number of infants at risk. Routine suctioning of the trachea after delivery is no longer recommended for vigorous infants, but remains an important preventive measure in depressed infants. Amnioinfusion has not been shown to reduce incidence or severity of MAS.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Definition: Persistent pulmonary hypertension of the newborn is a clinical syndrome, peculiar to the early neonatal period, characterized by severe arterial hypoxemia caused by increased pulmonary vascular resistance (PVR) with resultant right-to-left shunting of deoxygenated blood through fetal channels.

Etiology: Pulmonary hypertension of the newborn may be a primary disorder in infants with no associated lung disease, or secondary to a variety of disease conditions. Some of these are associated with hypoplasia of the lung parenchyma and decreased number of pulmonary arteries (i.e., pulmonary hypoplasia or CDH). Most commonly it occurs in infants with normal lung parenchyma and pulmonary vasculature because of a failure to make the normal transition at birth to decrease PVR (maladaptation). This may occur in intrapartum asphyxia, meconium aspiration syndrome, infection, and RDS. Cesarean delivery substantially increases the risk of PPHN due to maladaptation. Chronic intrauterine hypoxia causes pulmonary smooth muscle remodeling with increase in resistance across the vessels (maldevelopment). Severe polycythemia with sludging of blood in the pulmonary vessels can increase PVR. Recent evidence suggests that exposure to selective serotonin reuptake inhibitors (SSRIs) during late gestation is associated with a sixfold increase in the prevalence of PPHN. Pulmonary hypertension associated with severe bronchopulmonary dysplasia is a separate entity, but shares some of the same clinical features.

Epidemiology: Severe persistent pulmonary hypertension of the newborn affects approximately 1–2 infants per 1,000 live births, but some degree of transient pulmonary hypertension complicates the course of >10% of all neonates with respiratory failure. PPHN is typically seen in term infants with MAS, respiratory distress syndrome, sepsis, and congenital diaphragmatic hernia. Idiopathic pulmonary hypertension is responsible for only 10–20% of all infants with PPHN. Thought less common, PPHN may occur in preterm infants, especially in the presence of pulmonary hypoplasia due to prolonged preterm rupture of the membranes with prolonged oligohydramnios, CDH, or with sepsis.

Pathogenesis: High pulmonary vascular resistance (PVR) is the normal condition in utero. With the clamping of the umbilical cord at delivery, systemic vascular resistance increases and PVR begins to fall in response to alveolar expansion, clearance of lung liquid, decreasing carbon dioxide tension, and increasing oxygen tension. These changes are mediated by nitric oxide and prostacyclin pathways that cause pulmonary vascular smooth muscle relaxation. This reverses the fetal shunts and allows increasing blood flow to the lungs. The failure to achieve this normal circulatory transition is the fundamental problem in infants with PPHN.

Pulmonary hypoplasia is associated with a decrease in the number and cross-sectional area of pulmonary blood vessels with increased muscularization of pulmonary arterioles and increased vasoreactivity. Chronic fetal hypoxia induces vascular remodeling with increased smooth muscle proliferation resulting in thickening of the media and increased PVR. Premature closure of the ductus arteriosus from exposure to non-steroidal anti-inflammatory agents in the third trimester causes structural remodeling of the peripheral pulmonary vascular bed, resulting in PPHN. Maladaptation or failure to establish adequate vasorelaxation at birth from intrapartum asphyxia, meconium aspiration syndrome, and respiratory distress syndrome or release of vasoactive mediators that may contribute to pulmonary vasoconstriction as a result of infection leads to sustained high PVR and severe hypoxemia. Elective cesarean delivery without labor is associated with a slower fall in pulmonary vascular resistance and increased incidence of PPHN, because the normal process of labor leads to changes in the elaboration of mediators of vascular tone and prepares the fetus for successful transition to extrauterine life.

Clinical Manifestations: Severe hypoxemia out of proportion to the degree of lung disease is the hallmark of PPHN, often presenting as cyanosis and respiratory distress within a few hours of birth in a term or late preterm infant. Classically, there is great lability of oxygen saturation with frequent desaturation with any stimulation or stress and there may be a history of MSAF, fetal distress during labor, or antenatal ultrasound findings of CDH.

Diagnosis: The diagnosis of PPHN is suggested by the presence of cyanosis/labile hypoxemia and respiratory distress out of proportion to any lung disease that may be present. Examination of the heart sounds may reveal a harsh systolic murmur with a loud S2 secondary to tricuspid regurgitation. Pulse oximetry will demonstrate the severity of the hypoxemia. Simultaneous monitoring of pre-ductal (in the right hand) and a post-ductal (in any lower extremity) oxygen saturation may show significantly lower post-ductal saturation. This is a reflection of right-to-left shunting across the PDA, a finding also seen in neonates with a duct-dependent cyanotic heart lesion, coarctation of the aorta, or interrupted aortic arch. Consequently, pulse oximetry does not reliably differentiate PPHN from cyanotic heart disease. Additionally, if the ductus arteriosus is closed, no gradient will be seen,

because the shunting may be at the atrial level. CXR may show evidence of MAS, pneumonia, diaphragmatic hernia, or the pulmonary hypoplasia. In primary PPHN, the lung fields look clear and oligemic, similar to cyanotic heart disease with decreased pulmonary blood flow. Definitive diagnosis is made by echocardiography. This will help rule out cyanotic heart disease and identify signs of pulmonary hypertension. Echocardiogram typically shows right-to-left or bidirectional shunting across the PDA and PFO, tricuspid regurgitation, and flattening of the interventricular septum as a result of increased right ventricular pressure. By using peak velocity of the tricuspid regurgitant flow, it is possible to estimate pulmonary artery pressure. Echocardiogram is also vital in evaluating ventricular filling and ejection as sudden decompensation in neonates with PPHN can often be caused by poor myocardial function and right heart failure. Because in most infants the PVR is quite labile, the evidence of pulmonary hypertension may not be clear if the echocardiogram is done at a time the infant is responding to treatment and oxygenating well.

Differential Diagnosis: PPHN must be distinguished from cyanotic heart disease and severe parenchymal lung disease. When PPHN and severe lung disease coexist, it may be difficult to determine the relative contribution of pulmonary hypertension, in part because hypoxia and atelectasis itself increases pulmonary vascular resistance. Clinically, this may be done with the hyperoxia test. Briefly increasing the FiO2 to 1.0 will have no effect on oxygen saturation in an infant with a fixed intracardiac right-to-left shunt caused by cyanotic heart disease. A modest improvement in oxygenation is seen in infants with parenchymal lung disease and a dramatic improvement is often (but not always) seen when PPHN is the predominant cause of hypoxemia. Echocardiography will usually establish the diagnosis, but partial anomalous pulmonary venous drainage, which presents clinically with very similar findings, may be difficult to diagnose by echocardiography.

Treatment: Treatment of PPHN is focused on lowering pulmonary vascular resistance, supporting systemic blood pressure to keep it above pulmonary pressure, and providing gentle respiratory support in order to avoid complications, as the elevated PVR will eventually fall in most patients. Systemic blood pressure support can be achieved by judicious use of crystalloids (e.g., normal saline) in boluses of 10–20 mL/kg to improve circulating blood volume. This and the appropriate use of inotropic agents improve cardiac output and systemic blood pressure. Excessive use of saline can lead to volume and sodium overload. With adequate preload, the inotropic agents dopamine and dobutamine improve cardiac contractility and output. The use of epinephrine and higher doses of dopamine increase peripheral vascular tone and raise systemic blood pressure. Care should be exercised in the use of these agents, as they can be associated with tachycardia, arrhythmia, increased afterload, myocardial ischemia, and may increase PVR. Milrinone is a useful agent in PPHN, because it provides positive inotropic effect, does not cause systemic vasoconstriction, and achieves pulmonary vasodilatation because it inhibits phosphodiesterase 3, the enzyme that breaks down cyclic AMP.

Respiratory stabilization may require intubation and mechanical ventilation with the goal of providing sufficient mean airway pressure to achieve optimal lung volume, improve ventilation/perfusion matching, and lower pulmonary vascular resistance. Adequate oxygenation and avoidance of hypoxemia minimize pulmonary vascular resistance but supraphysiologic arterial oxygen tension should be avoided. Pulmonary vascular resistance only increases with PaO2 below 50 torr and no further fall in PVR is seen at PaO2 above 70 torr. Exposure to hyperoxia even for short periods of time increases oxidative stress and actually increases vasoreactivity of the pulmonary vessels and blunts response to inhaled nitric oxide (iNO). Target PaO2 therefore should be in the range of 60–80 torr. Acidosis increases PVR and should generally be avoided in patients with PPHN. Slightly alkaline arterial blood pH between 7.4 and 7.5 may be needed in some patients whose pulmonary hypertension fails to improve with more conservative ventilation and other appropriate therapies, including iNO. However, the practice of hyperventilation to achieve significant respiratory alkalosis is associated with increased likelihood of hemodynamic impairment, lung injury, chronic lung disease, and neurologic sequelae and is no longer recommended. The goal should be to maintain physiologic PCO2 between 35 and 45 torr. The use of alkali infusion (sodium bicarbonate) to increase blood pH has been used to reduce the need for respiratory alkalosis, but was associated with increased need for ECMO rescue in a large retrospective study. The choice of conventional ventilation or high-frequency ventilation (HFV) depends on availability and the underlying disease condition. HFV may offer advantages in patients with pulmonary hypoplasia, congenital diaphragmatic hernia, and airleak syndromes, and may be useful in achieving optimal lung inflation. Intravenous vasodilators have been used in the past, but lack specificity for the pulmonary circulation and generally have been ineffective. There is no sound evidence to support the widespread use of MgSO4 to treat pulmonary hypertension. Inhaled nitric oxide (iNO) has been studied extensively and is currently

the only specific pulmonary vasodilator approved for treatment of PPHN. Nitric oxide (NO) is generated by NO synthase from L-arginine. NO then activates guanyl cyclase leading to the production of cyclic GMP, which causes relaxation of the vascular smooth muscle by decreasing cytosolic calcium concentration. The use of iNO in doses of up to 20 PPM improves oxygenation and decreases the risk of death or need for ECMO by up to 50%, except in neonates with congenital diaphragmatic hernia in whom no significant benefit was demonstrated. Doses of iNO greater than 20 PPM do not result in greater efficacy but are associated with higher toxicity. iNO is most effective when the circulatory status and pH have been optimized and adequate lung expansion has been achieved. iNO in combination with HFV may be more effective than iNO used with conventional ventilation in infants with significant lung disease. Traditionally, iNO is started at oxygenation index (OI) levels of 25 or above; ($OI = [(F_IO_2 \times Paw)/PaO_2] \times 100$), where Paw is mean airway pressure and F_IO_2 is the fraction of inspired oxygen. However, when PPHN persists despite optimized ventilatory and hemodynamic support, iNO use at lower OI appears justified. Response to iNO should be evident within a short period of time when pH and perfusion have been optimized first. Treatment should be weaned as soon as possible after the FiO_2 has decreased to 70% or less by decrements of 5 PPM, down to 5 PPM, and more slowly thereafter with the goal of weaning from iNO by 3–4 days. Prolonged exposure to iNO will suppress endogenous nitric oxide production and make it more difficult to discontinue the drug. Although iNO has been shown to be safe and effective in the treatment of PPHN, it is expensive and not readily available everywhere. Sildenafil, a phosphodiesterase five inhibitor improves oxygenation in patients with PPHN. Sildenafil decreases the degradation of cyclic GMP resulting in higher concentrations of cyclic GMP locally, which in turn leads to relaxation of pulmonary vascular smooth muscles. Its lower cost and greater availability has made sildenafil very attractive to clinicians with no access to iNO. Despite the absence of definitive studies to determine the safest effective dose and to evaluate its safety profile in neonates, this drug is widely used in less affluent countries.

The general care of infants with PPHN is crucial to optimizing outcome. Correction of acidosis, glucose and other electrolyte derangements, aggressive treatment of sepsis, circulatory support, correction of coagulopathy, and institution of appropriate supportive treatments for perinatal asphyxia are vital determinants of response to treatment and survival. Minimal handling and use of adequate sedation/analgesia to avoid agitation are very important. Although routine use of paralytic agents is not recommended, at times they may be necessary to control agitation. Up to 40% of patients with PPHN and most infants with CDH do not respond to iNO. In these patients, ECMO is the ultimate rescue treatment and should be instituted while the infant has some degree of stability. It is vital for clinicians to recognize early those patients who are nonresponders to iNO and anticipate the need for ECMO where available. Institutions that do not have ECMO as a treatment option readily available should perhaps consider how nitric oxide is used and be prepared for early transfer of nonresponders to an ECMO center.

Prognosis: Prognosis in PPHN depends on the underlying diagnosis, response to treatment, and availability of rescue therapies. Mortality has been reduced to $<5\%$ with more optimal ventilatory support, iNO, and ECMO, but remains high where these advanced therapies are not available. An early and sustained response to inhaled nitric oxide is associated with clinical improvement and better outcomes. Patients with perinatal asphyxia, pulmonary hypoplasia, and CDH often have the worst prognosis. Residual chronic lung disease and/or sensorineural hearing loss have been reported to correlate with duration of hyperventilation.

Prevention: Many infants that develop PPHN exhibit signs of respiratory distress early in their course. Progression of respiratory disease with failure to establish adequate oxygenation and ventilation will impair the normal newborn transition and lead to the persistence of high PVR leading to PPHN. Recognition of infants with early respiratory disease and acting quickly to provide adequate respiratory support to maintain good oxygenation may reduce the progression to hypoxemic respiratory failure and PPHN. Many infants that develop PPHN were born late preterm via elective C-section who then exhibit signs of surfactant deficiency or retained lung fluid that can progress to PPHN. Avoiding elective delivery before 38 weeks of completed gestation will significantly reduce respiratory morbidity in this subgroup of patients. Prenatal ultrasounds are now able to readily identify infants with oligohydramnios and CDH so that delivery can occur in a tertiary center where optimal treatments can be instituted early.

Airleak Syndrome

Definition: Pulmonary airleak is defined as accumulation of air outside of the airway and alveolar space. Depending on the location of the air it may be described as a pneumothorax, pneumomediastinum, pulmonary

interstitial emphysema (PIE), pneumopericardium, or subcutaneous emphysema.

Etiology: Airleaks are caused by over-distension of alveoli or terminal bronchioles with resultant rupture and escape of air into the interstitium. Spontaneous pneumothorax can occur soon after birth due to the high pressures generated by the baby taking their first breaths. High positive airway pressure used during resuscitation may also cause airleak. Most airleaks are associated with lung diseases such as RDS, meconium aspiration syndrome, pneumonia, pulmonary hypoplasia, and congenital diaphragmatic hernia. The majority of airleaks are associated with mechanical ventilation, particularly with the use of inappropriately high inspiratory pressure or tidal volume, use of unsynchronized ventilation. Direct injury to the trachea or airway can occasionally result from suctioning through the endotracheal tube (ETT), use of introducers through the ETT for their placement, or central venous catheter placement.

Epidemiology: The overall incidence of airleaks in term infants is about 1%, although only about 10% of these are symptomatic. The incidence of airleak is significantly higher in preterm infants requiring mechanical ventilation and was reported to occur in 3–13% of infants less than 28 weeks gestation born between 2003 and 2007 from the NICHD Neonatal Research Network centers. PIE is predominantly seen in the extremely low birth weight infant with RDS on mechanical ventilation with a reported incidence of 3–5%.

Pathogenesis: The development of airleak starts with over-distension of alveoli or terminal bronchioles with subsequent rupture and escape of air into the interstitial tissue. This free air then tracks along the bronchial and vascular sheaths to the hilum of the lung. The air can escape into the mediastinum producing a pneumomediastinum or dissect through the visceral pleura producing a pneumothorax. A pneumopericardium may develop when the air dissects into the pericardial sac usually in association with a pneumothorax in ventilated infants. Free air in the mediastinal space can track into the subcutaneous tissues of the neck or chest wall as subcutaneous emphysema or into the abdomen causing a pneumoperitoneum. In ELBW infants with pulmonary interstitial emphysema, the lung connective tissue is more abundant and less dissectible, therefore the air remains in the bronchovascular sheaths splinting the alveoli in a state of inflation causing significant ventilation perfusion mismatch by impeding alveolar emptying and pulmonary blood flow.

Clinical Manifestations: The clinical presentation of airleak syndromes is varied from the asymptomatic to sudden acute decompensation depending on the amount of air that has collected and whether it is under tension compressing the lung and other intrathoracic structures. Most cases of pneumomediastinum are not associated with significant clinical symptoms because the air is usually not under tension. Subcutaneous emphysema can be recognized by a "crackly feeling" on palpation of the anterior chest wall or over the neck. Pneumoperitoneum may present with abdominal distension or rarely enlargement of the scrotum in boys. A small pneumothorax in an infant with little or no lung disease can be asymptomatic. This is typical with a spontaneous pneumothorax. Tension pneumothorax presents with respiratory distress, hypoxia, acute respiratory acidosis, and rapid deterioration. Clinical examination will show subcostal retractions, cyanosis, decrease or absence of breath sounds on the ipsilateral side, shift of heart sounds to the contralateral side due to mediastinal shift, and abdominal distention due to downward displacement of the diaphragm. There may be associated hypotension and bradycardia because of impaired cardiac output from impeded venous return. Pneumopericardium may be asymptomatic, but usually presents acute circulatory decompensation due to cardiac tamponade with distant heart sounds on auscultation. PIE is usually encountered in the ELBW infant on mechanical ventilation who has progressive worsening of respiratory status without localizing signs, unless it is unilateral.

Diagnosis: The diagnosis of airleak syndrome should be suspected in any infant with sudden respiratory deterioration particularly those with underlying lung disease on mechanical ventilation or CPAP. A pneumothorax can be diagnosed by the use of a high-intensity fiberoptic light placed firmly against the skin in the midaxillary line or anteriorly in a darkened room. Free air in the pleural space lights up the affected hemithorax. In an emergency when there is clinical suspicion of a pneumothorax thoracocentesis by aspiration of air with a syringe attached to a 23- or 25-gauge butterfly needle or an 20–22 gauge angiocatheter can be both diagnostic and therapeutic. Definitive diagnosis of all airleaks is made by chest x-ray. (Please see the paragraph on airleak in Chap. 21, "Complications of Mechanical Ventilation" for further description).

Differential Diagnosis: Pulmonary airleaks are easily recognizable on CXR although they may be confused with or coexist with other pulmonary diseases like congenital diaphragmatic hernia, cystic adenomatoid malformation, congenital lobar emphysema, and pulmonary abscess. Diminished breath sounds and mediastinal shift to the opposite side may be due to a large pleural effusion,

while diminished breath sounds with shift to the ipsilateral side may be due to atelectasis. In the delivery room, the scenario of a distressed, cyanotic infant with diminished breath sounds on one side and shift of the heart sounds to the other most often is due to a pneumothorax, but a congenital chylothorax or diaphragmatic hernia can have a similar presentation. The key difference is that with tension pneumothorax and pleural effusion the abdomen should be distended, whereas it is flat or scaphoid with diaphragmatic hernia.

Treatment: Most cases of pneumomediastinum, subcutaneous emphysema, and non-tension pneumothoraces cause few symptoms and resolve spontaneously. The patient should be observed for any sudden deterioration in clinical status suggesting worsening accumulation of air. Nitrogen washout with 100% oxygen is not recommended as the toxicity caused by high amounts of oxygen likely outweighs the problems caused by a non-tension pneumothorax. A tension pneumothorax represents a medical emergency and should be treated promptly. Immediate relief can be achieved by thoracocentesis with aspiration of air with a syringe attached to a 23- or 25-gauge scalp vein needle or an 18–22-gauge angiocatheter. Definitive treatment is by insertion of a chest tube into the anterior pleural space attached to underwater seal with continuous suction at 15–20 cm H2O. For infants on mechanical ventilation, the level of support should be evaluated to correct atelectasis by optimizing adequate but not excessive PEEP and reduce PIP/VT to the lowest value consistent with adequate CO2 elimination. High-frequency ventilation has advantages over conventional ventilation in the presence of airleak because adequate MAP can be provided with lower tidal volume and still remove CO2 efficiently. HFJV has unique benefits in the treatment of airleak, specifically PIE and bronchopleural fistula. When HFV is not available, rapid rate and short inspiratory times are preferable. Lateral decubitus positioning of the infant with unilateral PIE, placing the affected lung in a dependent position improves gas exchange and reduces mediastinal shift with faster resolution of PIE. Selective main-stem bronchus intubation is not always well tolerated, but is an effective way of resolving unilateral PIE.

Prognosis: Spontaneous resolution occurs in most infants with pneumomediastinum and pneumothoraces even when they require drainage. Tension pneumothorax is a known risk factor for intraventricular hemorrhage in preterm infants. Failure to recognize and quickly treat the acute hemodynamic compromise caused by tension pneumothorax and pneumopericardium can lead to sudden death. ELBW infants who develop PIE have substantially increased mortality and are at increased risk of developing BPD.

Prevention: Early provision of distending airway pressure in infants with respiratory distress to recruit and maintain optimal lung volume and avoidance of excessive tidal volume are the two steps most helpful in reducing the risk of airleak. Surfactant replacement therapy also reduces airleak. The infant with respiratory distress and progressive atelectasis that is not treated early is more likely to develop an airleak when subsequently placed on positive pressure support because most of the distending pressure will now be delivered to the compliant parts of the lung making them more prone to over-distension and airleak. Therefore early administration of surfactant in preterm infants with RDS and subsequent support with CPAP or mechanical ventilation as appropriate will maintain more uniform lung volume and reduce alveolar injury. Avoidance of hyperventilation with inappropriately high tidal volumes and peak airway pressure will lessen the likelihood of developing airleak. Although PEEP is generally lung protective and helps to achieve more uniform lung inflation, the optimal pressure required to maintain good lung volume should be reassessed frequently by checking lung expansion on CXR and lowering PEEP if the FiO2 is close to room air, as inappropriately high lung volumes can lead to alveolar rupture at peak inspiration and produce airleak. It is not clear that avoidance of mechanical ventilation with the use of noninvasive modes of ventilation reduces airleak; increased rate of airleak was reported in the CPAP arm of the COIN trial. Both volume-targeted ventilation and high-frequency ventilation have been shown to reduce airleak.

Pulmonary Hemorrhage

Definition: Pulmonary hemorrhage is assumed to be present when there is appearance of bloody fluid from the upper respiratory tract or the endotracheal tube (ETT).

Etiology: What is commonly referred to as pulmonary hemorrhage may be true hemorrhage originating in the lung parenchyma or the airways, but much more commonly is actually hemorrhagic pulmonary edema. Risk factors for the development of pulmonary hemorrhage include: extreme prematurity, surfactant treatment of RDS, left to right shunt through a patent ductus arteriosus (PDA), fluid overload, intrauterine growth restriction, hypoxic insults, and generalized coagulopathy.

Epidemiology: The overall incidence of pulmonary hemorrhage is reported to be 1/1,000 live births, but in ELBW infants with RDS it is as high as 4–7%.

Pathogenesis: True hemorrhage may result from trauma or coagulopathy. The more common hemorrhagic pulmonary edema occurs as a result of acute left ventricular decompensation leading to increased pulmonary capillary pressure. Many factors may contribute to acute decompensation, but most commonly this results from increased pulmonary blood flow caused by left to right shunting through a PDA. The association with surfactant therapy is thought to be due to rapid improvement of lung compliance and fall in pulmonary vascular resistance, allowing greater left to right shunt. The preterm myocardium has limited reserve and does not cope effectively with a large volume overload. Hypoxia and acidosis may also lead to decreased left ventricular function with resultant acute increase in pulmonary capillary pressure. Because of this increase in pressure, capillary ultrafiltrate leaks into the pulmonary interstitial space. The fluid is initially drained via the lymphatics, but as these get overwhelmed the fluid ruptures through the alveolar epithelial walls. As the leak worsens red cells and plasma escape into the alveolar space leading to hemorrhagic pulmonary edema. The fluid initially has a frothy bloody appearance and a hematocrit of about 10% but may progress to frank hemorrhage into the lungs. Coagulopathy is usually not present with hemorrhagic pulmonary edema, but does play a part in frank pulmonary hemorrhage in term infants.

Clinical Manifestations: The clinical presentation of pulmonary hemorrhage is usually sudden and catastrophic. Patients are usually ELBW infants on mechanical ventilation for RDS following surfactant therapy and usually have an underlying large left to right shunt via a PDA. Symptoms most commonly appear around the second or third day of life with sudden deterioration in the infant's condition manifested as acute fall in oxygen saturation, loss of chest wall excursion, respiratory acidosis, hypotension, and bradycardia. The appearance of bloody fluid in the ETT may accompany the sudden deterioration, but sometimes is only evident upon suctioning.

Diagnosis: The diagnosis of pulmonary hemorrhage is usually obvious from the clinical presentation and sudden appearance of bloody fluid in the ETT. Chest radiograph will typically show diffuse opacification or a complete "white out." The presence of the usual predisposing factors supports the diagnosis. Air bronchogram may not be seen, however, since the airways may be filled with hemorrhagic fluid.

Differential Diagnosis: Hemorrhagic pulmonary edema must be differentiated from local bleeding due to mucosal trauma. In this instance, the volume of blood is usually small, it does not appear frothy, and is typically not associated with the sudden deterioration seen in hemorrhagic pulmonary edema. The distinction is of critical importance, because the treatment is very different. True pulmonary hemorrhage is much less frequent, but may present with a large amount of almost pure blood in the trachea in the setting of coagulopathy or very high ventilator settings in a larger infant. Obtaining a hematocrit may help differentiate the two conditions, but is usually not necessary.

Treatment: Treatment of hemorrhagic pulmonary edema requires aggressive resuscitation starting with maintenance of adequate gas exchange. The urge to continuously suction blood from the ETT should be resisted, as any loss of distending airway pressure would worsen the hemorrhage. The fluid has low viscosity and will not clot in the airways. The use of PEEP as high as 10–12 cmH2O is the most effective means of stabilizing the patient and reversing the outflow of hemorrhagic fluid. This approach mitigates the left to right shunt through a PDA, promotes uptake of fluid into the pulmonary lymphatics and capillaries, clears the fluid from the airways, and improves lung compliance. Peak pressure adequate to achieve desired tidal volume or chest wall movement should be selected. High-frequency ventilation is often used, because clinicians are more comfortable using higher mean airway pressure with high-frequency devices. However, because of the acute nature of the crisis, changing ventilators may not be optimal; sufficient PEEP will achieve similar results with conventional ventilation. Inotropic support may be beneficial to optimize myocardial contractility, but aggressive volume expansion is contraindicated, because the infant is usually *not* hypovolemic and excessive volume administration may worsen the ventricular failure. Appropriate ventilator management limits intravascular volume loss and the need for replacement. An echocardiogram should be obtained if available and a significant PDA should be treated. Coagulopathy is usually not an issue, but, if present, should be corrected with the use of fresh frozen plasma and/or cryoprecipitate to supply clotting factors as needed. After stabilization, infants may benefit from surfactant replacement, as the hemorrhagic alveolar edema inevitably leads to inactivation of surfactant and secondary surfactant deficiency.

Mucosal bleeding usually subsides spontaneously with avoidance of further trauma. If persistent, coagulopathy/thrombocytopenia should be sought and corrected. Local administration of epinephrine via the endotracheal tube and lavage with iced saline are traditional therapies, although their value is unproven. These measures have *no place* in the treatment of hemorrhagic pulmonary edema.

Prognosis: Pulmonary hemorrhage has traditionally been associated with high mortality of up to 80%. With better understanding of the underlying pathophysiology and more appropriate therapy, the mortality rate has declined to <50%. However, these infants are usually the smallest and sickest, and are at high risk for long-term pulmonary morbidity (chronic lung disease) between 60% and 80% and an increased risk of developing intraventricular hemorrhage and retinopathy of prematurity.

Prevention: The use of prenatal steroids before preterm delivery has reduced pulmonary morbidity significantly including pulmonary hemorrhage. Timely recognition and treatment of a significant PDA will reduce the likelihood of hemorrhagic pulmonary edema, particularly in infants with history of hypoxia and poor left ventricular function.

Pulmonary Hypoplasia

Definition: Pulmonary hypoplasia refers to impaired growth and development of lung tissue and the pulmonary vascular bed.

Etiology: Pulmonary hypoplasia can result from (1) lack of adequate space for the lung to grow either from intrathoracic space occupying lesion, longstanding pleural effusion, or extrathoracic compression (asphyxiating thoracic dystrophies); (2) reduction in fetal breathing movements; and (3) decreased amniotic fluid volume. Rarely, pulmonary hypoplasia may be associated with Trisomy 21 due to reduced numbers of alveoli and a smaller alveolar surface area.

Epidemiology: The true incidence of pulmonary hypoplasia is unknown because many infants with severe pulmonary hypoplasia die in utero, during labor or at birth. The frequency of pulmonary hypoplasia is related to the incidence of underlying causes. In cases of premature rupture of membranes at 15–28 weeks gestation, the reported incidence of pulmonary hypoplasia ranges from 9% to 28%. The occurrence of congenital diaphragmatic hernia (CDH) is estimated at 1/2,500–3,000 live births and cystic adenomatoid malformation (CCAM) 1 per 25,000–35,000 pregnancies. Adding to the difficulty in estimating the frequency is the wide spectrum of severity and presentation.

Pathogenesis: Lung development starts with the ventral outpouching of the primitive foregut to form the lung bud which then subsequently divides and branches through several phases to form the airways and lung parenchyma. Pulmonary vasculature develops in parallel with lung parenchyma. Any physical limitation to the space available for lung growth may impair lung development. This may result from intrathoracic compression (CDH, CCAM, large pleural effusion secondary to hydrops or congenital chylothorax) or extrathoracic compression secondary to skeletal abnormalities (asphyxiating thoracic dystrophy). Fetal lung growth is also dependent on adequate distension of the lung by fetal lung fluid and on fetal breathing movements, which are impaired or absent in conditions such as fetal akinesia syndromes, congenital myopathies, and phrenic nerve agenesis. The fetal kidney produces proline which together with several growth factors found in amniotic fluid aid in lung collagen and mesenchyme formation. As fetal lung liquid pressure is slightly higher than amniotic fluid pressure any decrease in amniotic fluid volume will be associated with loss of lung liquid and a decrease in the distending pressure to the developing lung. Fetal urine is an important component of amniotic fluid and renal agenesis/dysplasia or complete urinary tract obstruction (e.g., posterior urethral valves) is associated with oligohydramnios leading to pulmonary hypoplasia. The severity of lung hypoplasia depends on the timing of the insult in relation to the stages of lung development. The earlier the insult in gestation, the more severe the degree of lung hypoplasia. Physical and histological examination of the hypoplastic lung will show reduced lung weight, fewer generations of airways, decreased number of alveoli with delayed epithelialization, as well as paucity and maldevelopment of the corresponding pulmonary arteries.

Clinical Manifestations: The clinical presentation of infants with pulmonary hypoplasia depends on severity of disease and the underlying cause. In the severe forms, respiratory distress, hypercapnia, and hypoxemia are universal together with signs and symptoms of associated conditions. Infants with CDH may have a scaphoid abdomen and decreased breath sounds on the affected side. Infants with severe oligohydramnios may present with a small chest, contraction deformities such as arthrogryposis, and "Potters facies." Severe hypotonia with a small chest compared to the rest of the body may indicate an underlying central nervous system abnormality. Pulmonary hypertension commonly accompanies pulmonary hypoplasia.

Diagnosis: Most conditions associated with pulmonary hypoplasia can be identified through antenatal ultrasound and magnetic resonance imaging (MRI). The presence of pulmonary hypoplasia should be expected with any of the underlying associated conditions. Chest x-ray after birth will show an underdeveloped "bell shaped" rib cage with decreased lung expansion in patients with history of oligohydramnios or underlying neurologic disease.

Conditions where there is restriction of lung growth from external compression are often unilateral and can be identified on x-ray with the ipsilateral lung affected more than the contralateral lung. Definitive diagnosis of pulmonary hypoplasia requires pathologic examination of the lung to determine lung weight, perform radial alveolar counts, and measure the total lung DNA. Hypoplastic lungs have a decreased number of airway generations, with fewer and smaller peripheral airspaces and decrease in the number and cross-sectional area of pulmonary vessels.

Differential Diagnosis: The degree of pulmonary hypoplasia, if any, may be difficult to determine in milder cases and also when associated with other conditions. Severe RDS with poor lung expansion in a premature infant is difficult to differentiate from pulmonary hypoplasia radiographically. If the lung fields are relatively clear but with very low lung volume, hypoplasia is more likely.

Treatment: Recognition of conditions associated with pulmonary hypoplasia and instituting appropriate resuscitative measures are key to early management. Infants with CDH require immediate intubation with avoidance of facemask ventilation and rapid decompression of the stomach (see ❯ section on CDH). Infants with pulmonary hypoplasia have severely decreased lung compliance requiring higher airway pressure to achieve adequate gas exchange. This, together with the underdeveloped lung parenchyma, places these patients at increased risk of developing an airleak syndrome. Pulmonary hypertension from decreased pulmonary vascular development requires specific therapy as discussed in the section on PPHN. It should be noted that excessive expansion of the hypoplastic lungs will worsen PPHN due to compression of the pulmonary capillaries. Distending pressure should therefore be used with caution. High-frequency ventilation can provide better support with its ability to remove CO2 more efficiently and to treat or mitigate airleak syndromes better than conventional ventilation. In most patients with pulmonary hypoplasia, surfactant replacement therapy has not been shown to be beneficial unless the infant is also premature. Inhaled nitric oxide therapy may only show a transient improvement. Caution should be exercised in considering patients with severe pulmonary hypoplasia as candidates for ECMO, as the degree of lung hypoplasia and pulmonary vascular underdevelopment may not be reversible.

Prognosis: The outcome of infants with pulmonary hypoplasia is dependent on the degree of lung underdevelopment and the nature of the underlying disease. Conditions that hinder lung development early in gestation are associated with more severe hypoplasia and have the worst prognosis. Most infants with severe pulmonary hypoplasia die in utero, during labor, or soon after birth. Associated conditions with poor prognosis include: renal dysplasia, asphyxiating thoracic dystrophy, congenital myopathies, and other neurologic conditions. Surviving patients may go on to develop chronic pulmonary insufficiency requiring long-term care.

Prevention: There are no proven methods of prevention for most of the conditions leading to pulmonary hypoplasia. Animal and human studies have shown that tracheal occlusion in utero will reverse pulmonary hypoplasia but because of the high incidence of preterm deliveries related to this intervention, it has not been widely accepted and remains experimental. In utero placement of pleuroperitoneal shunt to treat pleural effusion and vesicoperitoneal shunt to relieve bladder outlet obstruction has met with mixed success as well.

Congenital Diaphragmatic Hernia (CDH)

Definition: CDH refers to herniation of abdominal contents into the chest through a defect in the diaphragm and the associated pulmonary hypoplasia present at birth.

Etiology: CDH is a developmental abnormality of the diaphragm resulting in a defect with resulting herniation of abdominal viscera into the chest. The diaphragmatic defect occurs when some of the structures making up the fetal diaphragm fail to develop adequately or to fuse by the eighth week post conception. Abnormalities in the retinoic acid signaling pathway may be important in the maldevelopment of the diaphragm early in gestation and may independently contribute to pulmonary hypoplasia.

Epidemiology: CDH occurs in 1/2,500–3,000 live births with a slight preponderance of males (1.5:1 male to female ratio). Recurrence risk for future pregnancies is approximately 2%. Worldwide incidence appears to be the same as that in the United States: 85–90% occur on the left side, 10% and a small number are bilateral. There are two types of diaphragmatic hernias: the posterior Bochdalek hernia accounting for about 95% of the total and the anterior Morgagni hernia for the remaining 5%.

Pathogenesis: In the fetus with CDH, the bowel, sometimes stomach, spleen, or liver herniate into the chest impairing lung development. Lung hypoplasia is thought to be secondary to the in utero compression of the fetal lung. Both the ipsilateral and contralateral lungs are involved, because the herniated abdominal contents cause mediastinal shift. The degree of hypoplasia is often severe on the ipsilateral side with only a minute lung seen in the apex of the chest at surgery. The severity of pulmonary hypoplasia roughly correlates with the size of the

defect, which may range from a small posterior opening to complete agenesis of the hemidiaphragm. Lung hypoplasia involves not just a decrease in lung parenchyma, but a dramatic decrease in the number and cross-sectional area of the pulmonary blood vessels. Additionally, there is abnormal muscularization of the pulmonary arterioles and increased vasoreactivity, which often leads to associated refractory PPHN.

Clinical Manifestations: The severity of respiratory distress is highly variable. Most infants present in the delivery room with cyanosis, retractions, and tachypnea. Breath sounds are decreased on the affected side with shift of the breath sounds to the opposite side – all signs consistent also with the more common problem of spontaneous tension pneumothorax. The key differentiating factor is that the abdomen is distended in the presence of pneumothorax, while it is flat or scaphoid with CDH. Bowel sounds are rarely heard in the chest, but this sign is diagnostic, if present. Some infants have minimal signs initially and may not be recognized for some time. The clinical status often remains reasonably stable for the first 12–24 hours, a period referred to as the "honeymoon," followed by development of severe pulmonary hypertension.

Diagnosis: In industrialized countries, the majority of cases are diagnosed by antenatal ultrasound. Postnatal diagnosis is based on clinical presentation and radiographic confirmation. Initial chest films may not show the classical bowel pattern in the chest, if air has not yet filled the bowel, but may instead just show a water density mass with mediastinal shift.

Differential Diagnosis: CDH must be distinguished from eventration of the diaphragm, pulmonary sequestration, pleural effusion, or cystic adenomatoid malformation involving the lower lobes of the lung. Acutely, it must be distinguished from tension pneumothorax.

Treatment: Immediate intubation with avoidance of facemask ventilation is critical to avoid filling the bowel with air and causing further lung compression. A naso- or oro-gastric tube is rapidly placed for gastric decompression. Muscle relaxation is advocated by some to prevent the infant from swallowing air, but this is not usually needed when effective gastric decompression. Nasal CPAP or high-flow nasal cannula are to be avoided. Pulmonary hypertension is triggered or aggravated by pulmonary overexpansion; therefore distending airway pressure is applied cautiously. Gentle ventilation with either conventional or high-frequency ventilators, allowing moderate permissive hypercapnia and accepting just adequate oxygenation, appears to improve outcome, compared to the more aggressive traditional treatment, even when PPHN is present. Exogenous surfactant does not appear to be beneficial (unless the infant is premature) and was associated with worse outcomes in a large retrospective study. Infants with CDH and PPHN do not usually respond well to inhaled NO, but many show a modest transient improvement.

CDH is no longer considered a surgical emergency, since it is now well recognized that the fundamental problem is the pulmonary and pulmonary vascular hypoplasia, which is not reversed by removing the herniated contents from the chest. In fact it is now clear that early surgery at the time of greatest physiologic instability and highest pulmonary vascular resistance often makes matters worse. The surgical approach now is to await improvement in pulmonary status and delay surgery for 3–7 days or until the infant is on low ventilator settings and FiO_2. In unstable patients ECMO, where available, is offered prior to surgical repair. ECMO remains the treatment of last resort, but survival remains only about 50% in infants sick enough to require this rescue therapy.

Prognosis: Prognosis depends on the presence or absence of other anomalies, severity of the defect, and availability of state of the art treatment. Associated anomalies, especially chromosomal, portend a poor prognosis. Polyhydramnios, presence of liver in the chest, and low lung-to-head ratio (LHR) are poor prognostic factors. The LHR, is a ratio of the visible lung on the contralateral side to fetal head. MRI volumetry has been proposed as a better tool, but requires validation. Echocardiography is utilized to detect associated fetal cardiac anomalies. Various estimates of left ventricular mass and pulmonary artery diameters appear to be good indicators of pulmonary hypoplasia. Survival depends on the denominator used in the calculation. Many CDH pregnancies end in elective termination, spontaneous abortion, or stillbirth, especially when associated anomalies are found. A substantial number of live born infants succumb in the delivery room. Therefore, reported survival statistics from tertiary centers include only a selected group of infants who reached the center alive. This "hidden mortality" not seen at the tertiary center accounts for large differences in reported survival. When all CDH pregnancies are counted, survival may be as low as 25%. Infants reaching tertiary centers have a 60–80% survival with the most advanced care, but continue to have long-term sequelae, including growth failure, severe gastroesophageal reflux, and developmental delays. Late death may occur after apparently successful treatment from recurrent pulmonary hypertension.

Prevention: There is no known prevention for CDH, but in utero fetal therapy has been a subject of intense study. It has been shown that the lung hypoplasia can be reversed by fetal tracheal occlusion, but improved survival

has been difficult to demonstrate, in part due to high rate of preterm delivery associated with this procedure. The treatment remains experimental.

Bronchopulmonary Dysplasia (BPD)

Definition: Bronchopulmonary dysplasia is defined as lung injury in preterm infants resulting from oxygen and mechanical ventilation. Various definitions have been used since its initial description in 1967. Oxygen requirement at 36 weeks postmenstrual age has been the most widely used definition. Current definition has been modified to define severity of BPD and differentiate between infants of different gestational age. This definition, based on the NIH consensus conference in 2001, is shown in *Table 15.3*.

Etiology: BPD is believed to result from the combination of oxygen-mediated injury and exposure to mechanical ventilation in immature lungs with limited antioxidant defenses.

Oxygen exposure impairs secondary crest formation and alveolar septation, leading to a "simplified lung," which lacks adequate surface area and sufficient pulmonary capillaries in close proximity to the saccules. Mechanical ventilation results in disruption of cellular structures, release of inflammatory mediators, chemokines, and influx of activated neutrophils, beginning a sequence of injury, inflammation, and repair that eventually results in the clinical picture of BPD.

Epidemiology: The Neonatal Research Network study of 1,598 inborn survivors 501–1,249 g born between 2000 and 2002 showed that 31% received oxygen or ventilatory assistance at 36 weeks. Prematurity is the single most important predisposing factor for BPD; in one study, the incidence of BPD using the 36 weeks postmenstrual age definition was 42% for infants weighing 501–750 g, 25% for 751–1,000 g, and 11% for infants 1,001–1,250 g. Data from the Israeli National VLBW database showed that 19% of 3,689 VLBW infants met the definition of BPD. BPD is the most common form of chronic lung disease in infants in the United States with an estimated 7,000–10,000 new cases occurring each year.

Pathogenesis: Tissue stretch associated with mechanical ventilation results in disruption of airway epithelial and alveolar cells with early interstitial and alveolar edema which progresses to persistent structural changes, persistent inflammation, and fibrosis in the lung that ultimately result in significant effects on lung mechanics, gas exchange, and pulmonary vasculature. It is a heterogeneous condition and its manifestations vary. In some infants it is characterized primarily by arrest of normal lung development, resulting in a "simplified lung," which has decreased number of larger alveoli, paucity of pulmonary capillaries in close proximity to the saccules, and decreased total surface area for gas exchange (the "new BPD"). Various degrees of interstitial fibrosis and elastin deposition in alveolar walls may be associated with the more severe forms of BPD, as a result of the complex sequence of lung injury, inflammation, and remodeling. These infants typically have significant airway disease as part of their clinical picture with increased airway resistance, mucosal thickening, ongoing inflammation, increased mucus production, and varying degrees of airway smooth muscle hyperplasia.

The pathogenesis of PBD is complex and multifactorial. The role of inflammation is increasingly recognized with both prenatal and postnatal infection contributing substantially to the development of BPD. It has been shown that the rate of histologic chorioamnionitis is

Table 15.3
Diagnostic criteria for BPD

Gestational Age	<32 weeks	≥32 weeks
Time of assessment	36 weeks PMA or discharge, whichever comes first	28–56 days postnatal age or discharge, whichever comes first
	Treatment with oxygen >21% for at least 28 days, *plus*	Treatment with oxygen >21% for at least 28 days, *plus*
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days
		PMA or discharge, whichever
Moderate BPD	Need[a] for <30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need[a] for <30% oxygen at 56 days of age or at discharge, whichever comes first
Severe BPD	Need[a] for <30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need[a] for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days of age or discharge, whichever comes first

PMA postmenstrual age, PPV positive pressure ventilation, NCPAP nasal continuous positive pressure ventilation

[a]Need should ideally be defined by physiologic criteria, e.g., need to maintain SPO2 >90%. The optimal SPO2 targets are not yet well defined

inversely proportional to gestational age. Other contributing factors include excessive fluid intake, presence of patent ductus arteriosus, and exposure to high FiO2 and large tidal volume ventilation. Infection with Ureaplasma Urealyticum is associated with a high incidence of BPD, but its postnatal eradication does not appear to improve outcome. There is considerable variation in susceptibility to BPD and the underlying mechanisms for the genetic basis of this are under intense investigation.

Clinical Manifestations: BPD evolves insidiously when the initial RDS fails to resolve. The infant will have persistent or increasing oxygen requirement, tachypnea, and retractions with increased secretions noted in intubated infants. Some VLBW infants may have little or no RDS initially, but then gradually develop increasing oxygen requirement and classical features of BPD. Chest radiographs initially show diffusely hazy lungs with good lung expansion and this may progress to the more patchy, hyperinflated lung fields associated with classical BPD. The increased airway resistance is in part due to the poorly supported small airways with tendency to airway collapse at low lung volume. There is airway mucosal edema with increased secretions, but usually there is no active bronchoconstriction in the first few weeks of life. In later stages of BPD, reactive airway disease may develop. Severe cases of BPD may be associated with pulmonary hypertension and this is occasionally fatal.

Diagnosis: There is no single diagnostic test. The condition evolves over time, beginning within days of birth, but the formal diagnosis is based on oxygen or positive pressure ventilation requirement at 28 days or beyond. Radiographic changes are no longer a requirement for the diagnosis, but are typically present.

Differential Diagnosis: The main distinction is between BPD and chronic pulmonary insufficiency of prematurity (CPIP), related to insufficient rigidity of the chest wall leading to diffuse microatelectasis and consequent oxygen requirement. The differentiation is best made on chest radiographs. In both instances, there is increased opacification of the lung fields, but the lung expansion is normal or increased in BPD and reduced with CPIP. When respiratory status is deteriorating during the second or third week of life in a ventilated preterm infant, evolving BPD needs to be differentiated from ventilator associated pneumonia. This is not always easy, as endotracheal tube cultures and gram stains only indicate colonization, not necessarily infection. The chest x-ray may not be helpful, as diffuse pulmonary opacities are seen in both conditions. Acute deterioration is more likely to represent infection. Presence of leukocytes on gram stain of ET secretions and changes in peripheral white count support the diagnosis of infection. Recurrent aspiration pneumonia may contribute to or mimic BPD – evidence of gastroesophageal reflux should be sought in infants whose BPD is worsening over time.

Treatment: Treatment is primarily supportive with optimization of ventilator support and aggressive nutritional support. The ventilator settings need to reflect the longer time constants resulting from increased airway resistance. Therefore, inspiratory and expiratory time need to be sufficiently long. Overexpansion and air trapping are often seen in these infants. The common response to this is lowering of the PEEP setting, which is actually counterproductive. Air trapping typically results from airway closure at low lung volume and is made worse at low PEEP. This can be seen on the flow-volume loop with pulmonary function testing. Increasing the PEEP setting until the flow limitation at low lung volume resolves is helpful. Optimal oxygenation targets remain the subject of intense study. Higher targets appear to increase lung injury in the majority of infants. However, lower oxygen tension may over time lead to increased pulmonary vascular resistance and increase the risk of serious pulmonary hypertension. Current practice is to limit oxygen exposure until PMA of about 34–35 weeks by targeting SPO2 of 85–93% and to use somewhat higher targets beyond that period. In infants with documented pulmonary hypertension, SPO2 should be maintained in mid to high 90 s. The role of diuretics remains controversial. There is good evidence of short-term benefit in lung mechanics, but the diuretics often lead to electrolyte imbalance and their impact on ultimate outcome is unproven. Thiazides and spironolactone are most widely used for treatment of BPD. Furosemide is associated with more severe adverse effects, including osteopenia, rib fractures, and renal calculi. Bronchodilators are commonly used without evidence of long-term benefit. The elevated airway resistance in early BPD is not due to bronchoconstriction, therefore unlikely to be affected by bronchodilators. Later on, there may be a place for bronchodilators in selected infants, but lack of tools to measure airway resistance in non-intubated infants hampers rational use of these drugs. Methylxanthines are widely used and probably beneficial, although this may be more related to increased CO2 responsiveness and increased diaphragmatic contractility than bronchodilation.

Postnatal steroids were once used liberally and at high doses lasting up to 6 weeks. This practice was later recognized as increasing the incidence of abnormal neurologic outcome especially when started in the first week of life. Steroids are now used much more. Short courses Dexamethasone at doses of 0.15 mg/kg/d, divided q12 h appear to be effective and is thought to be safer than the much

higher cumulative doses used previously. Inhaled corticosteroids are widely used, but evidence of benefit is scant. No sound evidence exists to guide the treatment of pulmonary hypertension when it develops. The use of iNO has become widespread and it has at least transient benefits in most infants. Transition to an oral agent such as sildenafil, a phosphodiesterase 5 inhibitor appears warranted. Higher oxygen saturation targets and avoidance of hypercapnia are thought to be beneficial.

Prognosis: A small proportion of infants fail to wean from mechanical ventilation and go on to worsening lung disease with progressive pulmonary hypertension and death. Most infants ultimately outgrow the disease and become symptom free by early childhood. However, they remain at increased risk of lower respiratory tract infections, especially with respiratory syncytial virus, require more frequent rehospitalization, and are more likely to develop asthma. These infants may fail to thrive and are at risk of significant post-discharge morbidity and mortality. Careful pulmonary function testing at school age and beyond shows continued subtle abnormalities, but these are generally not functionally limiting. Infants with BPD have worse neurodevelopmental outcome compared to infants of similar gestational age without BPD.

Prevention: Prevention of BPD is the ultimate goal of care, but an elusive one. Antenatal corticosteroids, avoidance of injurious ventilation, use of noninvasive respiratory support, and surfactant administration are all important in limiting lung injury. Recent trials of HFV have failed to show clear benefit over lung-protective conventional ventilation. Vitamin A has been shown to reduce BPD, but requires frequent intramuscular injection. Early and continued treatment with caffeine reduces the risk of BPD by a similar amount and is much less onerous. Avoidance of excessive fluid intake is advisable. It is unclear whether early treatment of PDA reduces the incidence of BPD. Prophylactic use of iNO may be an effective strategy for BPD prevention when initiated at 1–2 weeks of life and administered for several weeks, but despite very strong laboratory evidence of efficacy, the clinical data are conflicting. Prevention of prematurity is the only definitive way of preventing BPD.

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