Systems Assessment and Management of Disorders

Respiratory System

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OVERVIEW

Neonatal respiratory compromise can be pulmonary in nature or related to other neonatal comorbidities, including congenital heart defects, congenital malformations, metabolic abnormalities, and disorders of the central nervous system (CNS). Regardless of origin, these infants often present in a similar fashion with respiratory distress that includes increased rate and effort of breathing, cyanosis, and oxygen requirement. Ninety percent of all respiratory distress in neonates is caused by respiratory distress syndrome (RDS), aspiration, transient tachypnea, air leaks, and congenital pneumonia (Fraser, 2021).

"Respiratory distress" is a global term that refers to disorders of the respiratory system that begin at or shortly following birth. Although most common in those infants born prior to term, respiratory distress can result from any neonatal condition that leads to progressive atelectasis, hypoventilation, and/or hypoxia. Diseases that affect the respiratory system in the early neonatal period may extend well into infancy or childhood.

If lung compliance is decreased, there is also a decrease in tidal volume, which is the amount of air that enters or exits the lungs with every inhalation or exhalation. For the neonate to achieve sufficient minute ventilation (tidal volume x respiratory rate per minute), the respiratory rate will increase (tachypnea) when tidal volume is small. Hypoxemia will also trigger an increased respiratory rate to compensate. Increased work of breathing is the result of mismatched pulmonary mechanics, including increased airway resistance, diminished lung compliance, or both (Reuter et al., 2014).

Complex mechanisms and structures bring about normal pulmonary development and function in the neonate. Both anatomic and physiologic processes occur to facilitate the maturation of the respiratory system. This process occurs along an orderly sequence of events from the fourth week of gestation through the eighth year of life.

RESPIRATORY SYSTEM DEVELOPMENT

Anatomic Development of the Respiratory System

Outgrowth of the laryngotracheal groove found in the floor of the caudal end of the anterior foregut starts the complex process of respiratory system development. By the end of the fourth week, this groove has protruded and developed into a

pouch-like structure, laryngotracheal diverticulum. The diverticulum lengthens and enlarges to form a globular lung bud from which the tracheobronchial tree originates. Initially, the right and left lung buds appear as lateral outpouchings of foregut on each side of the tracheal primordium. By the end of the fifth week of development, the tracheoesophageal septum has developed from the longitudinal growth and fusion of the tracheoesophageal folds. This septum separates the cranial portion of the foregut into a ventral part, laryngotracheal tube, and a dorsal part, which is the origin of the oropharynx and esophagus. Separation of the single foregut tube into trachea and esophagus occurs through a complex process requiring multiple signaling pathways and transcription factors.

Development of the Larynx

The larynx develops from the endoderm of the cranial end of the laryngotracheal tube. Cartilages develop from mesenchyme derived from neural crest cells. The mesenchyme grows rapidly, eventually producing the slit-like laryngeal inlet by the end of the sixth week. Temporary occlusion of the laryngeal lumen occurs thereafter with recanalization by the 10th week, during which time the laryngeal ventricles, vocal cords, and vestibular folds develop. The epiglottis arises from the caudal part of the hypopharyngeal prominence. Laryngeal muscles developed from myoblasts in the fourth and sixth pairs of pharyngeal arches are innervated by the vagus nerves (cranial nerve X). Of note, the larynx is situated high in the neck of the neonate, which allows the epiglottis to come in contact with the soft palate. This location provides almost complete separation between the respiratory and digestive tract to facilitate feeding later on. However, this also makes the neonate an obligatory nose breather. The larynx structurally descends over the first 2 years of life.

Development of the Trachea

During separation from the foregut, the laryngotracheal diverticulum forms the beginning of the trachea and primary bronchial buds. Splanchnic mesenchyme gives rise to the cartilage, connective tissue, and muscles of the trachea. This development goes through the 12th week of gestation.

Development of the Bronchi and Lungs

The respiratory bud that developed during the fourth week divides into two bronchial buds. The bronchial buds grow laterally into the pericardio-peritoneal canals forming the beginning of the pleural cavities. The buds and splanchnic mesenchyme evolve into the bronchi and their branches in the lungs. At the beginning of the fifth week, the connection of the bud to the trachea enlarges and forms the main bronchi. The right main bronchus is slightly larger than the left. The main bronchi subdivide, eventually forming three lobes on the right and two on the left. Progressive branching continues until the end of the seventh week, and 10 segmental bronchi in the right and eight or nine in the left form. By 24 weeks, about 17 orders of branches have formed, and bronchioles have developed. Additionally, seven more orders of branches develop after birth.

The splanchnic mesenchyme develops into cartilaginous plates, bronchial smooth muscle, connective tissue, and capillaries. As the lungs continue to develop, a layer of visceral pleura forms from the same splanchnic mesenchyme. Eventually, the lungs and pleural cavities grow caudally into the mesenchyme of the body wall and lie close to the heart.

Physiologic Development of the Respiratory System

Five overlapping microscopic stages comprise the maturation periods of the lungs: pseudoglandular, canalicular, saccular, surfactant, and alveolar (Moore et al., 2020).

Pseudoglandular: Weeks 5 to 17. At this point, the lungs are similar to exocrine glands. By 16 weeks, all major elements have formed except those involving gas exchange. Fetuses born during this time are unable to survive due to the lack of respiratory function to enable gas exchange.

Canalicular: Weeks 16 to 25. Lumen of the bronchi and terminal bronchioles becomes larger, and the lung tissue itself becomes very vascular. The production of surfactant begins around 20 to 22 weeks in small amounts, but it does not reach adequate amounts until later in gestation. Lamellar bodies store surfactant. Having adequately developed pulmonary vasculature that allows gas exchange and having the ability to produce surfactant are the two critical keys to neonatal survival for the extremely premature infants. By week 24, each terminal bronchiole has formed respiratory bronchioles, which further divide into early alveolar ducts. Respiration is possible near the end of this stage, because early alveoli have formed and the tissue is well vascularized. However, supplemental surfactant is necessary at this early stage.

Saccular: Weeks 24 to late in fetal development. More alveoli develop and the epithelium becomes very thin with capillaries protruding into the sacs to further facilitate gas exchange. Differentiation of type I and II pneumocytes occurs. Establishment of a blood-air barrier permits adequate gas exchange across type I pneumocytes if the fetus were born at this gestation. Surfactant (a complex mixture of phospholipids and proteins) is also being secreted by type II pneumocytes at this time; however, not in adequate amounts.

Surfactant: As stated earlier, these five microscopic stages overlap, and surfactant production begins around 20 to 22 weeks and does not reach adequate levels until later in gestation. Surfactant forms a thin film over the insides of alveolar sacs.

- Counteracts surface tension at the air–alveolar interface, thus preventing air sac collapse, which leads to atelectasis, decreases opening pressure of the alveoli, enhances alveolar fluid clearance, and provides a level of protection for the fragile epithelial cell surface (Gardner et al., 2021).
- Phosphatidylglycerol (PG), which is the second most common phospholipid in surfactant, usually appears at about 36 weeks' gestation and continues to increase until term.

- It is stored, recycled, and secreted in the neonatal lung; however, under certain conditions, the metabolism and/or effectiveness of surfactant will be altered. These include maternal conditions such as diabetes, infection, hypertension, drug use, and placental insufficiency, as well as infant conditions such as acidemia, hypoxia, need for mechanical ventilation, hypercapnia, twin gestation, sepsis, and prematurity (Gardner et al., 2021).
- Adequate amounts of surfactant to prevent atelectasis are generally not achieved until at least 32 weeks.

Alveolar: The alveolar stage is the late gestational period up to 8 years of age. By 34 weeks, each bronchiole ends with an alveolar sac. These sacs will eventually become alveolar ducts. By 38 weeks, the alveolar capillary membrane across which gas exchange occurs is very thin. Three adaptive changes must occur during transition from fetal life to extrauterine life: (1) parallel pulmonary and systemic circulations, (2) lungs transform from secretory organs to gas-exchanging organs, and (3) production of surfactant in the alveolar sacs. Much of lung development after birth results from multiplication of alveoli and capillaries. Approximately 150 million alveoli (half of the adult number) are present in the lungs at full term (Moore et al., 2020).

At birth, the lungs are partially filled with a fluid continually produced by the lungs. Aeration of the lungs requires rapid replacement of fluid with air in the alveoli. The fluid is cleared through the mouth and nose via compression of the thorax, moves into the pulmonary capillaries, arteries, and veins, and then travels into the lymphatics.

This transition to extrauterine life begins as the infant takes the first breath of air, usually in response to tactile stimulation upon birth. This first breath of the term infant requires an opening pressure of 60 to 80 cm of water with subsequent breaths requiring less as the surface tension of the liquid-filled airways and alveoli is stabilized.

Oxygen passively diffuses across the alveolar–capillary membrane, due to the difference in oxygen pressure, which is higher in the alveoli than in the capillary blood supply. Oxygen dissolves in the plasma and then binds to the hemoglobin and circulates systemically. Oxygen is deposited throughout the tissues in much the same passive manner. The oxygen pressure is higher in the arterial blood supply than in the tissues; therefore, the oxygen moves from the hemoglobin to the tissues.

RESPIRATORY SYSTEM ASSESSMENT

A thorough and systematic review of the prenatal and birth history will provide the clinician with information regarding specific risk factors that will impact neonatal care and resuscitation requirements. Certain maternal conditions greatly influence the development and subsequent function of the neonatal respiratory system. Maternal history is typically separated into three separate time frames: antepartum (during pregnancy), intrapartum (labor and delivery), and postpartum (following delivery). Maternal conditions, both chronic and acute, affect the fetal well-being, both in the short term and potentially the long term. Maternal serologies including

blood type, history of infection, ultrasound findings including estimated fetal weight, and gestation should be identified prior to delivery whenever possible.

An overall review of the infant's vital signs (heart rate, respiratory rate, temperature, and blood pressure) and general appearance during the adaptation to the extrauterine environment are the beginning of the infant assessment. Numerous specific visual clinical observations will provide information before a stethoscope is even placed on the infant's chest.

- **Respiratory rate:** Respiratory rates in an infant can be highly variable. Deviation from normal respiratory rates of approximately 40 to 60 breaths per minute can be due to numerous reasons, including pulmonary dysfunction, metabolic derangements, central nervous system (CNS) dysfunction, periodic breathing pattern related to prematurity, and blood gas abnormalities. Low respiratory rates can result in decreased minute ventilation, and high rates may be a result of low tidal volumes. Infants can adjust their respiratory rate to minimize the work of breathing. Visually counting the respiratory rate removes the error associated with interference or artifact from the EKG leads. Periodic breathing is a cycle of very shallow breaths or even apnea lasting 5 to 10 seconds interspersed with adequate respirations. This is common in premature infants related to the immature CNS. Bradypnea is a respiratory rate below 30 breaths per minute. Apnea is the cessation of respirations lasting longer than 20 seconds, and it can be a sign of impending respiratory failure requiring prompt initiation of assisted respirations.
- **Retractions:** Neonates have a very compliant chest wall resulting in very visible retractions in the suprasternal, substernal, subcostal, and intercostal areas. Negative intrapleural pressure generated by the diaphragm and respiratory accessory muscles causes retractions.
- **Nasal flaring:** Infants are almost exclusively nose breathers. Therefore, nasal resistance contributes to overall total airway resistance. Nasal flaring results from dilation of the muscles, thereby reducing nasal resistance and the overall work of breathing.
- **Grunting:** Exhaling through a partially closed glottis results in a grunting noise. This is a compensatory method to maintain functional residual capacity (FRC) to maintain alveolar distention and promote gas exchange. This may be heard audibly without a stethoscope. Grunting can be intermittent or continuous in nature. Grunting must be differentiated from gasping, which is a sign of impending respiratory failure during which immediate intervention with positive pressure ventilation is indicated.
- **Cyanosis:** The visible discoloration most easily noted on central mucous membranes can be purple or blue in appearance. Clinical cyanosis is visible at varying levels of oxygen saturation based on hemoglobin. Infants with anemia can exhibit low PaO_2 without obvious visible cyanosis. Conversely, patients with polycythemia may have clinical cyanosis but normal PaO_2 . Cyanosis is a classic sign of hypoxemia.
- **General appearance:** Symmetry of the chest, barrel chest or pigeon chest appearance, and scaphoid appearance of the abdomen can provide clues to pathology causing respiratory symptoms (and connect to) such as diaphragmatic hernia.

- Pallor, mottling, or poor color of the infant may indicate hypotension or acidosis.
- Tachycardia, bradycardia, blood pressure changes, and perfusion are important signs of cardiac compromise from congenital heart disease (CHD) or ongoing respiratory compromise and failure.
- Diminished muscle tone and poor activity are critical signs of profound hypoxia and acidosis.
- Auscultation of the chest is difficult due to the small size of the neonate and referred breath sounds. It includes:
 - Comparing and contrasting bilateral lung sounds
 - Quality and volume of air exchange
 - Adventitious breath sounds (crackles, rales, and decreased air entry)
 - Absence or asymmetric volume of air exchange
- Percussion and palpation of the neonatal chest have little diagnosis value.

Generalized Nursing Care

Nursing care of the neonate exhibiting respiratory distress is multifaceted and should be geared toward maintaining homeostasis within the body. Acquiring the nursing skills to adequately assess and care for the sick neonate requires a strong nursing education as foundation and additional mentoring by experienced neonatal nurses. Nurses must be efficient, gentle, and also acutely aware of maintaining a supportive environment for their young patients. In the case of neonates, sometimes a hands-off approach may be more supportive to the infant versus overstimulation.

- Maintaining a neutral thermal environment: Supporting the temperature regulation of the neonate by providing heat and/or humidity and eliminating heat loss or gain from evaporative, radiant, conductive, and convective sources. Avoiding hypothermia or hyperthermia allows the infant to conserve metabolic expenditure. Radiant warmers and incubators can be used to assist in temperature support.
- Any infant exhibiting respiratory distress should have close nursing support of glucose homeostasis. During the critical phase of respiratory management, this is accomplished by glucose and protein intravenous (IV) support. Nurses require skills in obtaining and maintaining IV access, ensuring appropriate rates of infusions, and checking blood sugar levels at appropriate intervals in accordance with the policy or guidance based on the provider order.
- Maintaining the ordered respiratory support is a key nursing skill. A variety of respiratory support devices (nasal cannula [NC], continuous positive airway pressure [CPAP] apparatus, conventional ventilator, and high-frequency ventilator) must be maintained by nurses in collaboration with respiratory therapists, medical team providers, and parents to achieve optimal success. Recognizing when clinical changes are occurring with the neonate and understanding what those changes may indicate are crucial. Using a variety of tools such as suctioning,

positioning, blood gas monitoring, and end-tidal CO_2 trending helps nurses optimize respiratory support. Maintaining an infant on CPAP is very labor-intensive for nursing staff. Generally CPAP devices have three interface options: mask, prong, and cannula. The mask must be situated such that it sits on the bridge of the nose, covers the nostrils, and rests on the philtrum. Improperly fitted/positioned masks may occlude the nares, sit on the lip, or cover the eyes. This results in an ineffective seal, pressure to the skin and eyes, and risk of skin irritation or breakdown. CPAP prongs must be sized such that they allow for the most air flow through them without putting undue pressure to the inside of the nostrils. The seal is imperative to achieve the desired CPAP. Use of a cannula-type device is being undertaken by some neonatal intensive care units and does not require a seal.

- Monitoring intake and output to avoid over- or underhydration is important depending on other clinical issues such as gestational age.
- Monitoring oxygen saturations and titrating oxygen as needed helps to achieve the ordered target range for the specific infant and disease process.
- Obtaining blood gases and other labs as needed via arterial, venous, or capillary sampling and understanding the results of these tests is a key skill.
- Vigilant nursing observation and assessment is needed to notice subtle changes in the infant's condition, such as sudden increase in work of breathing or oxygen requirement.
- Assisting with positioning of the infant helps achieve optimal radiographic images.
- Assessing and managing pain and agitation is performed using nonpharmacologic and/or pharmacologic measures.

In summary, generalized nursing care of the neonate exhibiting respiratory distress is complex and multifaceted. It requires continuous ongoing assessment by astute nurses.

Brief Overview of Blood Gas Analysis

The goal of blood gas analysis in the neonate is to determine the type and degree of disorder and presence of any compensation. Indications include all forms of respiratory distress, metabolic conditions, sepsis, and neurologic concerns. Cord gases may provide the clinician with a specific quantity in which to determine the degree of asphyxia experienced prior to birth (see Figure 1.1). Oxygen moves from the oxygen-rich alveolar–capillary membrane through passive measures to the blood, where the oxygen level is lower. This passive mechanism is the partial pressure of oxygen. The oxygen dissolves into the plasma and binds to the hemoglobin. This measure is reflected in the PaO_2 value.

Carbon dioxide moves rapidly across the cell membrane in response to ventilation. The movement from tissues is more efficient than oxygenation. The PaCO_2 reflects ventilation status.

Blood gas results must be evaluated based on the type of sample (capillary, venous, arterial). Arterial samples provide valid data pertaining to acid–base

FIGURE 1.1 Acid–base balance: diagnostic approach. (A) Low pH. (B) High pH.

Source: Gentle, S., Travers, C., & Carlo, W. A. (2020). Respiratory system. In C. Kenner, L. B. Altimier, & M. V. Boykova (Eds.), *Comprehensive neonatal nursing care* (6th ed., pp 127–146). Springer Publishing Company.

balance and oxygenation, whereas capillary samples are not useful for evaluating accurate PO_2 . Arterial samples are always preferred but not necessarily easily obtained since they require an advanced skill to perform arterial puncture when infants do not have an arterial line, such as a peripheral or umbilical artery line. Capillary specimens may not be accurate in the setting of hypotension, hypothermia, or shock where perfusion is not optimal. Warming the heel for 3 to 5 minutes prior to sampling optimizes conditions so the best quality sample may be obtained. Bicarbonate and base excess/deficit are calculated numbers based on measured pH and pCO_2 . Blood gas results for pH and bicarbonate are slightly lower than normal values in the first 48 hours of life (Karlsen, 2013).

The acid–base balance depends on the interaction between bicarbonate ions and carbon dioxide. Acidosis or low pH is not well tolerated by the neonate and can increase vasoconstriction in sensitive pulmonary vasculature, increasing the state of hypoxemia (see Figure 1.1; also see the MedCalc Acid–Base Calculator at www.medcalc.com/acidbase.html).

Common neonatal respiratory conditions are listed and described in the following text. Common diagnoses with a decision-making algorithm for the infant who presents with respiratory disease are included (see Figure 1.2). Specific care and treatment of these conditions are described under each topical heading.

FIGURE 1.2 Diagnostic algorithm for the neonate with acute respiratory distress.

Source: Gentle, S., Travers, C., & Carlo, W. A. (2020). Respiratory system. In C. Kenner, L. B. Altimier, & M. V. Boykova (Eds.), *Comprehensive neonatal nursing care* (6th ed., pp 127–146). Springer Publishing Company.

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RESPIRATORY DISTRESS SYNDROME

Incidence

- Inverse relationship to gestational age: Nearly all infants born at 22 to 24 weeks and decreasing as birthweight increases down to ~10% at 34 weeks and less than 1% at 37 weeks (Lagoski et al., 2020).
- European descent, late preterm delivery (35–36 weeks), and elective delivery in the absence of labor are well-known risk factors.
- Higher occurrence with maternal history of gestational or chronic diabetes (infant of a diabetic mother [IDM] or gestational diabetes mellitus [GDM]), chorioamnionitis, or perinatal asphyxia.
- Slight male predominance.

Pathophysiology

The causes of RDS are varied and may reflect disorders of alterations of normal lung development (e.g., in the case of oligohydramnios leading to hypoplastic lungs), or lack of development in the preterm infant, or failure to transition to extrauterine life.

- Histologic sampling of lung tissue of RDS yields uniform ruddy airless appearance much like hepatic tissue (Lagoski et al., 2020). Diffuse atelectasis with a few widely dilated alveoli is evident.
- Lining the airspaces of the bronchioles and alveolar ducts is an eosinophilic membrane. In RDS, this membrane contains fibrinous material and cellular debris from injured epithelium (Lagoski et al., 2020).
- Development is multifactorial:
 - Impaired or delayed surfactant production
 - Exposure to high oxygen concentrations
 - Effects of volutrauma

These factors trigger a proinflammatory response involving cytokines and chemokines causing more damage to the alveolar lining, which results in decreased surfactant synthesis and function (Lagoski et al., 2020).

The inflammatory cascade is often initiated secondary to the pulmonary cellular injury or globally in the case of perinatal/neonatal asphyxia. Inflammation causes increased metabolic workload on the neonate, including increased oxygen requirement, and can contribute to cell damage and death of the affected and surrounding tissues (Newnam et al., 2013).

Diagnosis

The RDS diagnosis is based on history, physical findings, blood gas analysis, x-rays, and exclusion of other causes such as infection or cardiac causes. Distress is usually present at birth or shortly thereafter. Progressive respiratory difficulty typically coincides with increasing atelectasis of the alveoli and may take place over the first few minutes of life or several hours following birth. Infants with poor or deficient respiratory effort can progress to respiratory failure rapidly, if effective intervention is not provided in a timely manner.

Blood Gas Analysis

- Respiratory acidosis; increased CO_2 levels as the atelectasis progresses.
- Increased acidosis (respiratory and metabolic) ensues as the hypoxemia progresses. The pH decreases, the CO_2 level increases, PaO_2 level decreases, and bicarbonate decreases.
- If aerobic respiration is compromised or cardiac function is impeded, the lactic acid builds up and increases systemically, predisposing the infant to a state of progressive systemic acidosis (lowering of pH and bicarbonate levels).

Radiographic Findings

- The anteroposterior (AP) view is usually sufficient for initial examination.
- Diffuse reticulogranular appearance caused by atelectasis and possibly pulmonary edema often described as ground glass is observed (see Table 1.1, Figure 1.3).
- Air bronchograms representative of aerated bronchioles superimposed on a background of nonaerated alveoli are notable (see Table 1.1, Figure 1.3).
- It is usually symmetric and homogeneous in appearance.
- In severe cases, the view may have complete opacification throughout the lung field.
- Heart size is generally normal or slightly enlarged. Cardiomegaly can be a sign of development of congestive heart failure.

Treatment

- Respiratory support includes:
 - Surfactant administration—a number of modalities have been studied to deliver surfactant including via endotracheal tube (ETT), via laryngeal mask airway, and brief tracheal catheterization with a thin catheter (Dargaville, 2019).
 - Nasal CPAP, “sigh” synchronized intermittent airway pressure (SiPAP), or noninvasive positive pressure ventilation (NIPPV) may be used.
 - Stabilize alveoli, maintain lung recruitment, and decrease work of breathing, which may reduce apnea of prematurity (AOP).
 - In recent years, strategies have focused on trying to avoid invasive ventilation for extremely low birth weights (ELBW). However, the frequency of need for supplemental oxygen at 36 weeks has not decreased and pulmonary function during childhood has not significantly improved (Doyle et al., 2017).
 - Mechanical ventilation pressure-controlled, volume-controlled, and high-frequency ventilation techniques may be employed.
 - Supplemental oxygen delivery—maintenance of distending pressure facilitates the alveolar expansion.
 - Low-flow NC humidified gas at less than 1 L per minute
 - High-flow NC humidified and warmed gas delivered at 1 L per minute or greater (Wilkinson et al., 2016)
 - Surveillance and management of comorbidities
 - Patent ductus arteriosus (PDA)
 - Sepsis
 - AOP

TABLE 1.1 Chest Radiographic Images of Varying Pathology

<p>Figure 1.3 Respiratory distress syndrome</p> <p>Granular, air bronchogram, ground-glass appearance.</p>	<p>Figure 1.4 Transient tachypnea of the newborn</p> <p>Fluid in the fissures. Streakiness and may be hazy.</p>

<p>Figure 1.5 Pneumothorax/air leak syndrome</p> <p>Right lung is collapsed with air accumulation, and the cardiac silhouette is shifted to the left.</p>	<p>Figure 1.6 Meconium aspiration syndrome</p> <p>Patchy irregular consolidation.</p>

<p>Figure 1.7 Meconium aspiration syndrome</p>	<p>Figure 1.8 Pneumonia</p> <p>Bilateral consolidation, often similar to RDS.</p>

RDS, respiratory distress syndrome.

Source: Images courtesy of Avera McKennan Hospital and University Health Center.

■ Pharmacologic management includes:

- Caffeine administration to prevent or reduce frequencies of apnea
- Broad-spectrum antibiotics as clinically indicated when high suspicion exists for possible sepsis following the culture

■ Nursing support by highly skilled caregivers provides optimal outcomes.

Prognosis

Survival rates for the preterm infant with RDS are based on gestational age, birth weight, degree of RDS, timely initiation of treatment and support, and underlying comorbidities, such as hypoplastic lung disease or diaphragmatic hernia. Prolonged use of mechanical ventilation, although lifesaving, has negative consequences for the pulmonary structures. The airway and alveolar pressure created with positive pressure can cause overdistention and scarring of the lung parenchyma, leading to long-term pulmonary sequelae often termed as bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD). BPD/CLD is generally thought of as mild, moderate, or severe depending on the duration of supplemental oxygen and/or respiratory support. Pulmonary morbidities and adverse neurodevelopmental outcomes were more prevalent as the severity of BPD/CLD increased (Reuter et al., 2014). Additionally, systemic oxygen toxicity can lead to or complicate retinopathy of prematurity (ROP).

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TRANSIENT TACHYPNEA OF THE NEWBORN

Incidence

- Transient tachypnea of the newborn (TTN) occurs in 5.7 per 1,000 live births in term and late preterm infants (Crowley, 2020).

- Risk factors: Delivery without labor, large for gestational age, maternal diabetes, maternal asthma, multiple gestation, and male gender (Crowley, 2020).

Pathophysiology

- TTN is a decrease in lung compliance caused by pulmonary edema secondary to retained lung fluid. The fetal lung fluid has a high-chloride concentration, higher than plasma, interstitial fluid, or the amniotic fluid. During labor, chemical release of catecholamines occurs that results in the reduction of active chloride and fluid transport into the fetal lung and the reabsorption of fetal lung fluid via a protein gradient and sodium channels. The fluid is transported to the lymphatic system, with an estimated two-thirds of the fetal lung volume removed prior to birth. Increased oxygen tension following infant birth increases the epithelium's capacity to transport sodium, further reducing the fetal lung fluid.
- Mechanisms for failure to clear retained fluid are not clearly understood:
 - Mechanical force of birth canal squeeze is now believed to be a minor contributor
 - Immaturity of the epithelial sodium channel may exist in a preterm infant.
 - Hormonal changes associated with spontaneous labor are missing.

As described in the "Respiratory Distress Syndrome" section, as lung compliance decreases, the tidal volume will decrease. In order for the neonate to achieve sufficient minute ventilation, the respiratory rate will increase (tachypnea). Hypoxemia also will trigger an increased respiratory rate to compensate.

The delayed clearance of the lung fluid by the lymphatics will cause an accumulation of fluid in the peribronchiolar lymphatics and cause bronchiolar collapse. Air trapping is the consequence of this bronchiolar collapse, which causes hyperinflation of the alveoli. Hypoxemia and hypercarbia result from inadequate perfusion at the gas exchange interface. This increased work of breathing is the result of mismatched pulmonary mechanics, including increased airway resistance, diminished lung compliance, or both (Reuter et al., 2014).

The differential diagnoses include both common and uncommon conditions including those with origins in other neonatal systems.

Diagnosis

The diagnosis of TTN is based on history, timing of the clinical presentation, gestational age, physical findings, blood gas analysis, and x-ray findings.

Physical Exam Findings

- Moderate-to-profound tachypnea (>60 breaths per minute)
- May have retractions (subcostal, substernal, intercostal, and/or supraclavicular)

- May present with nasal flaring
- May have oxygen requirement to maintain systemic oxygenation at PaO₂ at 50 to 70 mmHg
- Paradoxical or seesaw respirations

Diagnostic Procedures/Tests

- Blood gas results will typically show mild respiratory acidosis (see previously mentioned blood gas analysis).
- Radiology findings will include diffuse haziness and streakiness in both peripheral lung fields. Fluid-filled interlobar fissures with mild hyperinflation may be visible (see Table 1.1, Figure 1.4).

Treatment

- As noted previously, this diagnosis is one of exclusion, so other disorders should be ruled out.
- Blood gases should be serially monitored (see the "Brief Overview of Blood Gas Analysis" section).
- If history indicates risk factors for infection, broad-spectrum antibiotic therapy should be considered until blood culture results are negative for 36 to 48 hours.
- Supportive care includes:
 - Oxygen delivery by NC or nasal CPAP
 - Continuous oxygen saturation monitoring and cardiopulmonary monitoring
 - Thermoregulation to avoid increased metabolic load
 - Adequate fluid intake (mild fluid losses through increased respiratory rate)
 - Adequate nutrition (usually by gavage tube if resting rate [RR] >60 bpm to prevent aspiration)
 - Serial monitoring and management of blood glucose levels within acceptable range
- Fluid restriction and/or the use of diuretics has not been supported in the treatment of TTN (Crowley, 2020; Stroustrup et al., 2012).

Prognosis

TTN is usually self-limiting with excellent prognosis. The need for respiratory support is usually transient and improves steadily over several hours to days. A few infants will demonstrate high pulmonary artery (PA) pressures and symptoms of persistent pulmonary hypertension of the newborn (PPHN), which can complicate or prolong the infant's clinical course and outcome (see the "Persistent Pulmonary Hypertension of the Newborn" section).

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APNEA AND APNEA OF PREMATURITY

Incidence

- Apnea in full-term neonates occurs in less than 2% of infants and is typically related to other organic causes (sepsis, obstruction, or neurologic or metabolic influences).
- Present in nearly all infants less than 1,000 grams at birth.
- It is inversely correlated with body weight (Patrinos, 2020).
- It is not accompanied by cyanosis or changes in heart rate initially. Bradycardia and hypoxia will ensue if apnea is not corrected rapidly.
- Normal neurologic development reduces the episodes of periodic breathing and apnea around term gestation.

Pathophysiology

Neonates exhibit an irregular breathing pattern. Apnea represents one of the most common respiratory complications in the preterm infant. It is typically defined as cessation of respiratory effort for longer than 20 seconds in length. Most apnea occurs in the preterm infant, classified as AOP, and occurs independent of other organic causes. This is not to be confused with periodic breathing, which is recurrent sequences of pauses in respiratory effort for 10 to 15 seconds followed by a brief “catch up” phase of tachypnea.

AOP is typically classified into one of four types: central apnea, obstructive apnea, mixed apnea, or idiopathic apnea.

1. Central apnea is the absence of respiratory effort and airflow into the respiratory system with no apparent obstruction, and it accounts for approximately 15% of apnea. While the causes of central apnea in the preterm infant are not fully understood, contributing factors are chest wall afferent neuromuscular immaturity, chest wall instability, diaphragmatic fatigue, and the immature response to hypoxia and hypercapnia. Most AOP is in this classification (Martin, 2017).
2. Obstructive apnea is the absence of airflow with continued respiratory effort; it is thought to contribute to up to 30% of apneic events. This is usually caused by

the blockage of the airway at the pharynx or larynx, which can be obstructed due to poor head and neck position of the neonate. Other causes of obstruction may be congenital anomalies of the airway and are described in a later section.

3. Mixed apnea is a combination of obstructive and central apnea.
4. Idiopathic apnea is diagnosed when the baby has apnea that does not result from the other three types of apnea. The cause is unknown.

Apnea in the premature infant is believed to be due to the immature central respiratory center secondary to poor CNS myelination, decreased number of synapses, and dendritic arborization.

In the term infant, the chemoreceptors that are located centrally within the medulla and peripherally in the carotid and aortic bodies transmit important information regarding the pH and oxygen levels to the respiratory center in the brain via pathways along the vagus and glossopharyngeal nerves. Increased respiratory rate is triggered when these levels are low. In the preterm infant, these pathways are not well established and/or not responsive to systemic hypoxemia (Martin, 2017). This explanation supports the cessation of AOP secondary to the normal maturation of the preterm brain and plasticity/development of neuropathways. However, apneic events may also be a classic first sign of systemic stress in the preterm infant. Other pathologic causes should be considered prior to the assumption that events are caused by AOP. Apnea in the term newborn is always an abnormal finding and should be systematically investigated for other causes. A thorough history and physical assessment are crucial.

Diagnosis

The diagnosis of apnea for the preterm or term infant is based on history, physical findings, x-rays, and blood gas results.

Physical Exam Findings

- Prolonged pauses in the respiratory pattern longer than 20 seconds in length
- Bradycardia or pallor that will ensue if a spontaneous or assisted respiratory pattern does not occur

Treatment

- Prompt and gentle tactile stimulation is often sufficient to have the infant respond with spontaneous respiratory effort and avert further therapy.
- Maintain neck in neutral position with assistance of positioning aids, such as a small neck roll. (Educate the family.)
- Coordinate optimization of respiratory status and blood gases in collaboration with the medical staff members.
- Maintain oxygen saturations within targeted range by adjusting the oxygen concentration.

- Apneic events with profound associated bradycardia with or without cyanosis require more aggressive diagnostic and therapeutic interventions and investigation, including:
 - Close clinical observation and physiologic monitoring, including pulse oximeter reading and blood gas analysis on regular intervals (see the "Brief Overview of Blood Gas Analysis" section).
 - AP chest x-ray for evaluation of lung structures, including atelectasis, ventilation, and presence of air leaks. Also consider lateral decubitus film if concerned for air leaks.
 - Sepsis evaluation to include blood culture (urine and cerebral spinal fluid as well if indicated), complete blood count (CBC), C-reactive protein (CRP), and vital signs ensuring the infant is normothermic and perfusion is adequate. Antibiotic therapy is initiated as suggested by the clinical condition of the infant, CBC with differential, and blood gas findings for at least 36 to 48 hours.
 - Increased respiratory support, including nasal cannula (NC) for stimulation with or without supplemental oxygen, has been shown to be beneficial.
 - Nasal CPAP to provide support of FRC and reduce atelectasis in the preterm neonate may be required. A high-flow NC may also offer adequate support for infants who are flow dependent.
 - Intubation and provision of mechanical ventilation to support the infant's respiratory status will be required when other methods prove ineffective.
- Optimize oxygen-carrying capacity by avoiding or managing anemia.
- Xanthine therapy (caffeine, aminophylline) appear to exert a positive influence on respiratory neural output. Caffeine has a much longer half-life and can be dosed daily without the need for serial studies to evaluate the serum level.
 - Adverse effects include tachycardia, increased diuresis, and gastrointestinal symptoms (increased emesis or clinical gastroesophageal reflux symptoms).
 - Caffeine appears to have fewer side effects or toxicity concerns.
- Doxapram is a potent respiratory stimulant used only for apnea refractory to xanthine therapy (Fraser, 2021).
- Automated control of inspired oxygen and supplementation of inspired air with very low concentration of supplemental CO₂ to increase respiratory drive are novel treatments being studied (Martin, 2017).
- Mechanosensory stimulation using kinesthetic approaches may hold future promise (Shah et al., 2019).

Prognosis

The overall prognosis for preterm neonates with AOP is excellent, and infants will typically cease symptoms by 39- to 41-week corrected age. The prognosis for term

infants who demonstrate symptoms of apnea is based on the organic cause of the episodes. See the section that follows on pulmonary air leaks.

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AIR LEAK SYNDROME

Air leak syndrome includes pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, and subcutaneous emphysema.

Incidence

- Air leaks occur in 1% to 2% of term newborns.
- Incidence increases to 16% to 36% in those infants requiring delivery room resuscitation, nasal CPAP, bag-mask ventilation, or mechanical ventilation (Fraser, 2021).

Pathophysiology

Air leak syndrome is an overdistention of the alveolar sac that causes rupture. This rupture can occur spontaneously or by mechanical means during assisted ventilation or in resuscitation with positive pressure ventilation. When the air dissects from the alveolus, it can accumulate in five primary locations: the mediastinum, the pleural space, the space surrounding the heart, the peritoneal cavity, or subcutaneously.

In the healthy term infant, the required opening airway pressure during the first spontaneous breath is 60 to 80 cm of water, with subsequent breaths requiring less as the surface tension of the liquid-filled airways and alveoli is stabilized. If secretions or other mechanical obstructions prevent even air distribution, some areas of the newborn's lung will remain collapsed. The infant will generate additional pressure to open these collapsed areas, and spontaneous rupture of the open airways can occur.

Air leaks typically occur when a neonate has some underlying respiratory pathology. The preterm infant with RDS is at risk due to the noncompliant lung parenchyma. This “stiff” and nonresponsive lung status is at risk for air leak syndrome.

In the infant with meconium aspiration syndrome (MAS), the obstructive nature of the meconium may cause a ball-valve trapping of air, allowing air to flow into small airways and alveoli but not escape. This will cause hyperventilation and rupture in some cases. Positive pressure or respiratory care that is required to support ventilation and oxygen exceeds the capacity of the alveoli and rupture may result.

Diagnosis

Based on history, physical findings, x-rays, and blood gas results, physical exam findings include:

- A sudden deterioration may occur if the air leak is large (decreased saturation, increase in oxygen requirement, increased work of breathing, hemodynamic instability)
- Decreased breath sounds on the affected side or bilaterally
- Muffled heart sounds
- Bradycardia if cardiac tamponade is present
- Hypotension, due to the tension caused by the pneumothorax disallowing full cardiac filling and emptying
- Perfusion changes (mottled or pale coloring with prolonged capillary refill time)

Typical findings of diagnostic procedures/tests for *air leak syndrome* are:

- AP and/or lateral decubitus chest x-rays
 - In pulmonary interstitial emphysema (PIE), the affected alveoli may be bilateral or unilateral with microcystic areas throughout. This pattern has been described as a “shotgun” pattern. The lung fields are often hyperinflated with a flattened diaphragm.
 - A partial or complete pneumothorax will be a collapse of the lung field bilaterally or unilaterally (affected side). Without air inflation, the lung field is darkened without pulmonary markings. Other structures may be shifted to the right or left (heart, trachea; see Table 1.1, Figure 1.5).
 - In pneumomediastinum, the patient may develop a “sail sign” indicating the elevation of the thymus by surrounding air.
 - In pneumopericardium, a halo of air around the heart will be visible.

Treatment

- For pneumothorax:
 - Supportive care is needed, sometimes urgently.
 - If asymptomatic, no treatment may be needed as the air may spontaneously reabsorb.
 - If symptomatic, the treatment is removal of air with thoracentesis (needle aspiration) and/or chest tube placement until resolution.

- Thoracostomy (chest) tube is placed in the anterior chest on the affected side(s) and connected to a negative pressure system.
- Administration of oxygen may be beneficial in the absorption of the air leak for term infants (oxygen toxicity caution).
- For pneumomediastinum:
 - Supportive care is needed.
 - Monitor for worsening clinical condition or pneumothorax.
- For pneumopericardium:
 - This life-threatening condition requires immediate intervention.
 - Emergency treatment includes placement of the chest tube or long catheter into the pericardial sac with constant light negative pressure or pericardial window performed by a cardiologist or general or cardiac surgeon (may be completed with ultrasound guidance).
- For PIE:
 - Supportive care is needed.
 - If unilateral, the infant may be placed affected side down to aid in decompression of the hyperventilated areas.
 - Attempt must be made to minimize pressures through mechanical or noninvasive respiratory management.
 - High-frequency ventilation may optimize clinical status.
 - Selective intubation of unaffected mainstem bronchus may improve condition.

Prognosis

The overall prognosis will depend on the overall pathology of the lung as well as systematic influences. The newborn with spontaneous pneumothorax may resolve fully without intervention. The mortality rate with pneumopericardium, significant PIE, and/or pneumothorax in the extremely low birth weight (ELBW) or newborn with pulmonary hypoplasia is high.

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MECONIUM ASPIRATION SYNDROME

Incidence

- Meconium-stained amniotic fluid (MSAF) occurs in 8% to 29% of all term and near-term deliveries (Fraser, 2021).

- Increases in occurrence are noted with increasing gestational age.
- Overall incidence of MAS is 3% to 12% (Vain & Batton, 2017).
- Equal incidence occurs in males and females.
- Cesarean delivery is associated with a higher incidence of MAS.
- Associated mortality is 5% to 37%.

Pathophysiology

MAS has been described as the most common type of neonatal aspiration and is typically characterized by early and significant respiratory distress in the meconium-stained infant. During stress or perinatal asphyxia, intestinal peristalsis is stimulated and rectal tone is decreased. Meconium, containing a mixture of epithelial cells and bile salts, is then passed into the amniotic fluid. Fetal stress will often lead to primary or secondary apnea, where the infant makes gasping respiratory efforts while aspirating the meconium-containing amniotic fluid prior to delivery. Controversy surrounds whether the contact between vulnerable pulmonary structures and irritating bile salts or the stressed state of the fetus ultimately leads to significant respiratory distress. Meconium passage in utero has been correlated with a stressed state or asphyxia event prior to or during labor.

Following aspiration of the meconium-containing amniotic fluid, a partial airway obstruction can occur. As pulmonary structures are obstructed (atelectasis), others are hyperinflated through a ball-valve effect, resulting in ventilation–perfusion mismatch and hypoxemia. Air leaks such as pneumothorax or pneumomediastinum are a potential complication.

The neonatal inflammatory cascade will be triggered by the chemical pneumonitis. The lung compliance is altered, causing increased pulmonary vascular resistance (PVR) and increased hypoxemia. Meconium decreases the levels or inactivates the surfactant proteins, SP-A and SP-B, and phospholipids thus increasing respiratory distress, hypoxemia, acidosis, and/or risk for PPHN.

Diagnosis

The diagnosis of MAS is based on history, physical findings, and radiographic findings.

Physical Exam Findings

- Yellow-green–stained skin and nail beds or presence of meconium in the amniotic fluid at birth
- Respiratory distress ranging from mild and transient to severe
- Rales and rhonchi on auscultation
- No specific laboratory data for diagnosis

Diagnostic Procedures/Tests

- Chest x-ray may be specific for hyperexpanded areas mixed with patchy atelectasis or cotton-like appearance (see Table 1.1, Figures 1.6 and 1.7).
- Blood gas results are specific for acidosis (both metabolic and respiratory) with low PaO₂.

Treatment

- In the delivery room:
 - If the infant is vigorous with good respiratory effort and tone, the initial steps of care (drying, stimulating, providing warmth) with gentle bulb suctioning are indicated.
 - A nonvigorous infant with depressed respirations and/or poor tone should undergo the initial steps; if not breathing or heart rate is less than 100, positive pressure ventilation should begin.
 - Routine intubation for tracheal suction is not suggested. The infant should be cared for following neonatal resuscitation guidelines with positive pressure ventilation if no response to initial steps and progress to alternative airway as indicated (Weiner & Zaichkin, 2016).
- Provide assisted ventilation and/or supplemental oxygen as needed; also consider high-frequency ventilation.
- Consider inhaled nitric oxygen (iNO) if the infant demonstrates symptoms of PPHN affecting the oxygenation. Inhaled nitric oxide causes selective vasodilation of the pulmonary vasculature, thus potentially improving oxygen uptake.
- Use surfactant replacement as indicated in some cases. Although the mechanism is unclear, this intervention reduces ventilation–perfusion mismatch and probably reduces the risk of ventilator-associated lung injury (Greenberg et al., 2019).
- Use of corticosteroids has variable success and is generally not recommended routinely (Vain & Batton, 2017).
- Monitor for signs/symptoms of pneumothorax and intervene in a timely manner if suspected.
- Consider performing CBC with differential and blood culture and consider broad-spectrum antibiotic coverage while blood culture is monitored.

Prognosis

The overall prognosis for term neonates with mild MAS is excellent with supportive care. If the clinical picture is complicated with PPHN or severe asphyxia, mortality rates are higher.

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PNEUMONIA

Incidence

- The true incidence and impact on neonatal care is difficult to pinpoint due to the overlapping nature of the symptoms (Zaidi et al., 2016)
- Neonatal pneumonia can have early (within the first 7 days of life) or late (after the first 7 days of life) onset
- Early pneumonia
 - Congenital pneumonia
 - Subset of early neonatal pneumonia
 - Presents immediately after delivery
 - Acquired from aspiration of infected amniotic fluid, ascending infection through ruptured or intact membranes, or spread through placenta (Crowley, 2020)
 - Aspiration pneumonia
- Late pneumonia includes ventilator-associated pneumonia (VAP) and is usually nosocomial.

Pathophysiology

Bacterial, viral, and fungal agents can cause pneumonia (see Table 1.2).

An immature tracheobronchial ciliary system inhibits optimal removal of debris, mucus, and pathogens (Fraser, 2021). Inflammation will cause the alveoli to become edematous and fluid filled, complicating air exchange. Macrophages, in response to the invading organisms, will invade the pulmonary parenchyma.

Infants born to mothers with chorioamnionitis or prolonged rupture of membranes (>18 hours) are at a higher risk for congenital or prenatally acquired pneumonia. Systemic fetal infection can be caused by organisms that cross the placenta

TABLE 1.2 Common Organisms Associated With Neonatal Pneumonia

BACTERIAL	VIRAL	OTHER
<i>Group B Streptococcus</i>	Cytomegalovirus	<i>Candida</i> and other fungi
<i>Escherichia coli</i>	Adenovirus	<i>Ureaplasma</i>
<i>Klebsiella</i>	Rhinovirus	<i>Chlamydia</i>
<i>Staphylococcus aureus</i>	Respiratory syncytial virus	Syphilis
<i>Listeria monocytogenes</i>	Parainfluenza	<i>Pneumocystis jiroveci</i>
<i>Enterobacter</i>	Enterovirus	Tuberculosis
<i>Haemophilus influenzae</i>	Rubella	
<i>Streptococcus pneumoniae</i>		
<i>Pseudomonas</i>		
<i>Bacteroides</i>		
Other		

Source: Adapted from Battista, M. A., & Carlo, W. A. (1992). Differential diagnosis of acute respiratory distress in the neonate. *Tufts University School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Disease*, 2(3), 1–4, 9–11.

and enter the fetal circulation prior to delivery. Infants will often show symptoms of illness at birth or shortly thereafter.

Diagnosis

The diagnosis of pneumonia is based on history, physical findings, x-rays, and lab values.

Maternal history should be reviewed for significant findings to include:

- Maternal serologies
- History of maternal illness suspicious of infection, such as maternal fever and/or abdominal pain
- Evidence of chorioamnionitis
- Antenatal antibiotic therapy
- Gestational age

General History

- Postnatal history (intubation, prematurity, recent exposures to illness)

Physical Exam Findings

- Often unable to clinically distinguish from other respiratory or sepsis causes
- Symptoms of respiratory distress (cyanosis, hypoxemia, hypercapnia, grunting, retractions, and tachypnea)
- Diminished breath sounds with or without rales

Diagnostic Procedures/Tests

- Lab testing
 - A CBC may be specific for neutropenia, leukopenia, or left shift (abnormal ratio of immature to total neutrophils)
- Polymerase chain reactions (PCRs) looking for viral etiologies
 - Samples of blood for viral and bacterial culture should be obtained and monitored during treatment. Results are often negative unless systemic bacterial/viral sepsis is present.
 - Tracheal aspirate culture in an intubated infant
 - Blood gas analysis
 - Cerebrospinal fluid when stable as meningitis often occurs concurrently
 - Evaluation for coagulopathy
- Radiographic findings are variable (see Table 1.1, Figure 1.8)
 - Unilateral or bilateral infiltrates
 - Diffuse interstitial pattern
 - Pleural effusions
 - Similar in appearance to neonates with RDS

Treatment

- Neutral thermal environment/thermoregulation
- Monitor glucose levels and correct hypoglycemia or hyperglycemia as appropriate
- Maintain optimal hemodynamics by monitoring blood pressure and perfusion
 - Treat anemia with adding ferrous sulfate or by transfusions
 - Treat hypotension using volume infusion or vasoactive agents, such as dopamine or dobutamine
 - Close monitoring of intake/output
- Supportive respiratory management
 - Supplemental oxygen

- Assisted ventilation using NC, humidified and warmed high-flow nasal cannula (HFNC), nasal CPAP, and/or NIPPV
 - Intubation and mechanical ventilation as indicated
 - Monitor blood gases and adjust therapy as indicated
 - Consider surfactant replacement as warranted
 - Inhaled nitric oxide and/or extracorporeal membrane oxygenation (ECMO) for severe cases (timely transfer of infants to tertiary care centers where these treatments are available must be considered when symptoms warrant)
- Pharmacologic management includes:
- Broad-spectrum antibiotics
 - Antiviral therapies
 - Vasopressors as indicated

Prognosis

The overall morbidity and mortality rates for neonatal pneumonia are significant and depend on the severity of illness and causative agent.

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PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Incidence

- The condition complicates the course of up to 10% of infants with respiratory failure (Steinhorn & Abman, 2018).
- Typically occurs in term or near-term infants.

Pathophysiology

PPHN, formerly known as persistent fetal circulation, is a condition where high right-sided pressure at the PA is combined with right-to-left shunting through fetal

pathways (foramen ovale and/or ductus arteriosus). The increased pressure at the PA is caused by an elevated pulmonary vascular resistance (PVR), which is a process of maladaptation between fetal and neonatal circulation. The pulmonary vascular bed and heart are structurally normal. This vasoconstriction may be transient or persistent and reactive or resistant to therapy.

■ In utero:

- PVR is high secondary to pulmonary vasoconstriction
- Oxygenation of fetus occurs via placenta
- Majority of blood bypasses fetal lungs (84%; Lakshminrusimha & Steinhorn, 2017)
- In fetal circulation, blood is shunted through the ductus venosus, patent foramen ovale (PFO), and patent ductus arteriosus (PDA)

■ Following birth:

- Umbilical cord is clamped.
- Lungs expand with first breaths.
- Oxygenation occurs via the lungs.
- Lungs begin to clear fluid.
- PVR falls.
- Pulmonary blood flow increases.
- The fetal shunts begin to close.

The PVR usually falls by about 50% in the first 24 hours of life; however, when the PVR remains high, the transition from fetal to neonatal circulation is delayed. The pulmonary vessels in the neonate are reactive and respond to hypoxia or acidosis with vasoconstrictive properties. This high PVR further restricts pulmonary blood flow, which increases this acidotic state and makes oxygenation difficult. In cases of hypothermia, pulmonary vessels also increase resistance; therefore, infants undergoing therapeutic hypothermia are at a higher risk of PPHN.

■ Pulmonary hypertension is often divided into three categories (Steinhorn, 2020):

- Pulmonary vasoconstriction caused by lung diseases like MAS, RDS, or pneumonia
- Normal lung parenchyma and remodeled pulmonary vasculature: idiopathic, chronic intrauterine hypoxia, placental insufficiency
- Hypoplastic vasculature like congenital diaphragmatic hernia (CDH), congenital cystic adenoid malformation

Certain newborn conditions increase the risk for PPHN and include MAS, CDH, RDS, asphyxia, sepsis, pneumonia, hypoglycemia, polycythemia, or other neonatal stressors. Conditions that increase the acidotic state in the newborn, like

hypothermia, can also contribute to pulmonary vasoconstriction. Fetal stressors like systemic hypertension, maternal diabetes, maternal preeclampsia, maternal smoking, and premature closure of the ductus arteriosus increase the likelihood of PPHN (Fraser, 2021). Studies in animal models and humans suggest maternal usage of selective serotonin receptor inhibitors (SSRIs) and nonsteroidal anti-inflammatory agents may alter fetal PVR (Lakshminrusimha & Steinhorn, 2017). More research needs to be done in this area. These infants share several characteristics: elevated PVR, abnormal pulmonary vasoreactivity, diminished response to vasodilators (oxygen, medications), and increased blood levels of endothelin, a potent vasoconstrictor.

Clinical Manifestations

A complete, thorough physical examination is imperative. Hypothermia or hyperthermia may alter the metabolic load of the neonate. The hypoxic or hypotensive infant may require rapid intervention and is often associated with respiratory compromise. Clinical presentation is similar to other respiratory conditions and may be difficult to differentiate initially. See earlier section "Respiratory System Assessment." Additional assessment points:

- Pallor, mottling, or poor color of the infant may indicate hypotension or acidosis.
- Cyanosis or blue discoloration of the skin and mucous membranes is a classic sign of hypoxemia leading to hypoxia. This is a late and serious sign of compromise, and the infant will require immediate interventions. This is often associated with respiratory distress, leading to respiratory failure with severe metabolic acidosis.
- Tachycardia, bradycardia, blood pressure, and perfusion are important signs of cardiac compromise from CHD or ongoing respiratory compromise and failure.
- Diminished muscle tone and poor activity are critical signs of profound hypoxia and acidosis.

Diagnosis

The diagnosis of PPHN is based on history, physical findings, x-rays, and echocardiogram. Echocardiogram findings include right ventricular dilation, leftward bowing of the intraventricular septum, tricuspid regurgitation, and right to left or bidirectional shunting at the PFO and PDA. Estimation of PA pressures are cardinal findings.

Significant Prenatal and Delivery Findings

- Meconium-stained fluid, maternal infection, tight nuchal cord, hypovolemia (placental abruption, accreta, previa, or cord accident), maternal sedation

- History of hypoxia or asphyxia at delivery (low Apgar scores, required resuscitation, acidotic cord blood gases)

Physical Exam Findings

- Near-term or term infant
- Symptoms of respiratory distress
- Hypoxemia with or without cyanosis
- Low PaO₂ despite high levels of delivered supplemental oxygen

Diagnostic Procedures or Tests

- AP chest x-ray may be abnormal or normal. Usually obtained to rule out other pathology that could contribute to the state of hypoxia.
- Arterial blood gas is a good serial monitoring method to determine oxygenation and state of acidosis.
- Pre- and postductal oxygen saturation monitoring will be valuable to determine differences between the preductal measurement (right upper extremity) with postductal locations (lower extremities). If SpO₂ difference of 10% to 15% or if PaO₂ measurements from right radial artery and umbilical artery are more than 15 mmHg, this is an indication of ductal shunting.
- Echocardiogram is the gold standard and will rule out CHD and evaluate the structure and function of the heart and myocardium. The presence of bidirectional or right-to-left shunting across the foramen ovale or ductus arteriosus is confirmatory. Other signs such as flattened septum, tricuspid regurgitation, and right ventricle dilation suggest the diagnosis (Steinhorn & Abman, 2018).
- Hyperoxia test is placing the infant in 100% FiO₂ (fraction of inspired oxygen) and monitoring the oxygen saturations (postductal) or arterial PaO₂. If the infant's oxygenation does not significantly change, this is a clear sign of CHD or PPHN.
- Serum electrolytes are important to monitor glucose and serum CO₂ levels.
- Lactate will measure the state of systemic acidosis.
- CBC and blood cultures should be obtained for sepsis evaluation.
- Oxygen index calculation evaluates the severity of the disease process and is an important component in evaluation need for escalating intervention.

Treatment

- Minimal stimulation occurs as infants demonstrate significant alterations in PVR with even gentle handling and touch.

- Supportive care (based on the cause of PPHN) may include antibiotic therapy, cooling protocol, thermoregulation, maintenance of fluid, and electrolyte balance.
- A central arterial line may be placed to monitor systemic blood pressure and obtain serial arterial blood gases.
- A central venous line may be placed to administer fluids and vasopressors as indicated.
- Ventilation and oxygenation are supported with intubation, mechanical ventilation (conventional, high-frequency jet, high-frequency oscillatory ventilator), and supplementation oxygen (a potent vasodilator) as indicated. Oxygen targets suggest SpO₂ 91% to 97% and pre-ductal PaO₂ between 60 and 80 mm Hg.
- iNO, a selective pulmonary vasodilator, has been shown to improve oxygenation.
- Surfactant replacement should be considered for infants with parenchymal lung disease.
- Correct acidosis through ventilation and the administration of fluids over time. Judicious administration of sodium bicarbonate should be done only after adequate volume resuscitation and adequate ventilation. Sodium bicarbonate breaks down to water and carbon dioxide; therefore, adequate ventilation is imperative before administering. Acidosis leads to pulmonary vasoconstriction, and causing alkalosis is not optimal in these cases either (Steinhorn & Abman, 2018).
- Close evaluation and fluid adjustments are made based on urine output; avoid pulmonary edema.
- Optimize cardiac output and systemic hemodynamics using volume and medications.
- Extracorporeal membrane oxygenation (ECMO) should be considered when conventional therapies are not successful, if available in the region (by making determination to transfer the infant to an appropriate center).
- Pharmacologic intervention:
 - Sedatives to maintain calm state
 - Vasopressors to increase systemic blood pressure, thereby reducing PVR; this will decrease right-to-left shunting
 - iNO as discussed earlier
 - Sildenafil as an adjunct therapy to iNO to promote pulmonary vasodilation
 - Analgesics as an adjunct to sedatives to maintain calm state and reduce metabolic need during acute phase of illness

Prognosis

The overall prognosis for term neonates with PPHN is based on the underlying cause or disease process. Residual effects from PPHN include CLD from prolonged ventilation requirement, symptoms of withdrawal secondary to long-term narcotic/sedative requirement, sensorineural hearing loss, learning disabilities, and feeding challenges.

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PULMONARY HEMORRHAGE

Incidence

- Occurs in 5% of low birth weight infants and 10% in ELBW infants (Crowley, 2020)
- Eighty percent occur in first 72 hours
- May be associated with other complications (PDA, sepsis)
- Following surfactant administration incidence increases

Pathophysiology

Pulmonary hemorrhage is the presence of bloody fluid in the trachea or lung fields. The event can be a massive event or slow leak into the alveoli. Pulmonary hemorrhage is hypothesized to be caused by a sudden decrease in PVR resulting in increased left-to-right shunting, pulmonary edema, and rupture of pulmonary capillaries. This acute event can be life-threatening secondary to airway obstruction and/or hypovolemia. This condition will often accompany or be the complication of a comorbid condition such as disseminated intravascular coagulation (DIC), PDA, RDS, or CHD. Pulmonary hemorrhage is a known complication of surfactant administration or tracheal suctioning.

Diagnosis

The diagnosis of pulmonary hemorrhage is based on history, physical findings, and x-ray.

- Presents with sudden deterioration (vital sign changes, oxygen saturations)
- Symptoms of severe RDS
- Bright red blood or pink-tinged secretions noted in the endotracheal tube (ETT) when suctioning, if intubated
- Hypotension
- Anemia
- Shock
- X-rays demonstrate varying degrees of fluffy infiltrates to complete white out

Treatment

- Provide blood or blood products based on clotting studies
- Support respiratory requirements; additional positive end-expiratory pressure (PEEP) helps with oxygenation and acts to tamponade bleeding
- Suction/clear ETT; replacement may be indicated but risk for poor outcome
- Correct acidosis and anemia
- Assess for and treat PDA
- Treat underlying causes (sepsis)

Prognosis

The overall prognosis for term neonates with pulmonary hemorrhage is poor if massive bleeding cannot be stopped or slowed with PEEP or administration of fresh frozen plasma (FFP) and other blood products. If hemorrhage is small, the infant will recover unless the underlying cause is significant. Mortality approaches 50% in ELBW infants (Crowley, 2020).

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CONGENITAL ANOMALIES THAT AFFECT THE RESPIRATORY SYSTEM

PULMONARY HYPOPLASIA

Incidence

- Occurs in 9 to 11 of 10,000 live births
- Mortality rates 71% to 95%

- Equal incidence in male/female
- Frequently associated with oligohydramnios

Pathophysiology

Pulmonary hypoplasia is a rare but often lethal condition in which the lungs are underdeveloped, usually secondary to a space-occupying mass, renal anomaly, or urinary tract anomalies with oligohydramnios. Primary pulmonary hypoplasia is rare and caused by abnormalities of transcription factors and growth factors regulating early lung development (Kallaper & Jobe, 2020). Diaphragmatic hernia and diaphragmatic eventration are also present with symptoms of RDS secondary to pulmonary hypoplasia, as the displaced bowel occupies pulmonary space that prevents adequate growth (see the following section).

Hypoplastic lungs have a decrease in lung volume/mass under conditions of restricted space to develop in utero. This decrease occurs in both number of airway generations and smaller peripheral alveoli than normal term or preterm infants. The unaffected area of the lung has a structure that is appropriate for gestational age.

Infants who are affected by oligohydramnios have lung parenchyma that are structurally and biochemically immature for gestational age, although the exact mechanism for this is still undetermined. These infants have poor epithelial maturation, a lack of elastic tissue development, and low concentrations of lung phospholipids (Chen et al., 2010). It is uncertain if this condition is secondary to a lack of exposure to fetal lung fluid, which provides lung tissue the mechanical stretching necessary for development, or if it is a lack of growth factor secretion.

Assessment

Assessment is the same as other conditions of acute respiratory distress noted in the previous sections.

Diagnosis

The diagnosis of pulmonary hypoplasia is based on history, physical findings, blood gas results, and x-rays. Respiratory findings often mimic other causes of respiratory distress.

- Hypoxemia is difficult to manage with routine approach.
- If the condition progresses, the infant will have changes in cardiac function including decreased perfusion, pallor, tachycardia (early), and bradycardia (late).
- If the condition progresses, the infant will demonstrate CNS changes including lethargy, decreased or obtunded response to stimuli, and loss of muscle tone.

Diagnostic Procedures/Tests

- Arterial blood gas (analysis as described earlier)

Radiographic Findings

- AP view, which is usually sufficient for initial examination—generally reveals low lung volumes on the affected side or overall
- CT of the chest (if mass is suspected)

Treatment

- Respiratory support as indicated (may require intubation)
- High index of suspicion for signs/symptoms of pneumothorax
- Symptomatic management
- Palliative support for genetic anomalies

Prognosis

The overall prognosis for term neonates with pulmonary hypoplasia is poor, with mortality rates ~70% to 90%.

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CONGENITAL DIAPHRAGMATIC HERNIA

Incidence

- One in 2,500 live births
- Most symptomatic at birth with severe RDS
- Left-sided defect 90% of the time

Pathophysiology

This defect is caused by the herniation of abdominal contents, primarily intestine, into the chest cavity. This defect occurs as early as 4 to 5 weeks' gestation. The dual-hit hypothesis for the pulmonary hypoplasia has emerged (Crowley, 2020). Likely pulmonary development has been affected prior to diaphragm development and before the compression from abdominal organs occurs. The first hit affects both lungs and likely is the reason both lungs have some degree of pulmonary hypoplasia. The second hit affects the growth of the ipsilateral lung from compression of

herniated contents. CDH can be an isolated defect or associated with other congenital anomalies including cardiac, urogenital, chromosomal, and musculoskeletal issues (Crowley, 2020).

Antenatal measurements to predict morbidity to 28 weeks' survival have been evaluated. Lung area-to-head circumference ratio (LHR) done between 22 and 28 weeks, the presence of liver in the chest cavity, and estimated fetal lung volume on MRI have been helpful in prognosticating outcomes. The LHR ratio appears to be most helpful when compared to expected ratio at the gestation in question. The ability of these to predict survival has been inconsistent, but these data do give some information to guide families to plan treatment.

Delivery of these infants in a tertiary care center equipped to provide the whole complement of care strategies is recommended to attain the most optimal outcomes.

Assessment

- The infant with CDH may simply appear to have RDS or present with a scaphoid abdomen.
- Some degree of RDS may be observed, which may be mild to severe.
- Bowel sounds may be heard in the chest.
- Heart sounds may be shifted to the right side.

Diagnosis

The diagnosis of diaphragmatic hernia is based on history, physical findings, and x-rays. The diagnosis is frequently known before delivery but can be unknown prior to delivery.

Physical Exam Findings

- Symptoms of respiratory distress (cyanosis, hypoxemia, hypercapnia, grunting, retractions, and tachypnea)
- Diminished breath sounds (asymmetrical)
- May auscultate bowel sounds in chest

Diagnostics

- Dextrocardia may be present.
- Radiographic findings are significant for bowel presence above the diaphragm, most frequently in the left side of the chest.
- A CBC is performed.
- Samples of blood for viral and bacterial culture should be obtained and monitored during treatment. Results are often negative unless systemic bacterial/viral sepsis is present.

Treatment

- Once the diagnosis is suspected, avoid positive pressure ventilation as this can force air into the intestines, which are in the chest cavity and further compromise ventilation.
- If diagnosis is known prenatally, the infant should be intubated immediately to provide mechanical ventilation to the lungs.
- Proved respiratory support with ventilation and supplemental oxygen, gentle ventilation, and permissive hypercapnia are frequently used (Crowley, 2020).
- Use a decompression tube to suction (prevent bowel from filling with air).
- Consider iNO when symptoms of PPHN exist. However, the routine use of iNO is not supported by current data (Crowley, 2020).
- ECMO may be considered based on oxygen index (OI) greater than 40, persistent hypoxemia, failure of management to support oxygenation, and ventilation and tissue perfusion.
- Suggest a surgical consult—surgical repair is generally delayed until PPHN has resolved/improved.
- Hypotension is a common problem related to impedance on cardiac function and should be managed with volume resuscitation and medications as clinically indicated.
- Surfactant administration does not appear to be helpful.

Prognosis

The overall prognosis for term neonates with diaphragmatic hernia is poor with a high incidence of PPHN and ECMO sometimes used for management.

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CHOANAL ATRESIA

Incidence

- Occurs in one in 8,000 births (Fraser, 2021).
- Fifty percent of cases have bilateral blockages (Gentle et al., 2020).
- Affected infants have associated anomalies such as CHARGE syndrome (coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital/urinary abnormalities, and ear abnormalities and/or hearing deficit).
- It affects females more than males.

Pathophysiology

Infants are obligate nasal breathers, allowing them to breathe effectively during oral feedings. When nasal passages are blocked or obstructed by tissue or mucus, the infant will exhibit symptoms of RDS. Choanal atresia causes upper airway obstruction as the choanae or nasal passages do not connect to the nasopharynx. The majority of the blockages are bony occlusions with a small number being membranous.

Assessment

The degree of respiratory compromise at delivery usually determines the severity of the obstruction. If both nares are obstructed, the infant will require assistance to support oral airway patency and air exchange. If a single naris is obstructed, respiratory compromise may only be detected when the infant is feeding and the oral airway is obstructed with breast or bottle.

Diagnosis

The diagnosis of choanal atresia is based on history and physical findings.

History and Physical Exam

- Benign prenatal history and ultrasound results unless CHARGE association
- Severe respiratory distress (retractions, poor aeration)
- Cyanosis that becomes pink with crying due to breathing through oropharynx (Bean et al., 2017)
- Failure to pass a nasogastric tube (NGT) in one or both nares

Treatment

- Oral airway
- Tracheal intubation as indicated
- Maintain calm state with comfort measures
- Evaluation for CHARGE association (echocardiogram, renal ultrasound, eye exam, hearing evaluation)
- Eventual surgical correction

Prognosis

The overall prognosis for term neonates with choanal atresia is excellent. The mortality rate for surgical correction is less than 1%, and complications are rare.

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PIERRE ROBIN SEQUENCE

Incidence

- Sixty percent of affected patients have a cleft palate.
- It can be seen in isolation (50%–70%) or in combination with other anomalies (Stickler, 22q deletion, and Treacher Collins, primarily).
- It occurs in one per 8,500 to 14,000 live births (Lee & Bradley, 2014).
- Increased risk occurs in families with other children affected by Pierre Robin sequence (1%–5% chance).
- Between 13% and 27.7% of other family members are affected with cleft lip with or without cleft palate.
- Recent research has linked mutations in the *SOX₉* gene (Keller et al., 2018).

Pathophysiology

The major feature of the Pierre Robin sequence is micrognathia or small mandible, glossoptosis, and upper airway obstruction. Hypoplastic development of the mandible can lead to airway obstruction and cyanosis. The tongue is posteriorly placed close to the oropharynx and will obstruct the airway. The mandible is formed at about the fourth week of gestation from the first pharyngeal arch and migrating neural crest cells. At about 6 weeks' gestation, the trigeminal nerve innervates the area and promotes osteogenesis, forming the major structures of the mandible. Prenatal or genetic factors disrupt the normal growth of the mandible and micrognathia occurs.

Pierre Robin sequence without other genetic syndrome may be the result from intrauterine forces acting on the mandible, which restrict its growth. Due to the poor mandibular growth, the tongue is displaced between the palatal shelves. Cases of Pierre Robin sequence have been associated with oligohydramnios with an unclear etiology. In these cases, the micrognathia results from intrauterine molding, and the mandibular growth can continue following delivery. When the Pierre Robin sequence is combined with other genetic causes, varied responses to extrauterine growth are possible without surgical intervention.

Diagnosis

The diagnosis of Pierre Robin sequence is based on history and physical findings.

Physical Exam Findings

- Small mandible
- Respiratory distress and cyanosis that may be relieved when the infant is placed prone
- Tongue that appears large for mouth

Treatment

- Prone position to allow tongue to fall forward. Positioning will resolve the airway obstruction in ~70% of cases.
- Surgical tongue–lip adhesion, where the tongue is affixed to the lip with sutures to prevent airway obstruction from the tongue position.
- Oral feedings in a prone or side-lying position may be tolerated. Nasogastric feedings are often required initially.
- Mandibular distraction osteogenesis is an established technique used to treat infants with Pierre Robin sequence associated with severe airway obstruction. Mandibular distraction has shown favorable results with a 50% reduction in tracheostomy placement (Lee & Bradley, 2014).

Prognosis

Excellent survival rates are noted for these infants in the absence of lung hypoplasia. Mandibular growth contributes to resolution by 6 to 12 months of age. Prognostic outcomes in infants with comorbidities including syndromes or genetic diseases have various results based on those genetic conditions.

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CONGENITAL PULMONARY MALFORMATIONS

Congenital pulmonary malformations (CPMs) are a group of rare abnormalities that affect different parts of the neonatal lung or supporting structures, including the main or terminal airways, the parenchyma, and the supportive vasculature. These abnormalities are typically caused by aberrant embryologic lung development at

various stages and can be self-limiting or cause significant respiratory distress at birth or shortly thereafter.

CPMs are currently classified as five types according to location and tissue type found in the abnormal growth (Fraser, 2021). This condition was previously known as congenital cystic adenomatoid malformation (CCAM).

Incidence

- It occurs in one per 8,300 to 35,000 live births.
- Males and females are affected equally.

Pathophysiology

Pathophysiology is dependent on the type of congenital pulmonary airway malformation (CPAM; Fraser, 2021). All CPAMs develop from an overgrowth of abnormal lung tissue (Keller et al., 2018).

- Type 0: arise from tracheobronchial tree, lobulated, no alveoli involved
- Type 1: most common, usually limited to one lobe of lung, single or a few large cysts, communicate with bronchi
- Type 2: multiple, small cysts resembling bronchioles, 50% have other anomalies (sirenomelia, renal agenesis, extra lobar pulmonary sequestration)
- Type 3: large, solid lesion but made up of small cysts, resembles canalicular stage of lung development
- Type 4: similar to type 1 but larger cysts, usually in periphery of one lobe

Diagnosis

The diagnosis of CPAM is based on history, physical findings, and radiologic evaluation.

Physical Exam Findings

- Ranges from normal respiratory exam (75%) when the mass is small to acute distress.

Typical findings of diagnostic procedures/tests for CPAM are:

- AP chest x-ray will be specific for the location and size of the CPAM.
- Chest (thoracic) CT scan is required to identify subtle structures of the CPAM.

Treatment

- Some minor cases spontaneously regress without intervention.
- Surgical intervention with excision is typically recommended based on the severity.

- Of note: In fetal cases with CPAM and nonimmune hydrops, fetal resection or thoracoamniotic shunt have reportedly been effective.
- Type 1 CPAM can develop malignant changes, and long-term follow-up is needed.

Prognosis

Prognosis depends on the size and location of the CPAM and necessary treatment.

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