HYPOXIA IN THE Term Newborn:

PART TWO—PRIMARY PULMONARY DISEASE, OBSTRUCTION, AND EXTRINSIC COMPRESSION

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Abstract
Pediatric care providers are repeatedly called upon to evaluate a cyanotic newborn in the labor and delivery suite, or in the well-baby nursery. A myriad of disorders spanning all-organ systems exist as possibilities for each of these problems, although several causes for newborn cyanosis are particularly common. In this second of a three-part series, primary pulmonary disease, airway obstruction, and extrinsic compression of the lungs as causes for newborn hypoxia are explored. It is in this group of disorders that we find the answers for the greatest number of these cyanotic dilemmas. Knowledge of the breadth of diagnoses, and respect for the variety of clinical possibilities, is the first step in providing a patient with accurate diagnosis, treatment, and referral.

Key Words: Evaluation; Hypoxia; Newborn; Pulmonary; Respiratory.
What do newborn care providers need to know to meet the challenge of evaluating hypoxia in the term newborn infant? The first article in this three-part series (see Rohan & Golombek, 2009), discussed cardiopulmonary adaptation of the term newborn, definitions and features of neonatal hypoxia, cardiac causes of hypoxia in the newborn, and neonatal pulmonary hypertension. In this Part Two article, we describe causes of newborn hypoxia that have close origins to the respiratory system. These causes can be broken down into three distinct categories: (1) primary pulmonary disease (where pathology originates in the lung parenchyma), (2) airway obstruction (where pathology originates in the upper airways), and (3) extrinsic compression of the lung and airway (where pathology originates outside of the lung but impinges upon respiratory structures). In each of these separate categories is found an array of disorders that can cause respiratory dysfunction and resultant hypoxia (Table 1).

Primary pulmonary disease is the most common etiology for cyanosis and hypoxia in this population (American Academy of Pediatrics, 2002). The prudent clinician, however, will routinely consider alternatives, so as not to cause delayed diagnosis and its associated negative consequences for the infant with a less common disorder.

Primary Pulmonary Disease

Primary lung disease causes alveolar hypoventilation, decreased lung compliance, ventilation-perfusion inequality, intrapulmonary right-to-left shunts, and a resultant varying degree of hypoxia in the newborn. Logically, as such, the entire spectrum of neonatal respiratory disorders may present with cyanosis. In general, hypoxia associated with pulmonary disease presents as tachypnea, grunting, flaring, chest retractions, arterial blood gas usually showing carbon dioxide retention, rise in PaO₂ when supplemental oxygen is used, and evidence of lung disease on chest radiograph. There are numerous diagnoses included in the category of “primary pulmonary disease,” including:

- Transient Tachypnea of the Newborn
- Tracheoesophageal Fistula and Esophageal Atresia
- Aspiration Syndromes
- Respiratory Distress Syndrome
- Pneumonia
- Pulmonary Hemorrhage
- Pulmonary Hypoplasia
- Pulmonary Lymphangiectasia
- Congenital Pulmonary Cysts
- Pulmonary Lobar Emphysema

Transient Tachypnea of the Newborn (TTN). TTN is perhaps the most common respiratory disorder of the term newborn (Levine, Ghai, Barton, 2001). Like most primary respiratory diseases, TTN is a spectrum disorder—it ranges from a mild intermittent tachypnea, perhaps more
appropriately defined as “delayed transition to extrauterine life,” up to and including a disease with tachypnea, oxygen requirement and physical signs closer to respiratory distress syndrome. Typically, these infants have benign intrapartum courses and are not at risk for other illnesses. Many of them are delivered by cesarean section; some without labor. The most significant discriminatory findings are the onset of the illness and the degree of distress exhibited by the infant. Cyanosis and carbon dioxide retention are not hallmarks of the disease, however, are observed on occasion. Typically, the infant becomes tachypneic immediately after birth and has very mild respiratory distress. Infants are neurologically normal. The chest radiographs generally reveal hyperinflation with clear lung parenchyma except for perilobar linear densities and fluid in the fissures. There should be no areas of consolidation.

The pathophysiologic mechanism is the delayed resorption of fetal lung fluid which eventually clears over the next several hours to days (Kopelman & Mathew, 1995). If followed closely, infants remain stable for several hours and/or begin to improve. A worsening clinical picture should suggest another diagnosis.

**Tracheoesophageal Fistula and Esophageal Atresia.** Esophageal atresia and tracheoesophageal fistula occurs when the esophagus fails to differentiate and separate from the trachea. The most common anatomic type of this disorder is when the upper esophagus ends in a blind pouch, and there is a fistula connecting the lower esophagus to the trachea (Martin & Alexander, 1985). The infant typically presents with cyanosis and “choking” as a result of increased oral secretions. During physical examination, an orogastric catheter is typically unable to be advanced to the stomach, and if left indwelling during chest radiograph, the catheter is usually seen coiled in the area of the mid thorax. Pediatric surgical consultation is uniformly indicated.

**Aspiration Syndromes.** The pathophysiologic mechanism for illness in aspiration syndromes is the obstruction of large and small airways with the aspirated material (meconium).
um, blood, amniotic fluid, formula or breast milk). As the disease process progresses, the symptoms and severity of hypoxemia increase over the subsequent hours. Pulmonary hypertension may develop when aspiration occurs in conjunction with varying degrees of in utero asphyxia.

Meconium in the amniotic fluid occurs in approximately 20% of pregnancies; as a consequence, meconium aspiration syndrome (MAS) is considered to be a relatively common event (Wiswell, 2001). Infants with this disorder, and other forms of aspiration, typically have symptoms similar to infants with TTN, but an exaggerated presentation suggesting a more severe condition. In addition, while many infants have the onset of symptoms at birth, some infants have an asymptomatic period of several hours before respiratory distress becomes apparent. Infants with aspiration syndromes may require more oxygen, and have greater degrees of tachypnea, retractions, and lethargy. The arterial blood gases may reveal more acidosis, hypercapnia, and hypoxemia than in infants with TTN. The chest radiographs differ from that of TTN with significant heterogeneous lung disease, hyperinflated and hypoinflated areas, patchy and linear infiltrates and atelectasis.

The deleterious effects of gastroesophageal reflux (GER) in infants have been recognized with increasing frequency, and put the neonate at risk for aspiration of stomach contents. The spectrum of symptoms caused by GER in the infant is distinctly different than in the adult, but is frequently recognized in the neonatal period with intermittent episodes of hypoxia, during, after or between feedings, with or without vomiting. When presenting with cyanosis, diagnosis is generally made in the term infant by pH probe or esophagram study, only after other causes of hypoxia have been ruled out.

**Respiratory Distress Syndrome.** Respiratory distress syndrome (RDS), once known as hyaline membrane disease, is one of the most predominant lung problems experienced by neonates. It mainly strikes infants under 35 weeks gestation, however, it has been well documented in the term and late preterm infant (Golombek & Truog, 2000), classically in the infant of a diabetic mother, or in cases of perinatal hemorrhage.

The etiology of RDS is understood to be a deficiency in pulmonary surfactant either by lack of production, or, more commonly in the late preterm infant, by inactivation of this surfactant. Surfactant is thought to be produced near the 22nd week of gestation; however, production can easily be disrupted by hypoxemia, hyperthermia, or acidosis.

Infants with RDS have progressively more severe respiratory distress after birth. The classic findings of cyanosis, nasal flaring, intercostal and subcostal retractions, and tachypnea are present. Grunting classically occurs as the infant attempts to maintain the gas volume within the lung by causing expiratory braking using the vocal cords and glottis. Apnea may occur as work of breathing increases. There is decreased lung compliance, decreased lung volumes, atelectasis, decreased alveolar ventilation, hypoperfusion, and subsequent hypoxia. The symptoms of RDS usually worsen gradually for the first 48 to 72 hours, followed by stabilization, and a slow recovery period. Stabilization of the disease is often associated with diuresis. Like aspiration syndromes and pneumonia, pulmonary hypertension may develop when RDS occurs in the context of an opportune setting.

Chest radiograph in RDS has features suggesting generalized atelectasis. In the preterm infant, this presents with a generalized reticulogranular “ground glass” appearance of the lung fields with air bronchograms. In the term infant, however, there is not as typical a picture, and features of atelectasis vary from generalized to patchy. One must use history and clinical evaluation to differentiate between RDS and other generalized pulmonary diseases, although distinction from pneumonia, in particular, is very difficult at the onset.

**Pneumonia.** Enteric organisms such as *Escherichia coli* and Group B Streptococcus are the frequent causative bacterial agents of congenital pneumonia, and viruses are increasingly recognized as culprits for this infection. Rarely, a postnatally acquired pneumonia is observed in the early newborn. A table of organisms that can cause pneumonia in the neonate is in Table 2.

The diagnosis of neonatal pneumonia is typically an imprecise science. It is generally based on the history, physical examination, chest X-ray results, and lab data. While pneumonia in newborns is relatively rare, premature infants have at least a 10-fold increased incidence of infections when compared to term infants. Mothers with intrapartum fever and prolonged rupture of membranes have a greater risk of transmitting infections to their infants. Symptoms of pneumonia in a neonate, which often present within 48 hours of delivery, include vital signs instability and respiratory distress. Laboratory data often suggests infection. Chest radiograph typically depicts unilateral or bilateral streaky densities of the perihilar region in bilateral lung fields. Like RDS, symptoms are highly variable and dictate the degree of supportive care.

**Pulmonary Hemorrhage.** Rarely occurring in isolation, pulmonary hemorrhage is typically found in an infant sick with RDS, pneumonia, heart disease, or asphyxia. It has been noted with higher incidence in infants receiving pulmonary surfactant. Significant bleeding may also occur as a complication of trauma to the respiratory epithelium during airway suctioning.

The manifestation of pulmonary hemorrhage is the presence of blood or bloody fluid from the airway, and runs the spectrum from scant bloody aspirate to massive bleeding. It follows that clinical examination may be minimally altered from baseline, or range up to sudden deterioration with shock,
bradycardia and death. Clotting factors can be consumed rapidly, and supportive care may include management of coagulopathy blood product loss/consumption with transfusion.

**Pulmonary Hypoplasia.** Pulmonary hypoplasia is part of the spectrum of malformations characterized by incomplete development of lung tissue. Circulating amniotic fluid, composed primarily of fetal urine, is an important factor in the development of the fetal lung. When a fetus has absent or minimal urine production because of renal agenesis or other severe renal malformation, the result is oligohydramnios and concomitant pulmonary hypoplasia or pulmonary aplasia.

Originally described by Potter (1946), the “oligohydramnios sequence” (formerly called “Potters syndrome”) produces severe pulmonary hypoplasia with typically flattened facial features and limb deformation on the physical examination. There may be renal findings on abdominal exam, and the obvious oliguria. Lung hypoplasia can be seen on chest radiograph, but is overwhelmingly evident on clinical exam where the conscious infant has marked respiratory distress. Pulmonary hypertension leads to cyanosis and hypoxia, and failure of mechanical ventilation is often associated with pneumothorax. The spiral to death is inevitable in severe cases, due to failure of ventilation and advanced renal dysfunction. This “oligohydramnios sequence” can also occur, although often less dramatically, in the presence of a more benign renal abnormality, or when there is prolonged rupture of the membranes and chronic loss of amniotic fluid before 26 weeks gestation. In these cases, and depending on severity along the spectrum, less severe pulmonary hypoplasia can be supported with mechanical ventilation in the NICU.

**Pulmonary Lymphangiectasia.** This rare entity is also a result of developmental abnormality where there is congenital dilation of the pulmonary lymphatic channels. Prenatal sonography can typically detect the lobulation caused by diffuse dilation of the pleural lymphatics. At birth, in addition to severe respiratory distress, these infants may also have coexistent lymphedema. Congenital cardiac malformation is also common. Chest radiograph reveals variable patterns of marked hyperinflation and atelectasis. When
unanticipated, diagnosis of this rare disorder is difficult, since the clinical presentation often mimics more common forms of severe respiratory distress.

**Congenital Pulmonary Cysts.** Like pulmonary lymphangiectasis, congenital pulmonary cysts are uncommon, but can often be detected on prenatal sonography. Cysts can cause disease either as a result of pulmonary hypoplasia when there is generalized intrapulmonary cyst formation, or as a result of airway compression in the face of a large extrapulmonary cyst. The most common congenital pulmonary cyst is the congenital cystic adenomatoid malformation (CCAM) (Al-Bassam et al., 1999). This intrapulmonary disease has a wide range of presentations, from single to multiple cysts, affecting some or all the lung. Cystic adenomatoid malformations most commonly present with acute respiratory distress in the first few hours of life. Alternatively, it can present at several months of age as recurrent pneumonias.

Other rare forms of congenital pulmonary cyst include bronchogenic cyst and pulmonary sequestration. Similar to the case of pulmonary lymphangiectasis, without a suggestive prenatal sonogram, congenital pulmonary cysts can be an elusive diagnosis.

**Pulmonary Lobar Emphysema.** This congenital disorder is characterized by overdistention of one or more lobes of an infant’s lungs. This overdistension can be due to an intrinsic airway obstruction or alveolar overgrowth. Severity of symptoms depends upon the degree of overinflation, and the resultant compression of surrounding lung tissue. Symptoms often begin at 1 to 2 months of age, but also can present earlier in the neonatal period. Similar to pneumothorax, physical examination may reveal decreased breath sounds over the affected lobe and apical heartbeat displaced to the contralateral side. Chest radiograph will demonstrate the hyperinflated lobe, but may be difficult to differentiate from atypical pneumothorax, congenital pulmonary cysts, or diaphragmatic hernia. Diagnosis is radiographic—generally by CT scan after conventional radiograph is markedly abnormal. Because nearly 10% of infants displaying this condition have associated anomalies, especially congenital heart defects, genetic evaluation is suggested (Lacy, Shaw, Pilling, & Walkinshaw, 1999).

**Airway Obstruction**

The newborn is particularly disadvantaged to deal with airway obstructions because of very small tracheal and bronchial diameters. The risk of obstruction, even from mucus plugging is much increased in neonates than in adults. In addition, chest musculature is weak and the chest wall is relatively compliant, so coughing and deep breathing is comparatively ineffective.

Airway obstruction causes mechanical interference with ventilation and results in alveolar hypoventilation. The neonate with an airway obstruction is usually in obvious distress. Fortunately, physical examination or chest radiograph can usually reveal the source of the obstruction. Both physical examination and chest radiograph are highly variable, depending on the etiology of the obstruction, but in many cases, are diagnostic.

Some of the more common airway obstructions are:

**Choanal Atresia and Stenosis.** This is a complete or partial blockage at the posterior nasal chamber, which can be unilateral (80%-90%) or bilateral (Keller & Kacker, 2000). Infants usually present with respiratory distress immediately after birth, because the infant is an obligate nasal breather. Unusually, they become more pink with crying. During physical examination, a 6-Fr catheter cannot be passed into the nasopharynx. An artificial airway should be provided as soon as possible, until pediatric otolaryngologic evaluation is available.

**Pierre-Robin Sequence.** In this disorder, there is a hypoplastic mandible, usually associated with a cleft palate, and readily noted on physical examination. Hypoxia occurs secondary to airway obstruction when the tongue falls to the back of the oral cavity, obstructing the oropharynx. Pulling the tongue forward, caring for this neonate in the prone position, and possibly providing a nasopharyngeal or endotracheal airway may be necessary until otolaryngologic evaluation can be obtained.

**Macroglossia.** In a similar scenario to the Pierre-Robin sequence, macroglossia results in airway obstruction and hypoxia when the oversized tongue obstructs the oropharynx. On physical examination, the large—relatively large—tongue can be realized, and often is noted as one of several features of a genetic syndrome, such as Beckwith-Wiedemann syndrome or Trisomy 21.

**Thyroid Goiter.** Neonatal hyperthyroidism is rare in neonates, but is serious and potentially life threatening. In utero exposure to PTU or excessive iodine may result in goiter formation, or can result from the transplacental passage of immunoglobulins in mothers with Graves disease. Occasionally, a goiter is sufficiently large to compromise the neonatal airway, resulting in respiratory difficulty and hypoxia. These large goiters are typically diagnosed in utero by ultrasonography, but are readily evident on physical examination at birth.

**Cystic Hygroma.** Cystic hygroma arises as a result of abnormal development of the lymphatic channels, usually in the lateral neck. A large ill-defined mass presents in this...
area, and can extend to the scapular, axilla or thorax. Cystic hygroma of the mediastinum has also been reported, although this more likely presents as a supraclavicular mass. When evident, cystic hygroma distorts the subglottic area and usually compromises the airway, often requiring endotracheal intubation to secure oxygenation and ventilation.

**Laryngomalacia, Tracheomalacia, Subglottic Stenosis, and Tracheal Stenosis.** In some infants, a combination of a narrow tracheal diameter and insufficient cartilaginous support in the neck results in luminal compromise with each inspiration. A characteristic stridor is evident on physical examination, and is accentuated with crying. Usually this is a self-limiting condition that resolves by 6 to 12 months of age. In the rare case where excessive work of breathing and hypoxia is a feature, the high degree of airway obstruction may require tracheostomy (Gatz, 2001).

Other less common causes of airway obstruction in the newborn include, but are not limited to the following:

- **Subglottic Hematoma or Hemangioma**
- **Bronchomalacia or Bronchial Stenosis**
- **Laryngeal Web**
- **Vocal Cord Paralysis**
- **Foreign Body Aspiration**
- **Mucous Plugging**

**Extrinsic Compression of the Lungs and Airway**

Extrinsic lung compression occurs when a space-occupying lesion consumes volume within the thoracic compartment. Similar to the case of primary pulmonary disease, oxygen will usually improve a patient’s PaO\(_2\) if ventilation is adequate. In many cases, however, oxygenation and ventilation is still inadequate despite supplemental oxygen, and mechanical ventilation needs to be provided to treat hypoxia and hypercarbia.

**Pneumothorax and Pneumomediastinum.** The dissection of air from the alveoli into the mediastinum, and further into the pleural cavity, creates a pneumomediastinum and/or pneumothorax. This air leak occurs more frequently in the neonatal period than any other time in life (Fanaroff, Miller, & Martin, 2002). Spontaneous air leak typically presents as a complication of meconium aspiration, pneumonia, RDS, pulmonary hypoplasia, or any other disease associated with poor lung compliance, but can also occur in infants without underlying pathology. It is also commonly associated with positive pressure ventilation or vigorous resuscitation. Pneumothorax is reported to occur in approximately 1% of all live births, but this is probably underreported since asymptomatic air leaks often go undetected (Al-Bassam et al., 1999).

Clinical signs of pneumothorax include respiratory distress, tachypnea, nasal flaring and grunting, cyanosis, and even movement of the apical pulse away from the side of the pneumothorax. The most accurate diagnosis can be made from radiographs, although transillumination of the chest by a skilled clinician can be suggestive with large pneumothorax. Severe distress and displacement of the mediastinum (“tension pneumothorax”) may require evacuation of air with a needle or small catheter, or insertion of a closed system chest tube with continuous suction.

**Pleural Effusion or Chylothorax.** Fluid accumulation in the pleural space most typically represents a chylothorax in the neonate; however, a pleural effusion, empyema, or pleural hemorrhage can produce similar radiographic changes and clinical findings. Chylothorax is the accumulation of lymphatic fluid in the pleural space, and when found in the otherwise healthy term newborn, may represent. Thoracic duct rupture at delivery. This is the most frequent cause of a large pleural effusion in newborn. In chylothorax, pleural fluid is initially serous, but usually turns chylous after milk feedings. Chylothorax, and other types of pleural accumulations, are typically diagnosed and managed successfully with thoracenteses.

**Congenital Diaphragmatic Hernia.** Diaphragmatic hernia, which occurs in about 1 in 2,200 births, is an emergency at birth, and must be treated upon diagnosis (Golombek, 2002). Usually detectable on prenatal sonography, this anomaly presents with herniation of abdominal contents into the thorax because of incomplete formation of the diaphragm. Left sided hernias occur five times more often than those on the right (Braby, 2001; Golombek, 2002).

When the herniation occurs on the left side, the stomach and intestines may enter the thorax and compress the lung, pushing the mediastinum to the right. The degree of distress noted in the neonate depends on the severity of the herniation. As the neonate begins breathing, the presence of the abdomi-
nal contents compresses the lungs, making it very difficult to complete inspiration. As swallowed air further distends the intestines and stomach, compressing the lungs even more, the neonate’s respiratory distress worsens.

Symptoms of diaphragmatic hernia include cyanosis, respiratory distress, a scaphoid abdomen, and sometimes bowel sounds in the chest on auscultation. Chest radiograph showing the loops of bowel in the thorax confirms the diagnosis.

Immediate insertion of a nasal gastric tube attached to suction to evacuate abdominal gas is indicated. Ventilation is usually needed and should be done through an endotracheal tube, as bag and mask ventilation introduces air into the gastrointestinal tract, further compromising space in the chest cavity. Respiratory therapies should address the frequently associated hypoxia of persistent pulmonary hypertension. Urgent evaluation by a pediatric surgical team is requisite.

**Mediastinal Masses.** Mediastinal masses in neonates occur infrequently. Teratomas and dermoids are the most common of these lesions. They are neurogenic in origin, and typically located in the anterior mediastinum. On chest radiograph, soft tissue density characteristic, and there may be calcification or fat density areas within the region of the mass as well. Anterior mediastinal masses can displace the trachea, producing a clinical picture similar to airway obstruction. Middle and posterior mediastinal masses are less likely to produce respiratory distress and hypoxia, as displacement of the esophagus is more likely. Ultrasonography, CT, MRI and contrast radiographs are all useful in the evaluation of these lesions.

**Thoracic Dystrophies or Dysplasias.** Now exceedingly uncommon, these problems result from shortened ribs, an elongated thoracic cage and a resultant respiratory compromise. Many are associated with other congenital defects or dwarfism. Jeune syndrome (or "asphyxiating thoracic dysplasia") is one such complex disorder, which often results in death during infancy or early childhood.

**Extralobar Sequestration.** Extralobar sequestration occurs when lung tissue develops with no identifiable bronchial communication, and that receives its blood supply from one or more anomalous arteries. Infants can be asymptomatic, present with respiratory distress at birth, or present later in infancy with a chronic cough. In addition to vascular anomalies, the malformation has been reported in association with CHD (Harris, 2004). Diagnosis is generally made by CT scan after abnormal radiographic or sonographic evaluation. Surgical intervention or vascular embolization is often indicated.

Other less common causes of extrinsic compression of the airway and lungs in the newborn include:

- **Right/Double Aortic Arch**
- **Tracheal Vascular Ring**
- **Pulmonary Artery Sling**
- **Cricoid Cartilage Malformation**

In the final of this three-part series to be found in the July/August 2009 issue of MCN (volume 34, no. 4), neurologic, metabolic, and hematologic disorders will be reviewed as a basis for newborn hypoxia.

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