Respiratory Distress in Neonates

Underlying Causes and Current Imaging Assessment

Mark C. Liszewski, MD[a,*], A. Luana Stanescu, MD[b], Grace S. Phillips, MD[b], Edward Y. Lee, MD, MPH[c,d]

KEYWORDS

• Neonatal • Respiratory distress • Pulmonary • Preterm • Full-term • Congenital lung malformations

KEY POINTS

- Respiratory distress in the newborn can be caused by a variety of underlying conditions, and appropriate management depends on accurate and timely imaging and diagnosis.
- Imaging and pathologic features of congenital lung malformations often overlap and lesions are best considered on a spectrum, with each lesion demonstrating various degrees of parenchymal, airway, and vascular involvement.
- The leading cause of morbidity and mortality among premature infants remains surfactant deficiency disorder (previously known as hyaline membrane disease or respiratory distress syndrome) but advances in treatment, including prenatal glucocorticoids and exogenous surfactant, have altered the classic radiographic findings of surfactant deficiency disorder.
- Advances in treatment have resulted in a change in the radiographic features of chronic lung disease of prematurity (previously known as bronchopulmonary dysplasia). Though certain radiographic features are typical for chronic lung disease of prematurity, current diagnostic criteria for chronic lung disease of prematurity are based solely on clinical criteria.
- The congenital surfactant dysfunction disorders are a rare group of genetic diseases that lead to abnormal production and/or function of surfactant in the lungs and produce typical, though nonspecific imaging findings.

INTRODUCTION

Respiratory distress is among the most common clinical indications for imaging the newborn. A variety of underlying conditions can cause respiratory distress in the neonate, and familiarity with the imaging appearance of each of these conditions is essential to timely diagnosis and appropriate management. In this article, current imaging techniques and modalities are described and the most commonly encountered neonatal lung diseases are discussed, including congenital

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[a] Division of Pediatric Radiology, Department of Radiology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East, 210th Street, Bronx, NY 10467, USA; [b] Department of Radiology, Seattle Children's Hospital, University of Washington School of Medicine, 4800 Sand Point Way Northeast, Seattle, WA 98105, USA; [c] Division of Thoracic Imaging, Department of Radiology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA; [d] Pulmonary Division, Department of Medicine, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA
* Corresponding author.
E-mail address: mliszews@montefiore.org

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lung malformations and lung abnormalities in preterm infants, as well as full-term infants.

IMAGING MODALITIES AND TECHNIQUES

Radiography

Chest radiographs are the primary imaging modality used in the assessment of the newborn with respiratory distress. In many cases, the management of neonates relies only on chest radiographs without the use of other imaging modalities. Chest radiographs are relatively inexpensive, easy to obtain, and use a very low amount of radiation, making them an ideal initial test to evaluate many neonatal lung diseases. Radiation doses can be further minimized through shielding and proper coning of images.[1,2]

Most chest radiographs performed in neonates are obtained portably and consist of a single anterior-posterior (AP) view with the child in a supine position. In certain scenarios, a lateral view may be useful to localize a finding. AP lateral decubitus views may be used in select cases, such as to visualize layering pleural effusion or to better assess a suspected pneumothorax. Though chest radiographs are an indispensable tool, they do not provide the same anatomic detail as computed tomography (CT) or MR imaging, and these may be indicated to further evaluate a finding seen on chest radiograph.

Fluoroscopy

Fluoroscopy can be useful to evaluate dynamic disease processes that change throughout the respiratory cycle but its role in neonatal respiratory distress is limited to a few scenarios. Fluoroscopy may be used to evaluate diaphragmatic motion in cases of suspected diaphragmatic paralysis or eventration, though ultrasound is often preferred due to its portability and lack of radiation.[3] Airway fluoroscopy may be performed in cases of suspected tracheobronchomalacia to evaluate for large airway collapse during expiration.[4]

Ultrasound

In recent years, ultrasound has received increasing attention as a tool in the evaluation of lung disease, though inherent physical properties of the chest, including acoustic shadowing from air-filled lung and ribs, often impede ultrasound's diagnostic utility in the thorax. Despite these limitations, ultrasound can be very useful in selected scenarios.[5] When chest radiograph demonstrates a completely opacified hemithorax, ultrasound can help differentiate pleural fluid from pulmonary parenchymal disease.[5] Doppler ultrasound can assess for anomalous vasculature in cases of suspected pulmonary sequestration.[5] Real-time, cine, and M-mode ultrasound imaging are the preferred methods for assessing diaphragmatic motion in cases of suspected paralysis and eventration, and can be helpful in the evaluation of congenital diaphragmatic hernia.[3,6–9] The aerated lung can even be assessed in selected scenarios through analysis of B-lines, the comet-tail artifacts that are produced when the sound beam interacts with the interlobular septa at the pleural surface. Increased B-lines have been reported in transient tachypnea of the newborn (TTN) and surfactant deficiency,[10,11] though these entities are more commonly diagnosed and managed using chest radiography alone.

Computed Tomography

CT has the ability to produce cross-sectional images with excellent anatomic detail, making it a powerful tool in the evaluation of many thoracic diseases. CT uses ionizing radiation to produce images, and every effort should be made to use low-dose pediatric protocols and limit unnecessary CT scans, particularly in neonates who are inherently more sensitive to the effects of radiation than adults.[12–15] Alternative modalities that use less or no ionizing radiation, such as radiography, ultrasound, and MR imaging, should always be considered before performing CT. After considering these factors, CT is often the best imaging modality to assess many neonatal lung diseases given its excellent anatomic detail and is lower susceptibility to artifacts. The addition of intravenous contrast is often indicated to better evaluate the mediastinal structures and vasculature.

MR Imaging

MR imaging has received much attention due to its ability to generate images without the use of ionizing radiation, though its role in the evaluation of respiratory distress in the newborn is limited. Cost, availability, and physical properties of the lung, including low signal-to-noise ratio, respiratory and cardiac motion, and signal dephasing at air-tissue interphases, limit the routine use of chest MR imaging in neonates. Despite these limitations, MR imaging with MR angiography (MRA) may be used as a first-line alternative to CT in several specific conditions, including pulmonary sequestration, pulmonary artery hypoplasia, pulmonary vascular anomalies, partial or total anomalous pulmonary venous return, and vascular rings and sling.[16,17] Small-bore and modified MR imaging scanners have been used in research settings to evaluate changes of chronic lung disease of

prematurity (previously known as bronchopulmonary dysplasia [BPD]) in neonates,[18,19] though these techniques are not yet widely available in the clinical setting. Chest MR imaging using hyperpolarized gas (^{3}He or ^{129}Xe) as an inhaled contrast agent has the potential to quantify changes in lung microstructure, and has been studied in older children with a past history of chronic lung disease of prematurity[20] but has not been studied in the neonatal period.[21]

Nuclear Medicine

Nuclear medicine does not play a major role in the routine evaluation of most causes of neonatal respiratory distress. Pulmonary ventilation-perfusion (V/Q) scans, in which the pulmonary distribution of an inhaled radiotracer (eg, ^{99m}Tc-labeled diethylenetriamine penta-acetic acid [DTPA], ^{133}Xe, or Technegas) and an injected radiotracer (eg, 99mTc-labeled macroaggregated albumin) are imaged can be useful in certain diseases. For example, V/Q scans have been used to assess pulmonary hypoplasia in patients with history of congenital diaphragmatic hernia.[22–24] V/Q scans can provide information about severity and abnormalities in regional lung function in chronic lung disease of prematurity.[25,26] Perfusion scintigraphy can also be useful to determine differential pulmonary perfusion in cases of congenital heart disease, pulmonary hypoplasia, and scimitar syndrome,[27,28] and can be used to quantify right-to-left shunts.[27]

SPECTRUM OF UNDERLYING PULMONARY CAUSES OF NEONATAL RESPIRATORY DISTRESS

Congenital Lung Malformations

Congenital lung malformations are a group of developmental lesions involving the lung parenchyma, airway, and/or pulmonary vasculature. Symptoms are variable and can range from no symptoms to progressive respiratory distress requiring surgical intervention. The 3 most common congenital lung malformations detected in the neonate are congenital pulmonary airway malformation (CPAM), pulmonary sequestration, and congenital lobar overinflation (CLO). There is considerable overlap between these entities and they can be best considered as lesions on a spectrum with each lesion demonstrating various degrees of parenchymal, airway, and vascular involvement.[29–31] The classic radiographic and pathologic features of these lesions are discussed in the following sections and imaging findings are summarized in **Table 1**.

Congenital pulmonary airway malformation

CPAMs, previously known as cystic adenomatoid malformations, are congenital macrocystic or microcystic lung lesions that are associated with an abnormal bronchial tree and bronchiolar overgrowth.[32,33] Typically, CPAMs are associated with normal pulmonary vascular anatomy (**Fig. 1**), though pathologic features of CPAM are seen in 29% to 33% of pulmonary lesions with abnormal systemic arterial supply (**Figs. 2** and **3**) and up to 50% of lobar emphysemas.[31,34,35] Several different classification systems have been proposed to categorize CPAM lesions. Though no classification scheme is universally accepted, the system proposed by Stocker and colleagues in 1977[36] and updated in 2001[37] is often used. In this classification system, type 1 lesions are composed of 1 or more cysts measuring greater than 2 cm, type 2 lesions are composed of 1 or more cysts measuring less than 2 cm, and type 3 lesions appear as solid masses macroscopically but contain microcysts on pathologic analysis. Stocker also describes type 0 lesions (acinar dysplasia, which is incompatible with life) and type 4 lesions (large peripherally located lung cysts sometimes associated with pneumothorax), though these lesions are controversial.[38–43]

The clinical presentation of CPAM varies. With increased prenatal imaging, an increasing number of lesions are currently detected incidentally during routine fetal ultrasound (see **Fig. 2**). Some lesions cause no symptoms, whereas others cause varying degrees of respiratory distress soon after birth, particularly when large.[43–45] Lesions may present later in life due to superinfection or rarely due to development of associated malignancy.[43] Approximately half of type 2 lesions are associated with additional congenital anomalies, including cardiovascular malformations, extralobar pulmonary sequestration, tracheoesophageal fistula, renal agenesis, intestinal atresia, and congenital diaphragmatic hernia.[43,46]

The imaging appearance of CPAM depends on the type. Lesions with macroscopic cystic components (types 1 and 2) are typically filled with fetal lung fluid at birth and fluid partially or completely clears from the cysts in the first few days of life.[32] Initial chest radiographs typically demonstrate a dense lung lesion that becomes less dense as fetal lung fluid clears. CT and MR imaging demonstrate a cyst or cysts within the lung parenchyma, containing air and/or fluid.[29,32] Lesions composed of microscopic cysts (type 3) appear as solid masses macroscopically and, therefore, will appear as dense lung lesions on radiographs and as solid enhancing masses on CT and MR imaging.[29,32] When CPAMs present later in life with

Table 1
Imaging findings of congenital lung malformations

Congenital Lung Malformation	Imaging Findings	Pearls and Pitfalls
Congenital pulmonary airway malformation (CPAM)		
Stocker type 0[a] Stocker type 1[a] Stocker type 2[a] Stocker type 3[a] Stocker type 4[a]	Atretic large airways and lungs 1 or more cysts measuring >2 cm 2 or more cysts <2 cm Both imaging-wise and macroscopically solid mass composed of microcysts on pathologic analysis Large peripherally located lung cysts sometimes associated with pneumothorax	Type 0 CPAM lesions can be only seen in prenatal ultrasound or MR imaging In type 1 and 2 CPAM lesions initial CXR typically demonstrates a dense lung lesion that becomes less dense as fetal lung fluid clears Type 3 CPAM lesions remain dense because they are macroscopically solid masses On imaging studies, pleuropulmonary blastoma type 1 (pure cystic lesion) has similar imaging appearance to type 1, 2, and 4 CPAM lesions When CT or MR imaging is performed, contrast-enhanced CTA or MRA technique should always be used to evaluate for systemic arterial supply, seen in so-called hybrid lesions
Pulmonary sequestration	Cystic or solid lung mass Systemic arterial supply seen on US, CT or MR imaging Intralobar: venous drainage to pulmonary veins Extralobar: venous drainage to systemic pulmonary vein	Frequently detected during prenatal ultrasound Contrast-enhanced CTA or MRA are recommended in cases of suspected sequestration Most often occur in the lower lobes, left>right Extralobar sequestration may be intrathoracic or extrathoracic 3D volume rendered CT images can increase the diagnostic accuracy and confidence level for correctly identifying small anomalous vessels in patients with pulmonary sequestration
Congenital lobar overinflation (CLO)	Serial CXRs after birth first show an opacified lobe that becomes lucent and then hyperexpands LUL>RML>RUL>RLL & LLL	AKA congenital lobar emphysema Hyperexpansion often causes significant mass effect that may result in significant respiratory distress and necessitate lobectomy

Abbreviations: 3D, 3-dimensional; AKA, also known as; CTA, CT angiography; CXR, chest radiograph; LLL, left lower lobe; LUL, left upper lobe; MRA, MR Angiography; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

[a] Per the classification system described in: Stocker J. The respiratory tract. In: Stocker JT, Dejner LP, editors. Pediatric pathology. 2nd edition. Philadelphia: Lippincott, Williams & Wilkins; 2001. p. 466–73.

superinfection, chest radiographs typically demonstrate consolidation with air-fluid levels, and CT or MR imaging demonstrate cystic lung lesions containing air-fluid levels and a thick enhancing irregular wall.[29,32,33] Typically, CPAMs have a conventional pulmonary vascular anatomy but attention to vascular supply is essential because a proportion of CPAMs have a systemic arterial supply (so-called hybrid lesions; see **Figs. 2** and **3**).[34,35] Therefore, CT or MR imaging should be performed with contrast and CT angiography (CTA) or MRA techniques should be used.

Pulmonary sequestration

Pulmonary sequestration is typically defined as a disconnected bronchopulmonary mass or cyst with an anomalous arterial supply.[47] There are 2 types of sequestration that are commonly

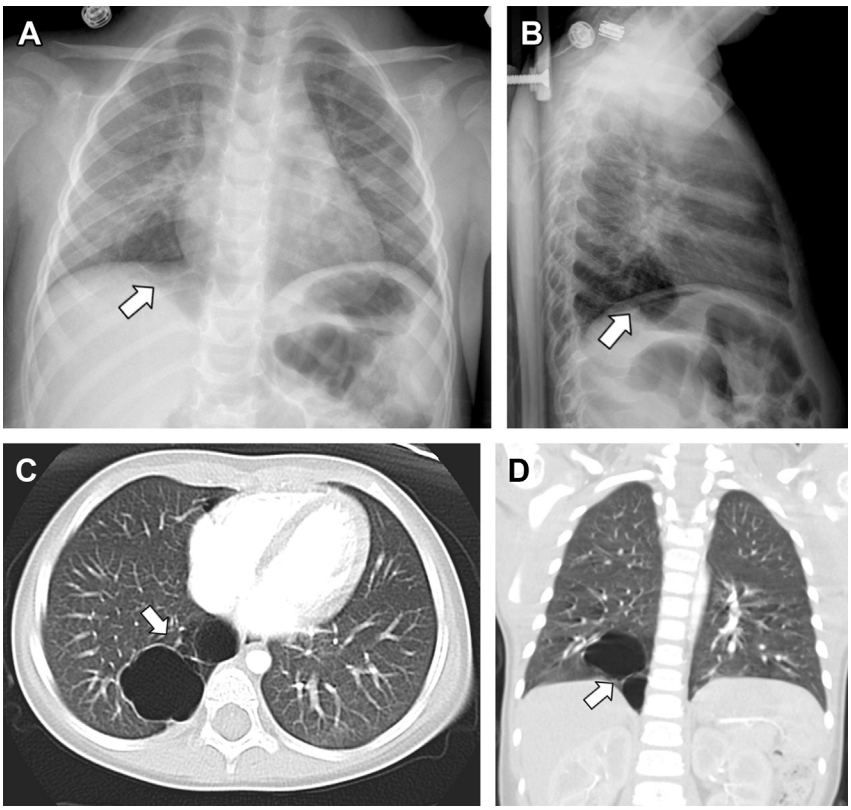

Fig. 1. A 2-year-old-boy with type 1 congenital pulmonary airway malformation (CPAM). Frontal (*A*) and lateral (*B*) chest radiographs demonstrate an air-filled multicystic lesion (*arrows*) in the right lower lobe. Axial (*C*) and coronal (*D*) lung window CT images show the lesion (*arrows*) is composed of multiple large air-filled cysts.

described: intralobar and extralobar. Intralobar sequestration is typically characterized by abnormal lung tissue that does not communicate with the tracheobronchial tree, has an arterial supply from the aorta or one of its branches, has venous drainage to the pulmonary vein, and shares a 1 visceral pleural covering with the adjacent normal lung.[29,32,33] Extralobar sequestration is also characterized by abnormal lung tissue that does not communicate with the tracheobronchial tree and has an arterial supply from the aorta or one of its branches. Extralobar sequestration differs from intralobar sequestration in that its venous drainage is to a systemic vein and its pleural covering is separate from the adjacent lung.[29,32,33] Extralobar sequestration is most often located within the lower

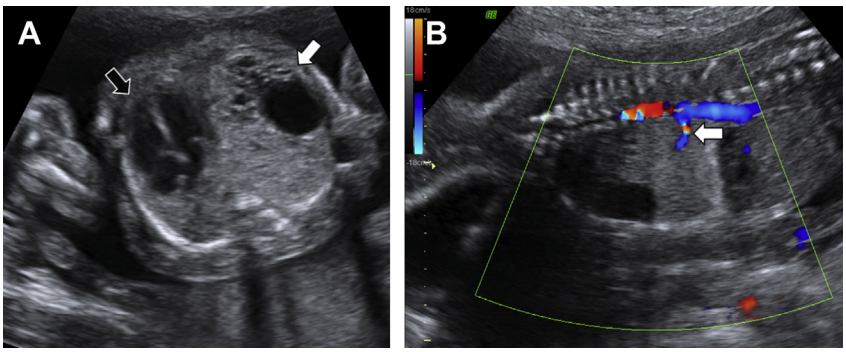

Fig. 2. A 22-week-old fetus with congenital pulmonary airway malformation (CPAM) and bronchopulmonary sequestration (hybrid lesion). (*A*) Grayscale prenatal ultrasound shows a multicystic mass (*white arrow*) in the left lung displacing the heart (*black arrow*) to the right. (*B*) Color Doppler ultrasound image demonstrates a feeding systemic artery (*arrow*) arising from the aorta.

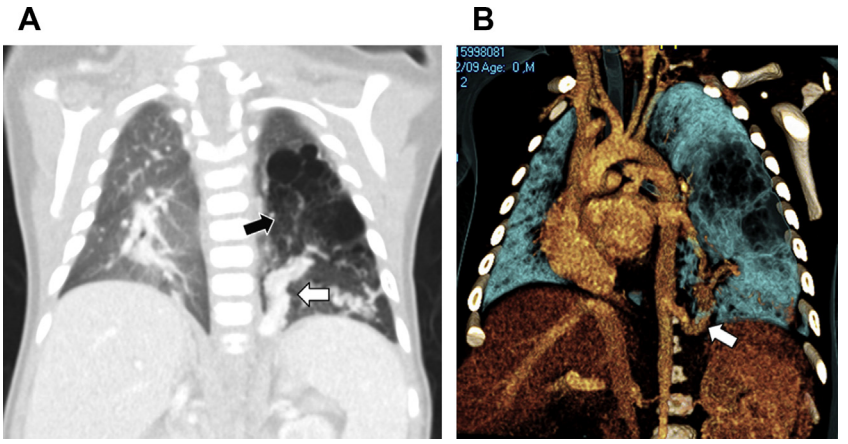

Fig. 3. A 5-month-old boy with congenital pulmonary airway malformation (CPAM) and bronchopulmonary sequestration (hybrid lesion) (same patient as Fig. 2). (*A*) Coronal image from contrast-enhanced CT angiography (CTA) demonstrates an air-filled multicystic lesion within the left lung (*black arrow*) with a large feeding systemic artery (*white arrow*). (*B*) Three-dimensional (3D) volume-rendered CT image shows the systemic feeding artery (*arrow*) arising from the aorta.

lung but can occur below the diaphragm or within the mediastinum. The traditional description of pulmonary sequestration has shortcomings and many lesions do not fit the strict definition. For example, lesions may have an abnormal arterial supply but normal tracheobronchial connection.[48] These issues have led some to propose alternative classification systems[34,38,49] but the terms intralobar and extralobar sequestration seem deep-rooted despite their inherent limitations.

Pulmonary sequestration is frequently detected incidentally during prenatal ultrasound as a pulmonary mass with anomalous systemic arterial supply (see Fig. 2).[44] At birth, most pulmonary sequestrations are asymptomatic and appear as a lung mass within a lower lobe, on the left side more often than the right side.[29] Postnatal chest ultrasound with Doppler imaging may demonstrate a lung mass with an anomalous systemic arterial vascular supply.[5] Contrast-enhanced CTA or MRA are recommended in cases of suspected sequestration.[17,29] Extralobar sequestration typically appears as a solid enhancing mass with systemic arterial and venous circulation that may be intrathoracic or extrathoracic. Intralobar sequestration typically appears as a cystic lung lesion with variable aeration (due to collateral air drift), arterial supply from the aorta or one of its branches, and venous drainage to a pulmonary vein (see Fig. 3; Fig. 4).[32] Intralobar sequestration can present later in life with superinfection and chest radiograph and CT may demonstrate increased consolidation and air-fluid levels within a pre-existing lesion.[29,32]

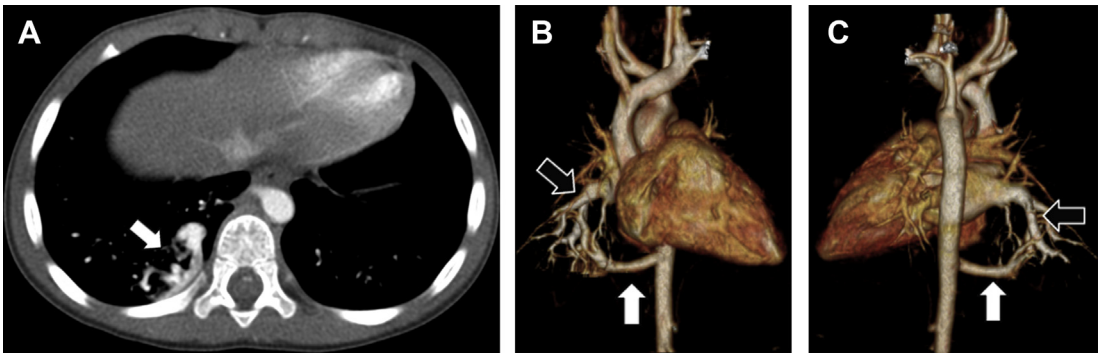

Fig. 4. A 21-month-old boy with intralobar bronchopulmonary sequestration. (*A*) Axial contrast-enhanced CT demonstrates a heterogeneous lesion in the right lower lobe containing large abnormal vessels (*arrow*). (*B*, *C*) 3D volume-rendered CT images show systemic feeding artery (*white arrows*) arising from the aorta and venous drainage (*black arrows*) to the pulmonary veins and left atrium.

Congenital lobar overinflation

CLO, also known as congenital lobar emphysema, is a lung lesion characterized by hyperexpansion of a lobe of the lung. The primary defect in CLO is bronchial obstruction due to compression from an external structure or intrinsic narrowing. The lung distal to the obstruction becomes hyperinflated. Mass effect from the hyperinflated lobe can result in significant symptoms, typically presenting within the first 6 hours of life. CLO affects certain lobes more frequently; from most to least: left upper lobe, right middle lobe, right upper lobe, right or left lower lobes.[50]

CLO produces a classic appearance on serial chest radiographs. The initial radiograph performed immediately after birth typically shows an opacified lobe due to entrapped fetal lung fluid. As the fluid clears, the lobe becomes more lucent and demonstrates progressive hyperinflation. Hyperinflation often continues to increase and causes mass effect on the mediastinum and diaphragm (**Fig. 5**A). Mass effect is frequently accompanied by worsening respiratory distress, requiring lobectomy. If clinically stable, preoperative CT is generally indicated to define the lobar anatomy before lobectomy (**Fig. 5**B, C).[29] Classically, CLO is associated with conventional vascular anatomy.

Lung Abnormalities in Preterm Infants

Advances in neonatal intensive care over the past 50 years have led to greatly improved survival rates for infants born before term. The leading cause of morbidity and mortality among premature infants is respiratory distress due to insufficient surfactant production. Complications of surfactant deficiency disorder, including pulmonary interstitial emphysema (PIE) and chronic lung disease of prematurity, can further contribute to morbidity and mortality in this patient group. The radiographic and pathologic features of these entities are discussed in the following sections and imaging findings are summarized in **Table 2**.

Surfactant deficiency disorder, hyaline membrane disease, or respiratory distress syndrome

Surfactant deficiency disorder, also known as hyaline membrane disease or respiratory distress syndrome (RDS), is primarily a disease of premature infants. Surfactant deficiency disorder occurs when immature type II pneumocytes are unable to produce sufficient surfactant to support normal lung function. In the healthy state, surfactant reduces surface tension within alveoli and is essential to normal alveolar expansion. Hyaline membranes, which contain necrotic cells, fibrin, and plasma transudate, form within the alveoli of the surfactant-deficient lung and further impair oxygenation. Antenatal corticosteroids (which accelerate surfactant production) and exogenous surfactant have improved survival among premature children.[51] Mechanical ventilation is often required to treat patients with surfactant deficiency disorder but efforts are focused on reducing barotrauma because this is a major cause of morbidity through air-leak phenomena and increased risk of chronic lung disease of prematurity.

Chest radiographs in untreated surfactant deficiency disorder typically demonstrate low lung volumes with diffuse homogenous granular opacities (**Fig. 6**). This classic appearance is altered by the administration of exogenous surfactant. After surfactant, granular opacities and lung hypoinflation may uniformly improve, asymmetrically decrease, or show no change.[52] Surfactant is often administered before the first radiograph, so even initial chest radiographs may not demonstrate the classic pattern of surfactant deficiency disorder. Asymmetric improvement can produce radiographic findings similar to neonatal pneumonia or meconium aspiration, and correlation with clinical history is essential in these cases.[51] Surfactant deficiency disorder is typically managed using radiographs alone, and other imaging modalities are rarely used.

Fig. 5. A 9-month-old girl with left upper lobe congenial lobar overinflation (CLO). (*A*) Frontal chest radiograph demonstrates hyperlucent left upper lobe with mild mass effect on the mediastinum. Axial (*B*) and coronal (*C*) contrast-enhanced CT images show hyperlucent left upper lobe.

Table 2
Imaging findings of the most common lung abnormalities in preterm infants

Lung Abnormality	Imaging Findings	Pearls and Pitfalls
Surfactant deficiency disorder, hyaline membrane disease, or respiratory distress syndrome (RDS)	Low lung volumes with diffuse homogenous granular opacities After surfactant granular opacities may uniformly improve, asymmetrically decrease, or show no change	Initial CXR may not demonstrate the classic pattern of surfactant deficiency disorder because surfactant is often administered before the first radiograph is obtained CXR may show asymmetric improvement after surfactant is administered and can appear similar to neonatal pneumonia or meconium aspiration
Pulmonary interstitial emphysema (PIE)	CXR: bubbly and/or linear lucencies CT: line-and-dot pattern due to interstitial air surrounding the bronchovascular bundles	Most common in mechanically ventilated patients with surfactant deficiency disorder Surfactant given to treat surfactant deficiency disorder can cause localized acinar overdistention that may mimic PIE
Chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD)	Coarse reticular opacities, cystic lucencies and hyperexpansion	New diagnostic criteria for BPD are based solely on clinical features, and do not include radiographic features

Pulmonary interstitial emphysema

PIE is a condition that occurs when air ruptures through the bronchoalveolar junctions and dissects into the pulmonary interstitium.[53] PIE occurs most commonly in mechanically ventilated patients with surfactant deficiency disorder but can also occur in meconium aspiration syndrome (MAS) or neonatal pneumonia. PIE may be accompanied by additional air-leak phenomena, including pneumothorax, pneumomediastinum, pneumopericardium, and pneumoperitoneum.

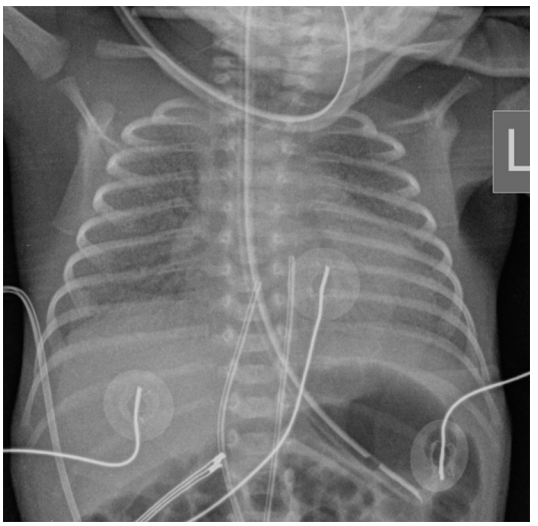

Fig. 6. Newborn girl born premature at 28 weeks gestation with surfactant deficiency disorder. Frontal chest radiograph demonstrates diffuse bilateral hazy pulmonary opacities and low lung volumes.

Chest radiographs in PIE typically demonstrate bubbly or linear lucencies with morphology different from air-bronchograms or normal air within alveoli (**Fig. 7**).[54,55] PIE may be focal, diffuse, unilateral or bilateral.[55] If PIE persists for longer than 1 week, it is termed persistent PIE (PPIE) (see **Fig. 7**C). The involved lung can enlarge and cause mass effect.

Other entities can occasionally mimic the appearance of PIE on chest radiographs. Exogenous surfactant given to treat surfactant deficiency disorder can cause localized acinar overdistention that produces an appearance of bubbly lucencies that may mimic PIE.[51] In this scenario, consideration of the child's clinical condition is essential: patients with PIE tend to decompensate and patients with acinar distention from exogenous surfactant tend to improve.[51] Localized PPIE can mimic CPAM and CLO on chest radiographs but prior imaging studies typically demonstrate a characteristic pattern of PIE in the same region.[53] If the diagnosis of PPIE is unclear, CT may be performed and demonstrate interstitial air surrounding the bronchovascular

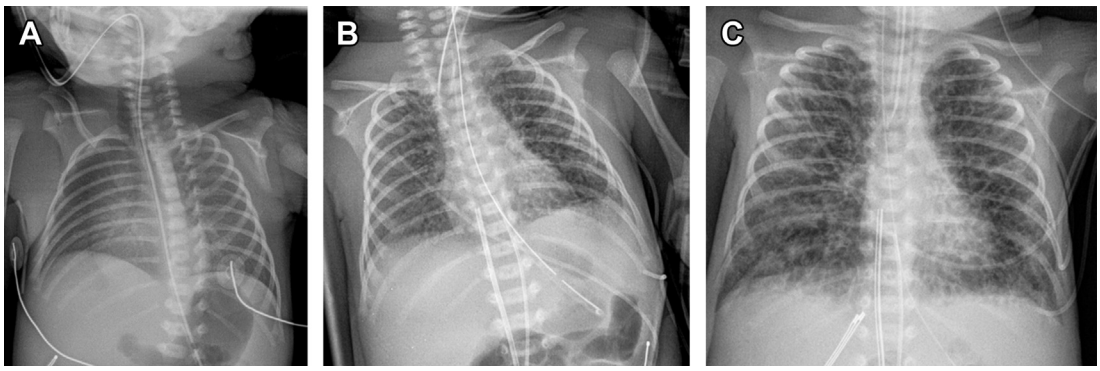

Fig. 7. Newborn girl born premature at 29 weeks gestation with surfactant deficiency disorder and persistent pulmonary interstitial emphysema (PIE) (PPIE). (*A*) Chest radiograph at day 1 of life shows diffuse bilateral hazy pulmonary opacities of surfactant deficiency disorder. (*B*) Chest radiograph at day 2 of life demonstrates new bilateral bubbly and linear lucencies that do not conform to the shape of air-bronchograms, compatible with PIE. (*C*) Chest radiograph at day 9 of life shows persistent bubbly and linear lucencies of PIE, compatible with PPIE.

bundles, producing a line-and-dot pattern.[55–57] Bubbly lucencies in PIE can also mimic lucencies seen in chronic lung disease of prematurity, and consideration of the time course and patient age are essential to differentiate these entities. PIE generally occurs as an acute event during the first week of life, whereas imaging findings of chronic lung disease of prematurity tend to appear gradually around the second and third week.[58]

Presence of PIE should be reported to neonatal intensive care unit (NICU) staff immediately because patients will often be changed from conventional mechanical ventilation to high-frequency oscillatory ventilation.[56] Most PIE responds to conservative management and resolves spontaneously. A minority of cases persist, leading to PPIE. Most PPIE is managed conservatively. A small number of cases of PPIE require surgical resection due to mass effect.[56] CT is often indicated in these cases to aid surgical planning.[55–57]

Chronic lung disease of prematurity or bronchopulmonary dysplasia

Though many patients with surfactant deficiency disorder completely recover, a subset of patients develops persistent pulmonary disease called chronic lung disease of prematurity, also known as BPD. Northway and colleagues[59] first described this condition in 1967, describing 4 stages of BPD occurring in a subset of patients with surfactant deficiency disorder and treated with mechanical ventilation. In the classic BPD described by the investigators, chest radiographs evolve from findings of surfactant deficiency disorder in the first days of life to diffuse bilateral opacities that are slowly replaced by coarse reticular opacities, cystic lucencies, and hyperexpansion beginning around day 10 and progressing beyond 1 month of age (**Fig. 8**). Pathologically, chronic lung disease of prematurity is characterized by emphysema, atelectasis,

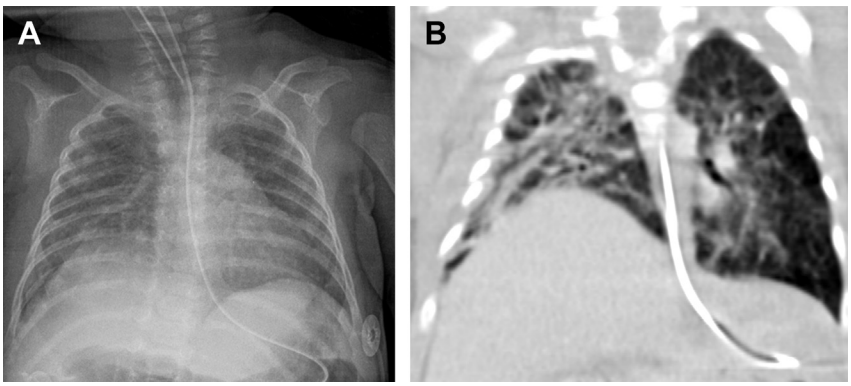

Fig. 8. A 3-month-old girl born premature at 26 weeks gestation with chronic lung disease of prematurity. (*A*) Chest radiograph shows bilateral coarse interstitial opacities, atelectasis, and right hemidiaphragm elevation due to right lung volume loss. (*B*) Coronal lung window CT image demonstrates bilateral ground glass opacities, septal thickening, and atelectasis that are greater on the right with right hemidiaphragm elevation.

smooth muscle hypertrophy, and pulmonary fibrosis. Patients with chronic lung disease of prematurity have persistent respiratory distress requiring continued respiratory treatment ranging from supplemental oxygen to long-term mechanical ventilation.

There have been many changes in the treatment of surfactant deficiency disorder and chronic lung disease of prematurity since the original 1967 description by Northway and colleagues.[59] These changes include antenatal glucocorticoid therapy, exogenous surfactant, use of lower oxygen concentrations, and less harmful ventilation techniques. This has resulted in survival of larger numbers of infants who have low and extremely low birth weight, many of whom go on to develop chronic lung disease requiring long-term respiratory support. The imaging features of chronic lung disease in this group often differ from the original findings described by Northway and colleagues,[59] leading to the term *the new BPD*. For example, early chest radiographs in extremely premature infants may only demonstrate mild perihilar opacities and fine granularity in a pattern termed immature lung[60] but subsequent radiographs often demonstrate typical features of BPD, including coarse interstitial opacities, cystic lucencies, and hyperexpansion.[51,53] Because the radiographic features in these patients often differ from those originally described by Northway and colleagues,[59] the National Institute of Child Health and Human Development's National Heart, Lung, and Blood Institute Workshop developed new diagnostic criteria for BPD that are based solely on clinical features and do not include a consideration of the radiographic findings because they did not increase the established diagnostic sensitivity or specificity.[61,62] This workshop recommended continued use of the term BPD, though many now prefer the term chronic lung disease of prematurity given the evolution of the disease since the original description by Northway and colleagues.[59]

Treatment of chronic lung disease of prematurity is supportive. Oxygen toxicity and barotrauma are major risk factors for developing chronic lung disease of prematurity[63]; therefore, high supplemental oxygen concentrations and positive pressure ventilation are limited as much as possible. Inhaled bronchodilators may be used for temporary symptom relief, though they do not improve long-term outcomes.[63,64] Systemic corticosteroids can improve lung function but are reserved for only the most severe cases due to serious potential side effects, including neurologic dysfunction.[65–67]

Lung Abnormalities in Full-Term Infants

A variety of conditions may lead to respiratory distress in full-term newborns, often leading to NICU admission. Conditions range from rare genetic diseases, such as congenital surfactant dysfunction disorders, to more common conditions, including TTN, MAS, and infection. The radiographic and pathologic features of these entities are discussed in the following sections and imaging findings are summarized in **Table 3**.

Congenital surfactant dysfunction disorders

The surfactant dysfunction disorders are a rare group of genetic diseases that lead to abnormal production and/or function of surfactant in the lungs, and can cause respiratory distress in the newborn. Several mutations have been identified, including mutations in genes for surfactant protein B (**Fig. 9**), surfactant protein C, adenosine triphosphate (ATP)-binding cassette transporter protein, thyroid transcription factor-1, and granulocyte-macrophage colony-stimulating factor–Rα.[68–72]

Patients affected with surfactant dysfunction disorder are typically born at term with respiratory distress. Symptoms may range from mild to severe. Chest radiograph typically shows bilateral patchy or diffuse hazy opacities.[73–75] Findings on CT may include ground-glass opacities, consolidation, and interlobular septal thickening.[73–76] Definitive diagnosis can be established with genetic testing. Some cases are related to yet-unknown genetic mutations and, in these cases, biopsy is required for diagnosis.

Transient tachypnea of the newborn

TTN is a condition caused by retained fetal fluid within the lung after birth, resulting in respiratory distress. Fetal lung liquid is cleared through the airway, lymphatic channels, and capillaries.[51] Clearance is promoted by adrenergic stimulation that occurs during the normal vaginal birth process.[77–80] Therefore, TTN is more common among infants born by cesarean section or precipitous vaginal delivery.[81,82] Retained fluid in TTN is located within the alveoli, pulmonary interstitium, and enlarged lymphatics. This distribution is very similar to the distribution of fluid in pulmonary edema; therefore, the imaging findings are similar.

Chest radiographs obtained soon after birth typically show perihilar interstitial opacities, indistinct pulmonary markings, and small pleural effusions (**Fig. 10**). Lung volumes may be normal or increased. Symptoms are usually mild and typically resolve by days 2 to 3 of life. Chest radiographs also typically normalize during this time period.

Table 3
Imaging findings of the most common lung abnormalities in full-term infants

Lung Abnormality	Imaging Findings	Pearls and Pitfalls
Surfactant dysfunction disorders	CXR: bilateral patchy or diffuse hazy opacities CT: ground-glass opacities, consolidation, and interlobular septal thickening	Entities include surfactant protein B and C deficiency, ATP-binding cassette transporter protein deficiency, thyroid transcription factor-1 deficiency, granulocyte-macrophage colony-stimulating factor–Rα deficiency Definitive diagnosis is established with genetic testing or biopsy
Transient tachypnea of newborn (TTN)	CXR soon after birth: Perihilar interstitial opacities, indistinct pulmonary markings, and small pleural effusions. Lung volumes may be normal or increased. Aeration improves on CXR after 2–3 d	Caused by retained fetal fluid within the lung after birth Clearance of fluid is promoted by adrenergic stimulation that occurs during the normal vaginal birth process Therefore, TTN is more common after cesarean section or precipitous vaginal delivery
Meconium aspiration syndrome (MAS)	Hyperinflation with asymmetric irregular opacities Pneumothorax in 10%–40% Pleural effusion in 10%–20%	Exogenous surfactant may be given to replace surfactant that has been chemically inactivated by meconium Affected neonates are at higher risk for pneumonia and imaging findings are similar to neonatal pneumonia, therefore patients are often treated with antibiotics
Pulmonary infection	Most commonly, bilateral alveolar opacities Findings may be identical to RDS or TTN CXR can be normal	Fever is not typical, temperature instability is more common May be difficult to differentiate neonatal pneumonia from other entities based on imaging findings alone, therefore patients are often treated presumptively with antibiotics

Abbreviation: ATP, adenosine triphosphate.

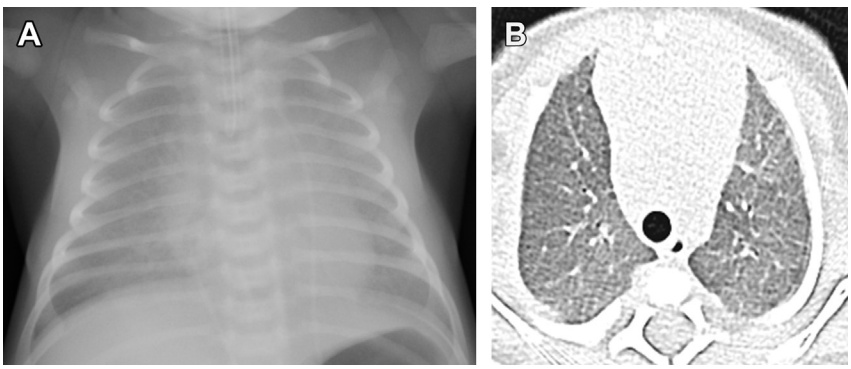

Fig. 9. A 26-day-old girl born at full term with congenital surfactant protein B deficiency. (*A*) Chest radiograph demonstrates diffuse bilateral hazy pulmonary opacities. (*B*) Axial lung window CT image shows diffuse ground glass opacity throughout bilateral lungs.

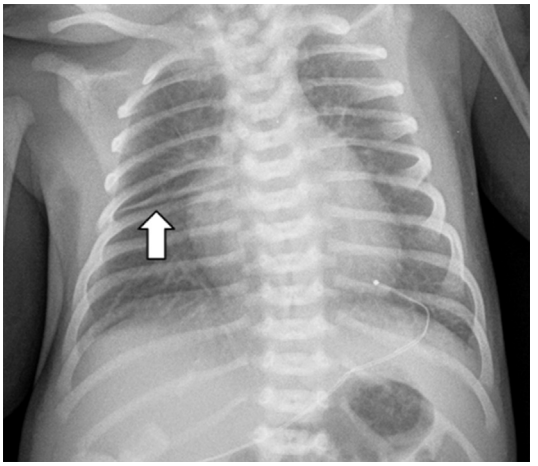

Fig. 10. A 3-hour-old full-term boy born via cesarean section with transient tachypnea of newborn (TTN). Frontal chest radiograph demonstrates bilateral pulmonary interstitial opacities and trace fluid (*arrow*) in the minor fissure.

Meconium aspiration syndrome

MAS occurs when meconium is passed and aspirated during birth. Meconium is a thick and tenacious chemical irritant. When aspirated, it causes small and medium airway obstruction, chemical pneumonitis, and inactivation of surfactant. MAS is more common in children born after 40 weeks gestation.[83] Respiratory distress may range from mild to severe. MAS is the most common cause of mortality in term infants.[84]

Chest radiographs in MAS typically show hyperinflation with asymmetric irregular opacities due to combination of air-trapping, atelectasis, and chemical pneumonitis (**Fig. 11**). Pneumothorax is relatively common, seen in 10% to 40% of cases.[51,83,85] Pleural effusion is seen in 10% to 20% of cases.[51,85] Occasionally, the only finding on chest radiograph is pneumothorax, with clear lungs.[51]

Patients with MAS are managed supportively to maintain oxygenation. Mechanical ventilation is optimized to reduce risk of pneumothorax and pneumomediastinum through use of low positive airway pressures and high-frequency oscillatory ventilation in select cases. Exogenous surfactant may be given via endotracheal tube to replace surfactant that has been chemically inactivated by meconium.[83,86] Extracorporeal membrane oxygenation may be required in severe cases to maintain oxygenation. Because patients with MAS are at higher risk for superimposed bacterial infection and their imaging findings are similar to neonatal pneumonia, patients with MAS are usually treated with antibiotics.[51]

Infection

Pulmonary infection and sepsis can be acquired via hematogenous transplacental spread in utero, during labor and delivery, or in the period soon after birth. Possible causes of neonatal pneumonia and sepsis include group A and B streptococcus, *Escherichia coli*, listeria, herpes simplex virus, and cytomegalovirus, among others. Signs and symptoms typically include respiratory distress and temperature instability.[87] Fever is not typical. Risk factors for neonatal pneumonia include maternal infection and prolonged rupture of membranes.

The imaging findings in neonatal pneumonia are variable. In a series by Haney and colleagues,[87]

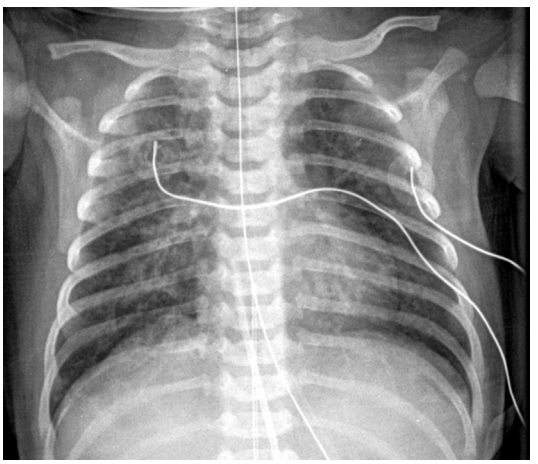

Fig. 11. A 1-day-old girl with meconium aspiration syndrome (MAS). Frontal chest radiograph demonstrates asymmetric bilateral irregular pulmonary opacities.

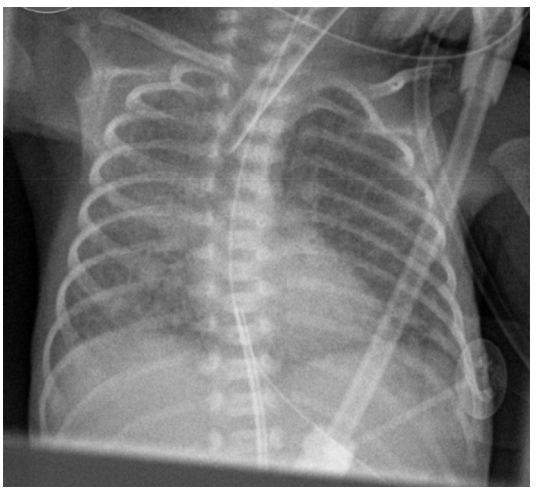

Fig. 12. A 7-day-old girl with group B streptococcus sepsis. Frontal chest radiograph shows bilateral diffuse hazy pulmonary opacities.

the most common pattern was bilateral alveolar opacities seen in 77% (**Fig. 12**). Findings were identical to RDS in 13% and identical to TTN in 17%.[87] Chest radiographs can be normal in up to 10%.[87] Because of the crossover in imaging findings with other entities, neonatal pneumonia may be difficult to differentiate from other causes of neonatal respiratory distress based on imaging findings alone. Blood or sputum culture are helpful when positive, though are often falsely negative. Therefore, affected patients are often treated presumptively with antibiotics.

SUMMARY

Respiratory distress has a variety of causes in the newborn. Conditions such as surfactant deficiency disorder and chronic lung disease of prematurity have been described since the beginning of pediatric radiology but advances in treatment have changed the patient population with these conditions and altered the imaging findings. A greater understanding of congenital lung malformations has changed the way clinicians approach imaging CPAM, pulmonary sequestration, and CLO. Newly characterized genetic causes of neonatal respiratory distress, including the congenital surfactant dysfunction disorders, have advanced appreciation of rare, previously unexplained cases of neonatal lung disease. An up-to-date knowledge of the imaging findings in the full range of neonatal lung diseases is essential for accurate diagnosis and optimal management.

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