Pediatric Imaging • Review

Childhood Interstitial (Diffuse) Lung Disease: Pattern Recognition Approach to Diagnosis in Infants

OBJECTIVE. The purpose of this article is to discuss imaging techniques and a pattern-based approach for diagnosing childhood interstitial (diffuse) lung diseases in infants.

CONCLUSION. Childhood interstitial (diffuse) lung disease in infants consists of a heterogeneous group of disorders previously classified with clinical, radiologic, and pathologic features. By use of an imaging-guided algorithm, the assessment of lung volumes and the presence of ground-glass opacities or cysts can assist the radiologist in making an accurate and timely diagnosis.

Childhood interstitial (diffuse) lung disease (chILD) consists of a rare and heterogeneous group of lung conditions with underlying alteration of alveolar and airway architecture [1, 2]. The reported frequency ranges from 0.13 cases/100,000 children younger than 17 years [3, 4] to 16.2 cases/100,000 children younger than 15 years [3, 5]. Given the complexity and rarity of the diagnosis, the exact frequency of each subcategory has been difficult to estimate. However, the largest reported studies of chILD found that infants and children are disproportionately affected, with estimates of 31–68% of total involvement during infancy or before the age of 2 years [2, 6–8]. Although they are rare, these disorders are associated with substantial morbidity and mortality, with reported mortality rates up to 100% in neonates with mutations in the gene for surfactant protein B [3, 9]. More commonly than in the adult population, interstitial lung disease in children (and especially infants) is thought to arise as the result of an underlying developmental or genetic disorder, and a comprehensive search for a correct diagnosis can expedite appropriate treatment [8, 10].

The most widely accepted classification of chILD was developed and initially published in 2007, through the collaborative efforts of clinicians, pathologists, and radiologists in the Children’s Interstitial Lung Disease Research Cooperative [8, 10–12]. This classification was based on a retrospective review of infants from 11 pediatric institutions in North America with 186 lung biopsies performed between 1999 and 2004 [8, 10–12]. In 2013, this classification system was incorporated into the latest official American Thoracic Society clinical practice guidelines on the classification, evaluation, and management of chILD in infancy [13].

In brief, the American Thoracic Society clinical guidelines for diagnosis of chILD in patients younger than 2 years require the exclusion of some types of diffuse lung disease, including cystic fibrosis, congenital heart disease, bronchopulmonary dysplasia, pulmonary infection, aspiration, and primary ciliary dyskinesia [13]. Once these diagnoses have been excluded, if the infant meets at least three of the following criteria—respiratory symptoms (e.g., cough or difficulty breathing), respiratory signs (e.g., tachypnea, clubbing, or failure to thrive), hypoxemia, or diffuse abnormalities on chest radiograph or CT—then the infant can be given a diagnosis of chILD syndrome [13]. Once a diagnosis of chILD syndrome is established, further noninvasive diagnostic testing, including genetic screening, echocardiography, and high-resolution CT (HRCT), are recommended. If the diagnosis is not apparent at completion of less invasive testing and the patient has persistent symptoms (at least 2 months) and progressively worsening or life-threatening disease, a surgical biopsy is recommended to make a more specific multidisciplinary diagnosis [2, 13].

The chILD classification divides pediatric interstitial (diffuse) lung disease into those.
more common in infancy, those not specific to infancy, and a third group of unclassifiable pathologic entities. Disorders more common in infancy are further subdivided into four main categories: diffuse developmental disorders, alveolar growth abnormalities, surfactant dysfunction disorders and related abnormalities, and specific conditions of unknown or poorly understood cause [8, 13]. Each of these categories is further subdivided into multiple pathologic entities as shown in Table 1 [1, 3, 8, 13].

In this review, imaging techniques and a pattern-based approach for chILD in infants are discussed to assist the radiologist in efficient and accurate diagnosis of various chILD in the infant population.

**Imaging Techniques**

**Radiography**

In infants with suspected chILD, chest radiography is typically the preferred initial imaging modality. Although it is less specific and accurate for the diagnosis of chILD compared to CT, chest radiography remains a fast, inexpensive, readily available, and reproducible tool with low radiation for initial screening and follow-up of previously characterized disease [14, 15]. A challenge with chest radiographs is that, although most infants with chILD do show abnormalities, most commonly hyperinflation, some radiographs may appear normal in the setting of early or mild forms of chILD [15, 16]. Thus, further characterization with CT is usually necessary.

**CT**

CT has become the standard imaging modality for assessment of infants with suspected chILD, because it can confirm its presence, better characterize its extent and distribution, and visualize specific features unique to some diseases [14–16]. In addition, CT allows the radiologist to suggest an optimal biopsy site and can be used for anatomic planning before surgery [14–16]. In recent years, technologic advances with MDCT have allowed volumetric scanning of the entire chest in seconds, along with the ability to retrospectively create high-resolution multiplanar thin-section reconstructions to further minimize respiratory motion and improve evaluation [3, 15]. Because infants are unable to cooperate with respiratory instructions, sedation and intubation with respiratory control may be needed to obtain optimal quality inspiratory and expiratory CT for evaluation of underlying interstitial lung disease. After sedation and intubation, ventilator settings and techniques can be adjusted to best time the inspiration or expiration accordingly [15–18].

**MRI**

MRI offers an imaging modality lacking ionizing radiation. However, it remains a challenge to use in the imaging of chILD as a result of the inevitable respiratory motion artifact, because it must be obtained over a period of time with the patient freely breathing, and has limited spatial resolution compared to CT. However, its utility has recently been evaluated in comparison with HRCT for the evaluation of chILD. Sodhi and colleagues [19] found that 3-T MRI detected abnormalities such as consolidation, parenchymal bands, and fissural thickening, whereas MRI remained limited in the evaluation of septal thickening, groundglass opacities, nodules, and cysts, which are often diagnostic features for differentiating the causes of chILD [19]; thus, MRI remains limited in its clinical application.

**Diffuse Developmental Disorders**

Diffuse developmental disorders consist of a group of rare and variably well understood primary disorders of lung development, originating in utero during the earliest stages of lung development. These include congenital acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of pulmonary veins [8, 13]. Congenital acinar dysplasia was recently discovered to originate from a mutation in the T-box transcription factor gene TBX4 [20]; it is characterized histologically by a virtually complete absence of alveolar development. Congenital alveolar dysplasia is a poorly understood disorder in which the lungs of a full-term infant resemble those of a premature infant with bronchopulmonary dysplasia, showing incomplete alveolarization and thickened alveolar septa [21]. Infants with alveolar capillary dysplasia with misalignment of pulmonary veins show both abnormal alveolar and vascular changes, with maldevelopment of the secondary pulmonary lobules, deficient alveolar capillar-

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**TABLE 1: Classification of Childhood Interstitial Lung Disease in Infants**

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
</tr>
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<tbody>
<tr>
<td>Diffuse developmental disorders</td>
<td>Acinar dysplasia</td>
</tr>
<tr>
<td></td>
<td>Congenital acinar dysplasia</td>
</tr>
<tr>
<td></td>
<td>Congenital alveolar dysplasia</td>
</tr>
<tr>
<td></td>
<td>Alveolar capillary dysplasia with misalignment of pulmonary veins</td>
</tr>
<tr>
<td>Alveolar growth abnormalities</td>
<td>Prenatal conditions—pulmonary hypoplasia</td>
</tr>
<tr>
<td></td>
<td>Postnatal conditions—chronic neonatal lung disease</td>
</tr>
<tr>
<td></td>
<td>Associated chromosomal abnormalities (such as trisomy 21)</td>
</tr>
<tr>
<td></td>
<td>Associated congenital heart disease in chromosomally normal infants</td>
</tr>
<tr>
<td>Surfactant dysfunction disorders</td>
<td>SFTPB mutation</td>
</tr>
<tr>
<td></td>
<td>SFTPC mutation</td>
</tr>
<tr>
<td></td>
<td>ABCA3 mutation</td>
</tr>
<tr>
<td></td>
<td>NXX2-1 mutation</td>
</tr>
<tr>
<td></td>
<td>Others with histologic findings consistent with surfactant dysfunction disorder without a recognized genetic mutation</td>
</tr>
<tr>
<td>Specific conditions of unknown or poorly understood cause</td>
<td>Neuroendocrine cell hyperplasia of infancy</td>
</tr>
<tr>
<td></td>
<td>Pulmonary interstitial glycogenosis</td>
</tr>
</tbody>
</table>
ies, malpositioning of the pulmonary veins adjacent to arteries and small airways, and medial hypertrophy of the small pulmonary arterioles [1, 3, 15]. Most infants with alveolar capillary dysplasia with misalignment of pulmonary veins have associated extrapulmonary anomalies of the cardiovascular (e.g., aortic coarctation and septal defect), gastrointestinal, or genitourinary systems [15, 16, 22], and up to 40% have inactivating mutations in the gene FOX1 [23, 24]. Some of the associated anomalies, such as an absent gallbladder, are quite specific for alveolar capillary dysplasia with misalignment of pulmonary veins in this clinical setting and can help a radiologist suggest the diagnosis.

Infants with diffuse development disorders typically present at term with worsening respiratory distress and cyanosis immediately or shortly after birth, pulmonary hypertension, and up to 100% fatality within 1 month if no lung transplant is performed [22, 23, 25]. Because these diseases are extremely rare and typically present with a severe clinical presentation in early infancy, the imaging investigations typically only consist of chest radiographs. On radiographs, there is typically moderate-to-severe airspace opacification, with associated pneumothorax or pneumomediastinum in 50% of patients, likely secondary to barotrauma; however, the imaging findings can be quite nonspecific and can even remain normal [25–27].

Pattern-Based Algorithm of Childhood Interstitial (Diffuse) Lung Disease in Infants

The remaining three categories of chILD in infants consist of a variety of conditions that have been previously divided as summarized in Table 1. The alveolar growth abnormalities involve presumably normally programmed alveolar growth (unlike diffuse developmental disorders) and are thought to be the result of an alteration, either during the prenatal or postnatal period, by a superimposed condition or event, resulting in defective alveolarization with lobular simplification [8, 13] (Table 1). The surfactant dysfunction disorders consist of different genetic mutations resulting in inborn errors of surfactant metabolism [8, 13] (Table 1). The final category of chILD presenting in infants is specific conditions of unknown or poorly understood cause, which consists of two interstitial lung disorders unique to infants: neuroendocrine cell hyperplasia of infancy (NEHI) and pulmonary interstitial glycogenesis (PIG) [8, 13] (Table 1).

Rather than sorting these remaining three categories by clinical presentation or histologic appearance, it is much easier and more practical for a radiologist to classify each disease type according to the characteristic imaging appearances. We offer a pattern-based approach using CT in infants with suspected chILD with three practical steps: first, lung volumes; second, ground-glass opacities; and third, cysts (Table 2). The first step is to assess the lung volumes, to determine whether they are high (with evidence of hyperinflation or air-trapping), normal, low, or variable. When assessing for lung volumes, it is important to be aware that patients can show hyperinflation attributable to intubation, which can confound true lung volume assessment. Next, the radiologist needs to determine whether ground-glass opacification is present. Finally, the last step is to assess for the presence of cysts. After these three steps, and in conjunction with the patient’s clinical history, the radiologist should be able to narrow the differential diagnosis and help make a diagnosis appropriately (Table 2).

High Lung Volume and Hyperinflation Disorders at CT

Filamin A Mutation

Lung growth disorders in full-term infants can be associated with genetic mutations. For example, the filamin A gene (FLNA) is an X-linked gene encoding the actin-binding protein filamin A, which is involved in cell signaling and maintenance of cell shape and motility. Mutations in FLNA have been associated with disordered alveolar growth [13, 28–32]. FLNA mutations are also associated with disorders of neuronal migration (e.g., gray matter heterotopia), vascular function, connective tissue integrity, and skeletal development [28, 29]. Affected patients are typically female because of the X-linked early lethality in male patients.

The lung growth abnormalities associated with FLNA mutation appear as multilobar hyperinflation and hyperlucency at CT, predominantly affecting the upper and middle lobes, with coarse septal thickening, varying lower lobe atelectasis, and pruning of peripheral pulmonary vasculature [3, 15, 28] (Figs. 1A and 1B). Using our CT pattern approach, these patients would fall under the category of hyperinflation or high lung volumes, without the presence of ground-glass opacity or cysts (Table 2). In the neonate, these features can resemble congenital lobar emphysema, which can make the diagnosis challenging and ultimately requires a multidisciplinary approach. Microscopic examination in these patients shows defective alveolarization with lobular simplification, deficient alveolar septation, and airspace enlargement [12] (Fig. 1C).

Neuroendocrine Cell Hyperplasia of Infancy

NEHI, originally reported as persistent tachypnea of infancy, usually presents in full-term infants before the age of 2 years, with a prolonged course of tachypnea, hypoxia, and retractions that do not improve with corticosteroids [8, 15, 16, 33]. At CT, infants with NEHI characteristically show high lung volumes and hyperinflation, with geographic ground-glass opacities, most marked in the right middle lobe and lingula [8, 33] (Fig. 2). Using our CT pattern approach, these patients fall under the category of hyperinflation or high lung volumes, with ground-glass opacities, but without the presence of cysts (Table 2). Brody and colleagues [33] previously investigated the utility of HRCT in 23 patients with biopsy-proven NEHI and reported that HRCT was 100% specific for the diagnosis of NEHI in infants, thereby potentially obviating the need for lung biopsy in patients presenting with classic clinical symptoms and characteristic imaging findings. However, with a sensitivity of only 78%, HRCT is unable to completely exclude NEHI as a potential diagnosis [33]. Microscopically, NEHI reveals an abnormally increased number of bombesin-immunopositive airway neuroendocrine cells, in the absence of other significant changes [12].

Normal Lung Volume Disorders at CT

Trisomy 21

Trisomy 21 (Down syndrome) is an example of a lung growth disorder associated with genetic mutation presenting in full-term infants. The first reported association between trisomy 21 and subpleural cysts, which represent small cystic dilatations along the subpleural surface of the lungs, was in 1986 in two infants [34, 35]. Since then, the reported frequency of subpleural cysts in patients with trisomy 21 has ranged from 20% to 36% [34–36].

Using the CT pattern–based algorithm, these patients fall under the normal (or hypoplastic) lung volume category, without ground-glass opacity, but with cysts present (Table 2). The cysts are usually 1–2 mm in size, and subpleural along the lung periphery, pulmonary fissures, and bronchovascular bundles, and involve the anteromedial portion of the lungs [34–36] (Figs. 3A and...
### CT of Childhood Interstitial (Diffuse) Lung Disease

#### TABLE 2: CT Pattern–Based Approach for Assessment of an Infant With Childhood Interstitial (Diffuse) Lung Disease

<table>
<thead>
<tr>
<th>Step 1: Lung Volumes</th>
<th>Step 2: Ground-Glass Opacities</th>
<th>Step 3: Cysts</th>
<th>Additional Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Absent</td>
<td>Absent</td>
<td>Ground-glass in right middle lobe and lingula</td>
</tr>
<tr>
<td>Filamin A mutation</td>
<td>Absent</td>
<td>Absent</td>
<td>Cysts are subpleural in location along the lung periphery, pulmonary fissures, and bronchovascular bundles, and involve the anteromedial portion of the lungs</td>
</tr>
<tr>
<td>Neuroendocrine cell hyperplasia of infancy</td>
<td>Present</td>
<td>Absent</td>
<td>Associated neurologic and thyroid abnormalities</td>
</tr>
<tr>
<td>Normal</td>
<td>Absent</td>
<td>Present</td>
<td>Septal thickening</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>Absent</td>
<td>Present</td>
<td>Can see associated causes in secondary pulmonary hyperplasia</td>
</tr>
<tr>
<td>NKX2-1 mutation</td>
<td>Present</td>
<td>Can be present or absent</td>
<td></td>
</tr>
<tr>
<td>Pulmonary interstitial glycogenosis</td>
<td>Present</td>
<td>Can be present or absent</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Surfactant deficiency</td>
<td>Present</td>
<td>Can be present or absent</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
</tbody>
</table>

3B). Although the clinical relevance of these subpleural cysts is still not understood, they have been found in other chromosomal abnormalities, such as trisomy 10 [3], and it is important not to confuse this with other diseases. Microscopically, lungs from patients with trisomy 21 show enlarged subpleural airspaces resembling small cysts [34] (Fig. 3C). They may also show hypoplasia and, sometimes, changes attributable to accompanying congenital heart disease.

#### Thyroid Transcription Factor–1 Deficiency

Thyroid transcription factor (TTF)–1, the protein product of the NKX2-1 gene, is thought to be important for the structural development of the lung and expression of surfactant proteins B and C and the adenosine triphosphate–binding cassette transporter 3 [37, 38]. TTF-1 is also thought to be essential for the normal development of the thyroid and brain. Mutations causing haploinsufficiency of NKX2-1 can result in neurologic abnormalities (e.g., chorea), hypothyroidism, or severe respiratory distress in infants, known together as brain-thyroid-lung syndrome [37, 38]. The clinical presentation of TTF-1–deficient lung disease is highly variable and can present in infants as mild-to-severe respiratory distress, with some dying from respiratory failure [37], whereas in others, it may manifest as only chronic interstitial lung disease later in life [38].

At CT as per the pattern algorithm, patients with NKX2-1 mutation will typically have normal lung volumes, diffuse ground-glass opacities, and may sometimes have small cysts present (Table 2 and Figs. 4A and 4B). The history of simultaneous neurologic and thyroid abnormalities, although not consistently present, further supports a diagnosis of a TTF-1 deficiency. The microscopic appearance of NKX2-1–associated lung disease has been variable; however, most cases have shown disrupted surfactant homeostasis and evidence of disrupted lung growth, with alveolar enlargement and septal fibrosis, type 2 pneumocyte hypertrophy, and variable presence of airspace proteinosis and macrophages [37, 38] (Fig. 4C).

#### Pulmonary Intestinal Glycogenosis

PIG is a rare cause of chILD in infants and most recently was categorized as a disorder of unknown cause by the American Thoracic Society [13]. It typically presents as respiratory distress in infants within the first 6 months of life [39]. There are two subtypes of PIG: diffuse and patchy. The patchy form is more common and typically is associated with underlying growth abnormalities, such as pulmonary hypoplasia, chronic lung disease of prematurity, and pulmonary hypertension. The diffuse form is rarer and usually not associated with any underlying growth abnormalities [1, 3, 15].

In the CT pattern–based approach, both subtypes of PIG show normal lung volumes, diffuse ground-glass opacities, and variably present cysts (Table 2 and Fig. 5A). The diffuse form of PIG does not typically show cysts, whereas the patchy form may show multiple small scattered cysts of variable size [15]. Additional imaging findings associated with PIG include interlobular septal thickening and subpleural reticular changes [39] (Fig. 5A). Microscopically, PIG is characterized by expansion of alveolar septa by small round glycogen-laden mesenchymal cells [12, 39] (Fig. 5B).

#### Low Lung Volume Disorders on CT

### Pulmonary Hypoplasia

Pulmonary hypoplasia can be caused by multiple different mechanisms that result in alveolar growth abnormalities. Pulmonary hypoplasia can rarely manifest as primary pulmonary hypoplasia with intrinsic abnormal lung development, but more commonly presents as secondary pulmonary hypoplasia with compromised lung development secondary to intrauterine limitations on the thoracic space [1, 3, 15, 16]. The most common cause of secondary pulmonary hypoplasia in infants is congenital diaphragmatic hernias [3] (Fig. 6A). Additional causes of secondary pulmonary hypoplasia include severe oligohydramnios (as may be seen in renal dysplasia, placental abnormalities, and prolonged rupture of membranes), and thoracic skeletal dysplasia (e.g., thanatophoric dysplasia and Jeune syndrome) [3].

Using the CT pattern algorithm, patients with pulmonary hypoplasia show low lung volumes, without evidence of ground-glass opacities or cysts (Table 2). Additional imaging findings include the presence of emphysematous changes, and in infants with
secondary pulmonary hypoplasia, the associated causes can usually be identified (Fig. 6A). Grossly, hypoplastic lungs typically show low weight and volume (Fig. 6B). Microscopically, there are decreased radial-alveolar count and airspace enlargement [12].

**Surfactant Dysfunction**

Surfactant dysfunction disorders can be caused by mutations in multiple genes, including genes for surfactant protein B (SFTPB), surfactant protein C (SFTPC), and adenosine triphosphate–binding cassette transporter protein A3 (ABCA3) [40]. Mutations in SFTPB, SFTPC, and ABCA3 are thought to represent approximately 25% of all severe refractory diffuse lung disease in infants [13]. SFTPB mutations are autosomal recessive and typically manifest in full-term infants with respiratory distress and failure. These disorders clinically and radiographically resemble respiratory distress syndrome in premature infants but may, of course, occur in the absence of respiratory distress syndrome risk factors [13, 40]. The symptoms are usually progressive and unresponsive to medical treatments, with reported mortality rates up to 100% without lung transplantation [3, 9]. Genetic testing in children with surfactant dysfunction has been used to help better characterize the disease, assess for complications, and perform preoperative assessment. At CT, these patients present with disordered lung aeration, with a combination of alveolar septal fibrosis, atelectasis, and hyperinflated lung, resulting in variable lung volumes [45–47] (Table 2 and Figs. 9A and 9B). Additional CT findings include bronchial wall thickening, coarse reticular pulmonary opacities, and cystic lucencies [45–47]. Areas of decreased attenuation have been previously suggested to correlate with severity of disease [47]; however, no scoring system has been appropriately validated for assessment of patients with bronchopulmonary dysplasia [48].

Given the emergence of extremely premature infants (at 24–26 weeks’ gestation) and modern ventilation strategies, there is now a new bronchopulmonary dysplasia disorder [47]. These patients will have received prenatal corticosteroids and have been ventilated for shorter periods with new ventilator settings, resulting in subtle imaging abnormalities with less-pronounced alveolar septal fibrosis and inflammation [47]. Microscopically, bronchopulmonary dysplasia is characterized by alveolar enlargement, often with increased variation in airspace size and variable chronic airway injury, fibrosis, and chronic pulmonary interstitial emphysema [12] (Fig. 9C).

**Conclusion**

In infants, chILD constitutes a diverse group of lung abnormalities that can be complex and challenging to diagnose. Aside from the infants with diffuse development disorders, who typically are imaged with chest radiographs only, the remainder of the diseases in the chILD spectrum presenting in infants can be approached with a CT algorithm using the stepwise assessment of lung volumes, ground-glass opacities, and cysts. In conjunction with the patient’s demographics and clinical presentation, this algorithm can aid the radiologist in making an accurate and timely diagnosis.

**References**

CT of Childhood Interstitial (Diffuse) Lung Disease


(Figures start on next page)
Fig. 1—Two infants with filamin A mutation. 
A and B, 6-month-old girl. Frontal chest radiograph (A) and coronal CT image (B) show scattered areas of hyperexpansion within right lung, most predominantly within right lower lobe. Corresponding expiratory CT image (not shown) shows air trapping within corresponding right lower lung. Mild coarse septal thickening and pruning of vasculature are seen on right. No pulmonary nodules, ground-glass opacities, or cysts are present. 
C, 5-week-old girl with ventricular septal defect and pulmonary hypertension. Photomicrograph (H and E, ×100) of biopsy specimen shows characteristically enlarged airspaces.

Fig. 2—2-month-old boy with neuroendocrine cell hyperplasia of infancy (NEHI). 
A, Axial CT image shows extensive hyperlucency predominantly in bilateral lower lobes, with nonspecific diffuse ground-glass opacities throughout all lobes, centrally and peripherally. No pulmonary nodules or cysts are present. 
B, Follow-up axial CT image obtained at age 17 months shows hyperinflation, with areas of air trapping in bilateral lower lobes (on global review of images), and diffuse ground-glass opacification throughout lingula and right middle lobe, which is characteristic of NEHI.

Fig. 3—Two children with trisomy 21. 
A and B, 2-year-old girl. Frontal chest radiograph (A) and coronal CT (B) show normal lung volumes and diffuse subpleural cysts (significantly better appreciated on CT) along lung periphery, pulmonary fissures, and bronchovascular bundles, with associated pleural thickening. 
C, 14-month-old girl with trisomy 21 and congenital heart disease. Photomicrograph (H and E, ×100) of biopsy specimen shows maldevelopment, including large subpleural airspaces.
CT of Childhood Interstitial (Diffuse) Lung Disease

Fig. 4—5-month-old boy with NKX2-1 mutation.
A, Axial CT image shows diffuse ground-glass opacification throughout lungs and discrete small 1- to 2-mm cysts. Patient had normal lung volumes.
B, Follow-up axial CT image obtained at age 9 months shows persistent ground-glass opacification with coarsened interstitial changes and subtle cysts in keeping with findings of thyroid transcription factor–1-deficient interstitial lung disease.
C, Autopsy (age 10 months) showed airspaces, some cystically dilated, filled with eosinophilic proteinaceous material and macrophages. On photomicrograph (H and E, ×200) of autopsy specimen, type 2 pneumocyte hyperplasia is prominent.

Fig. 5—39-day-old boy with patchy pulmonary interstitial glycogenosis (PIG).
A, Coronal CT shows normal lung volumes, diffuse ground-glass opacification, interstitial thickening, and multiple small cysts in both lungs, in keeping with patchy PIG.
B, Photomicrograph (H and E, ×600) of biopsy performed at age 2 months shows alveolar septa expanded by small round interstitial cells with vacuolated cytoplasm.

Fig. 6—Two patients with large left congenital diaphragmatic hernia.
A, 15-month-old boy with displaced small and large bowel, most consistent with Bochdalek hernia, with associated low volume and hypoplasia of left lung. No ground-glass opacities or cysts are seen on coronal CT image.
B, 14-month-old girl. Photograph of autopsy specimens shows unilobate left lung with marked hypoplasia.
Fig. 7—4-month-old girl with SFTPC mutation. A and B, Frontal chest radiograph (A) and coronal CT image (B) show low lung volumes and diffuse ground-glass opacification throughout both lungs and peripheral interstitial thickening, but no cysts (better seen on CT), in keeping with surfactant deficiency.

C, Photomicrograph (H and E, ×400) of biopsy specimen obtained at age 4 months shows extensive type 2 pneumocyte hyperplasia and markedly increased numbers of intraalveolar and airway luminal macrophages, constituting desquamative interstitial pneumonialike pattern.

Fig. 8—Female patient with surfactant deficiency due to ABCA3 mutation. A, In addition to low lung volumes appreciated on review of entire study, axial CT image at age 11 weeks shows diffuse bilateral ground-glass opacification throughout lungs, septal thickening, and several small cysts in lung bases, consistent with patient’s history of congenital surfactant deficiency syndrome.

B, Follow-up axial CT image obtained at age 13 months shows expected progression of chronic findings related to ABCA3 mutation, as evidenced by increased interlobular septal thickening, persistent ground-glass opacification, and increased size and number of cysts.

C, Photomicrograph (H and E, ×400) of biopsy specimen obtained at age 7 weeks (left) shows abundant intraalveolar eosinophilic granular material and prominent type 2 pneumocytes. At time of transplantation, explanted lungs were grossly cystic (middle). Microscopically (H and E, ×200), they showed fibrosis and type 2 pneumocyte hyperplasia, without prominent proteinosis (right).
**CT of Childhood Interstitial (Diffuse) Lung Disease**

*Fig. 9—Two patients with chronic lung disease of prematurity.*  
**A** and **B**, 4-month-old girl born prematurely. Chest radiograph (**A**) and axial CT (**B**) show mosaic attenuation of both lungs with areas of hyperinflation in right middle and lower lobes, and chronic collapse of right upper lobe and posterior basal left lower lobe, in keeping with chronic lung disease of prematurity.  
**C**, 14-month-old girl born at 25 weeks' gestation. Photomicrograph (H and E, ×100) of autopsy specimen shows variation in alveolar size with many enlarged airspaces. Pulmonary hypertension is also evident.

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