Interstitial Lung Disease in Children Younger Than 2 Years

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Children's interstitial lung disease (chILD) represents a highly heterogeneous group of rare disorders associated with substantial morbidity and mortality. Although our understanding of chILD remains limited, important advances have recently been made, the most important being the appreciation that disorders that present in early life are distinct from those occurring in older children and adults, albeit with some overlap. chILD manifests with diffuse pulmonary infiltrates and nonspecific respiratory signs and symptoms, making exclusion of common conditions presenting in a similar fashion an essential preliminary step. Subsequently, a systematic approach to diagnosis includes a careful history and physical examination, computed tomography of the chest, and some or all of bronchoscopy with bronchoalveolar lavage, genetic testing, and if diagnostic uncertainty persists, lung biopsy. This review focuses on chILD presenting in infants younger than 2 years of age and discusses recent advances in the classification, diagnostic approach, and management of chILD in this age range. We describe novel genetic entities, along with initiatives that aim at collecting clinical data and biologic samples from carefully characterized patients in a prospective and standardized fashion. Early referral to expert centers and timely diagnosis may have important implications for patient management and prognosis, but effective therapies are often lacking. Following massive efforts, international collaborations among the key stakeholders are finally starting to be in place. These have allowed the setting up and conducting of the first randomized controlled trial of therapeutic interventions in patients with chILD.
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triphosphate binding cassette family member 3 (ABCA3) mutations and have a poor prognosis, particularly if they present in the neonatal period.1, 7–9 Similarly, idiopathic pulmonary fibrosis, the most common and severe of the idiopathic interstitial pneumonias in adults, 10, 11 is not found in children. On the other hand, there are forms of ILD that are unique to infants and children younger than 2 years of age, 7 hence the use of adult terminology and classification does not adequately address pediatric entities. Therefore, new appropriate codes have recently been added for several chILD disorders in the International Classification of Diseases, Ninth Revision. 12 Moreover, the multi-institutional ChILD Research Cooperative has recently developed a classification system specifically for young children. 7,13 Despite some conceptual and practical limitations (eg, it focuses exclusively on young children who underwent diagnostic lung biopsy, thus providing little guidance in cases without a confirmatory lung biopsy, and does not address properly those cases showing features of >1 entity), this classification system groups disorders with similar clinical and/or pathologic features, and provides consensus terminology, diagnostic criteria, and a useful framework for approaching chILD, particularly entities unique to young children (Table 1). The chILD scheme is also applicable to patients in the 2- to 18-year-old group, although additional entities, such as lymphoproliferative disorders, hypersensitivity pneumonitis, or pulmonary hemorrhage syndromes, need to be included.14, 15

TABLE 1 Classification of ILD in Children Aged 0 to 2 Years

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples of Specific Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse developmental disorders</td>
<td>Acinar dysplasia</td>
</tr>
<tr>
<td></td>
<td>Congenital alveolar dysplasia</td>
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<tr>
<td></td>
<td>Alveolar capillary dysplasia with misalignment of pulmonary veins</td>
</tr>
<tr>
<td>Alveolar growth abnormalities</td>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td></td>
<td>Chronic neonatal lung disease</td>
</tr>
<tr>
<td></td>
<td>Associated with chromosomal disorders (eg, trisomy 21)</td>
</tr>
<tr>
<td></td>
<td>Associated with congenital heart disease</td>
</tr>
<tr>
<td>Specific conditions of undefined etiology</td>
<td>NEHI</td>
</tr>
<tr>
<td></td>
<td>PIG</td>
</tr>
<tr>
<td>Surfactant dysfunction disorders</td>
<td>Mutations in SP-B, SP-C, ABCA3, NKX2.1/TTF1; histology consistent with surfactant dysfunction disorders but without documented genetic cause</td>
</tr>
<tr>
<td>Disorders related to systemic disorders</td>
<td>Collagen vascular disease (systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis)</td>
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<tr>
<td></td>
<td>Storage diseases</td>
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<tr>
<td></td>
<td>Sarcoidosis</td>
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<tr>
<td></td>
<td>Langerhans cell histiocytosis</td>
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<tr>
<td></td>
<td>Malignant infiltrates</td>
</tr>
<tr>
<td>Disorders of the normal host-presumed immune intact</td>
<td>Infectious/postinfectious processes</td>
</tr>
<tr>
<td></td>
<td>Environmental agents (hypersensitivity pneumonitis, toxic inhalation)</td>
</tr>
<tr>
<td></td>
<td>Aspiration syndromes</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic pneumonia</td>
</tr>
<tr>
<td></td>
<td>Opportunistic infections</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic</td>
</tr>
<tr>
<td></td>
<td>Related to transplantation and rejection</td>
</tr>
<tr>
<td></td>
<td>Diffuse alveolar damage (unknown etiology)</td>
</tr>
<tr>
<td>Disorders of the immunocompromised host</td>
<td>Arterial hypertensive vasculopathy</td>
</tr>
<tr>
<td></td>
<td>Congestive changes related to cardiac dysfunction</td>
</tr>
<tr>
<td></td>
<td>Veno-occlusive disease</td>
</tr>
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<td></td>
<td>Lymphatic disorders</td>
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Signs and symptoms of chILD are nonspecific, and the diagnosis of chILD may not be considered initially. In fact, the rarity of these conditions hampers the acquisition of adequate knowledge, which almost invariably results in delayed diagnosis. Compared with adult disease,16 chILD occurs far less frequently, with a prevalence of idiopathic ILD among immunocompetent children aged 0 to 16 years being estimated at 3.6 cases per million, 17 although this is likely to be an underestimate.18

Our understanding of chILD remains incomplete. However, important advances in disease mechanisms, diagnostic approach, and management have been recently made. In this review, we summarize and discuss these with special attention to conditions that are unique to infants.

**DIAGNOSTIC APPROACH**

The primary diagnostic step is to identify children who require further investigation for chILD. To this end,
more common causes of diffuse lung disease (eg, cystic fibrosis, immunodeficiency, or congenital heart disease) sharing a common presentation with chronic respiratory symptoms (eg, tachypnea, cough, and hypoxemia) and diffuse radiographic infiltrates should be excluded. Once major non-chILD disorders have been excluded, the term “chILD syndrome” is used to refer to children who meet at least 3 of the following 4 criteria: (1) respiratory symptoms (cough, rapid breathing, or exercise intolerance), (2) signs (resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) appropriate diffuse abnormalities on chest imaging.1

A systematic approach to patients with chILD is crucial in establishing the diagnosis (Fig 1). Clinical context can provide valuable differential diagnostic clues. For instance, neonates presenting acutely with respiratory distress and hypoxemia are more likely to have developmental lung disorders, whereas a family history of siblings with similar lung conditions may suggest a genetic or familial lung disease, such as inborn errors of surfactant metabolism. However, further diagnostic testing is always required; the pace of testing depends on the clinical situation: in an ill child, a lung biopsy may be performed urgently, but if the child is stable, it may be appropriate to await the results of genetic testing. It is important to plan investigations so as to minimize the number of general anesthetics for the child; so for example, unless it is likely that bronchoscopy will be diagnostic, and obviate the need for a lung biopsy, the procedure should probably be better combined with lung biopsy under the same anesthetic.

**Lung Function Tests**

Most experience is in older children, whereas data in infants are limited. The biggest data set is in neuroendocrine cell hyperplasia of infancy (NEHI), which is characterized by airflow obstruction and hyperinflation.19 At school age, lung function tests typically show a restrictive ventilatory defect with reduced total lung capacity, forced vital capacity, and forced expiratory volume in 1 second with a normal or elevated forced expiratory volume in 1 second/forced vital capacity ratio.20 Elevated residual volume and residual volume/total lung capacity ratio suggest air trapping.

**Imaging**

Chest computed tomography (CT), compared with plain chest radiographs, provides more precise information about extent and distribution of parenchymal abnormalities. It is used to confirm that chILD is indeed the underlying problem and to guide the site of a biopsy; in addition, it can sometimes be used to make specific diagnoses. Common radiographic patterns include ground glass opacity (GGO), geographic hyperlucency, consolidation, septal thickening, lung cysts, and nodules.21, 22 In some cases, CT findings are highly suggestive or even characteristic, thus obviating the need for invasive procedures.23 CT may also provide prognostic information (eg, NEHI has a favorable prognosis, whereas growth abnormalities and surfactant mutations carry substantial mortality).

**Bronchoalveolar Lavage**

The most common indication for pediatric bronchoalveolar lavage (BAL) is detection of infection both in immunocompromised and immunocompetent hosts.24 Occasionally, this procedure may also provide useful information in children with suspected chILD.25 For example, in the appropriate clinical setting, BAL may help to identify diffuse alveolar hemorrhage or aspiration by the presence of hemosiderin-laden or lipid-laden macrophages, respectively.6 Other patterns of BAL cellularity (eg, lymphocytosis or eosinophilia) are less indicative of specific conditions.

**Genetic Testing**

If positive, genetic testing may allow the diagnosis of known single-gene disorders. However, at present, a genetic cause has been identified for only a minority of chILD (eg,
mutations in surfactant protein B [SP-B] and SP-C genes, the gene encoding the surfactant processing protein ABCA3 and thyroid-transcription-factor 1 [TTF-1]. In addition, as the results of genetic tests may not be available for several weeks, a lung biopsy may still be necessary to make a secure diagnosis in severe or progressive cases.

**Lung Biopsy**

Lung biopsy remains the gold standard for chILD when less invasive tests have failed to secure a diagnosis. Open lung biopsy and video-assisted thoracotomy are the most reliable ways to obtain adequate tissue for diagnosis. Whatever technique is used, adequate processing of lung biopsies is essential to ensure optimal diagnostic yield. Similarly important is that such biopsies are interpreted by a pathologist with expertise in pediatric lung disease.

**TREATMENT OPTIONS AND OUTCOME**

Most patients with chILD require treatment of some sort. Management is generally supportive, including supplemental oxygen for chronic hypoxemia, adequate nutrition, proper immunization, avoidance of environmental pollutants, and treatment of intercurrent infections. Further treatments can be divided into specific therapies (for example, etanercept for sarcoidosis, inhaled granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis due to circulating anti-granulocyte-macrophage colony-stimulating factor autoantibodies) and nonspecific pharmacological treatment, which is based on small case series and low-quality evidence with treatment decisions being made on a case-by-case basis.

There are currently no randomized controlled trials of any treatment of chILD. Systemic steroids and hydroxychloroquine remain the treatment of choice for most patients with chILD, based on the assumption that suppressing inflammation may prevent evolution to fibrosis. European treatment protocols have recently been published.

**Systemic Steroids**

Steroids can be administered orally or intravenously depending on disease severity. Oral prednisolone is generally administered at a dosage of 1 to 2 mg/kg per day, whereas methylprednisolone is usually given at a dosage of 10 to 30 mg/kg per day for 3 consecutive days, followed by single monthly pulses for a minimum of 3 cycles. Dosage and duration of treatment depend on disease severity and clinical response, and should be weighed against the morbidity of steroid treatment. Broadly speaking, conditions that tend to respond to steroid therapy include DIP and nonspecific interstitial pneumonia (NSIP) (when no underlying diagnosis has been made) and idiopathic pulmonary hemosiderosis.

**Hydroxychloroquine**

Hydroxychloroquine is an antimalarial agent with a number of immunologic effects that may be beneficial in chILD. Recently, Braun and colleagues performed an extensive literature search and identified 85 case reports or small case series of children with ILD treated with either chloroquine or hydroxychloroquine published between 1984 and 2013. Clinical response varied widely, although, overall, a positive treatment effect was more likely to be seen in cases of lymphocytic interstitial pneumonia, idiopathic pulmonary hemosiderosis, or cellular interstitial pneumonia. An ophthalmologic examination at the start of treatment is recommended due to the known risk of ocular toxicity.

A number of other treatments have been used in various chILDs, including azithromycin, methotrexate, azathioprine, cyclosporine, and rituximab. The evidence base for efficacy is, however, even less than for corticosteroids and hydroxychloroquine.

Lung transplantation is an option for children with end-stage disease, with long-term outcomes comparable to lung transplant recipients with cystic fibrosis and pulmonary vascular disease. The prognosis for children with ILD is highly variable, with pulmonary hypertension (PH) being the single greatest clinical predictor of mortality. Infants with NEHI generally have a favorable prognosis, although they may remain symptomatic and require long-term oxygen. At the other end of the spectrum, children with growth failure, PH, and severe fibrosis have a poor prognosis. Indeed, in the ChILD Research Cooperative study of children <2 years of age, mortality was highest (100%) in developmental disorders and ABCA3 mutations, and lowest in NEHI, pulmonary interstitial glycogenosis (PIG), and SP-C mutations, although fatal cases of PIG and SP-C mutations also have been described.

**DISORDERS MORE PREVALENT IN INFANTS AGE 0 TO 2 YEARS**

The initial classification, although an excellent first attempt, can be criticized. It is based only on biopsies, thus excluding conditions not requiring a tissue diagnosis. Newer work has highlighted other disorders not covered by the original classification, and it includes conditions (obliterative bronchiolitis and bronchopulmonary dysplasia, for example) that many would not consider as chILD; and the fact that the same condition can cause >1 type of abnormality was not
really appreciated. Clearly, chILD classification is an ongoing work in progress; nonetheless, the initial article has given us a very useful framework.

**Diffuse Developmental Disorders**

Diffuse developmental disorders, which include acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia associated with misalignment of pulmonary veins (ACDMPV), are a group of poorly understood primary disorders that occur during the earliest stages of lung development. Accordingly, biopsies from these patients display arrest in lobular development, reduced alveolar capillary density, and hypertensive arterial remodeling. ACDMPV is also characterized by markedly dilated bronchial veins due to prominent right-to-left intrapulmonary vascular shunt (eg, pulmonary artery–bronchial artery anastomoses, which bypass the alveolar capillary bed; the pulmonary veins themselves are not in fact misplaced, what is seen are the hypertrophied bronchial veins). In addition, ACDMPV is often accompanied by cardiovascular, gastrointestinal, or genitourinary system anomalies. Without lung transplantation, diffuse developmental disorders are almost universally fatal due to rapidly progressive respiratory failure and PH, which develop within days of birth. However, longer survivors have also been reported. Recently, inactivating deletions and point mutations within the FOX transcription factor gene cluster on 16q24.1 have been identified in cases of ACDMPV with distinct congenital malformations, suggesting the utility of genetic testing in neonates presenting with respiratory failure and PH, especially when gastrointestinal, cardiovascular, or genitourinary abnormalities coexist.

**Alveolar Growth Abnormalities**

Alveolar growth abnormalities are the most common cause of chILD in infants. Unlike diffuse developmental disorders, in infants with alveolar growth abnormalities, abnormal pulmonary development is secondary and may be seen in a variety of settings, including pulmonary hypoplasia associated with prenatal conditions (eg, oligohydramnios, abdominal wall defects, or neuromuscular disease), prematurity (eg, chronic neonatal lung disease), chromosomal abnormalities (eg, trisomy 21; Fig 2 A–D), congenital heart diseases, and, in term infants, postnatal lung injury. Affected children present with varying degrees of respiratory distress and hypoxemia. Although rarely diagnostic, characteristic imaging findings are seen in specific conditions. For instance, chronic neonatal lung disease of prematurity (which many would doubt is a true chILD) is characterized by hyperlucent areas corresponding to alveolar enlargement and reduced distal vascularization, and linear opacities, which reflect fibrotic changes. Histologically, disorders in this category are characterized by variable lobular simplification with alveolar enlargement and deficient septation. Mortality rate, at 34%, is substantial with prematurity and severity of the growth abnormality representing the strongest predictors of poor outcome.

**NEHI**

NEHI is a disorder of unknown etiology that typically manifests in the first year of life with chronic tachypnea, retractions, hypoxemia, and crackles on chest auscultation. Chest radiograph almost invariably shows hyperinflation, whereas high-resolution CT (HRCT) imaging typically shows air trapping in a mosaic attenuation pattern affecting at least 4 lobes; geographic GGO is most conspicuous in the right middle lobe and lingula. When interpreted by experienced pediatric
thoracic radiologists, the sensitivity and specificity of HRCT for NEHI is 78% to 83% and 100%, respectively (Fig 3 A–C), thus obviating the need for a confirmatory lung biopsy.  

 Diagnosis on biopsy is based on essentially normal histology on standard staining, with an increase in Bombesin-positive cells on specific staining. However, although hyperplasia of neuroendocrine cells within bronchioles (as demonstrated by immunohistochemistry), the only consistent pathologic finding, may be seen in a variety of disorders, including bronchopulmonary dysplasia, bronchiolitis, and PH.  

 Neuroendocrine cell prominence with otherwise normal histopathology is a distinguishing feature of NEHI.  

 These other conditions all have specific features, which would preclude diagnostic confusion with NEHI. Reported familial cases suggest that NEHI may have a genetic basis, although, to date, no mutation has been consistently identified. Long-term outcome is generally favorable with most patients gradually improving over time, although persistent airway obstruction mimicking severe asthma and relapse with respiratory infection also have been reported.  

 PIG  

 PIG is a rare disorder that manifests within the first few weeks of life with respiratory distress and diffuse interstitial infiltrates.  

 Histologically, PIG is characterized by interstitial thickening by immature vimentin-positive mesenchymal cells containing abundant monoparticulate glycogen, without inflammation or fibrosis (Fig 4 A and B). Imaging findings vary considerably based on whether PIG occurs as an isolated condition (diffuse PIG), or associated with an underlying lung growth disorder (patchy PIG). Typical HRCT features include GGO, reticular changes, and hyperinflated areas in a predominantly subpleural distribution. In patchy PIG, these abnormalities overlap with those of the underlying lung growth disorder. Long-term use of corticosteroids is not recommended, particularly in PIG occurring in the setting of lung growth abnormalities, due to their negative effect on postnatal alveolarization and neurologic development, and lack of efficacy. Unlike diffuse PIG, which has an excellent prognosis, the outcome of PIG associated with growth abnormality is variable, being related to the severity of the primary lung disorder.  

 Surfactant Dysfunction Disorders  

 The identification of mutations within genes encoding proteins involved in surfactant function...
Table 2: Surfactant Dysfunction Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>SP-B Deficiency</th>
<th>SP-C Deficiency</th>
<th>ABCA3 Deficiency</th>
<th>Brain-Thyroid-Lung Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locus</td>
<td>SP-B</td>
<td>SP-C</td>
<td>ABCA3</td>
<td>NKX2.1/TTF-1</td>
</tr>
<tr>
<td>Chromosome</td>
<td>2p11.2s</td>
<td>8p23</td>
<td>16p13.3</td>
<td>14q13.3</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Autosomal recessive</td>
<td>Autosomal dominant or sporadic</td>
<td>Autosomal recessive</td>
<td>Sporadic or autosomal dominant</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Birth</td>
<td>Birth—adulthood</td>
<td>Birth—childhood</td>
<td>Childhood</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Loss-of-function</td>
<td>Gain-of-toxic-action or dominant negative</td>
<td>Loss-of-function</td>
<td>Loss-of-function, (haploinsufficiency)</td>
</tr>
<tr>
<td>Phenotypes</td>
<td>Neonatal RDS</td>
<td>Neonatal RDS, ILD</td>
<td>Neonatal RDS, ILD</td>
<td>Neonatal RDS, ILD, childhood chorea, congenital hypothyroidism</td>
</tr>
<tr>
<td>Natural history</td>
<td>Generally lethal</td>
<td>Variable</td>
<td>Generally lethal, may be chronic</td>
<td>Variable</td>
</tr>
<tr>
<td>Treatment</td>
<td>Lung transplantation, or compassionate care</td>
<td>Potential benefit from early treatment (eg, steroids or hydroxychloroquine); supportive care or lung transplantation if progressive</td>
<td>Lung transplantation (if progressive)</td>
<td>Supportive care</td>
</tr>
</tbody>
</table>

and metabolism has dramatically improved our understanding of these disorders, which cause significant morbidity and mortality in neonates, older infants, children, and adults. Because surfactant dysfunction disorders display considerable overlap in their clinical and histologic features, genetic analysis is essential for establishing a specific diagnosis. However, immunohistochemical and ultrastructural examination also may provide valuable diagnostic clues.

**SP-B Deficiency**

SP-B deficiency is a rare autosomal recessive disorder that most frequently presents with rapidly progressive neonatal respiratory distress syndrome (RDS), although partial SP-B deficiency may be associated with a milder phenotype and longer survival (Table 2). More than 40 loss-of-function mutations within the SP-B gene, resulting in partial to complete absence of SP-B protein, have been identified thus far. The most common one, a GAA substitution for C at genomic position 1549 in codon 121 (the “121ins2” mutation), which accounts for ~70% of cases of SP-B deficiency, results in an unstable transcript and absent pro- and mature SP-B protein. The absence of SP-B disrupts the formation and structure of lysosome-related secretory organelles, called lamellar bodies (eg, on electron microscopy, the well-organized concentric rings of phospholipid membranes that characterize lamellar bodies are replaced by large, disorganized multivesicular bodies), thus leading to abnormal surfactant composition and function. Abnormal lamellar bodies on electron microscopy are a strong pointer to SP-B mutations. Histologically, SP-B deficiency is characterized by alveolar accumulation of granular, eosinophilic, periodic acid-Schiff-positive, lipoproteinaceous material.

Clinical estimates suggest an incidence of 1 per million live births. Most infants with SP-B deficiency present within hours of birth with respiratory failure requiring mechanical ventilation. Chest radiograph and HRCT appearances mimic that of hyaline membrane disease in premature infants with diffuse haziness and air bronchograms. However, infants with SP-B deficiency are only transiently or minimally responsive to surfactant replacement and, with rare exceptions, all patients succumb without lung transplantation. The rare infants with mutations that allow for partial expression of the SP-B protein appear to survive longer and go on to develop chronic ILD.

**SP-C Deficiency**

SP-C deficiency was originally described in an infant and mother with NSIP and DIP, respectively. Both carried a heterozygous guanine-to-adenine substitution, leading to skipping of exon 4 and deletion of 37 amino acids. A large 5-generation kindred was later identified with 14 affected family members, including 4 adults with histologic usual interstitial pneumonia and 3 children with NSIP, all carrying a rare heterozygous missense mutation predicted to hinder processing of SP-C precursor protein. More than 35 dominantly expressed SP-C mutations have been identified, half of which arise spontaneously, thus resulting in sporadic disease, whereas the remainder are inherited. The most common mutation, a T-to-C transition at genomic position 1295, leads to a threonine substitution for isoleucine in codon 73 (I73T), and accounts for a quarter of cases. The pathophysiology of lung disease due to SP-C mutations is thought to involve aberrant surfactant protein folding, decreased endogenous SP-C secretion, endoplasmic reticulum stress, and apoptosis of alveolar type II cells. Age at presentation and natural history of lung disease are highly variable: a large proportion of patients present in late infancy/early childhood; a minority present acutely in early infancy (Fig 5A and B), whereas others are discovered in adulthood. SP-C mutations account for a large minority of familial cases of pulmonary fibrosis, whereas they are a rare cause of sporadic forms of RP.
idiopathic interstitial pneumonia. Whether the nature and location of SP-C mutations affect the severity of lung disease is unknown. However, affected family members harboring the same SP-C mutation display considerable variability in the onset and severity of lung disease. In this regard, it is well established that viral infection may trigger the disease and negatively affect its clinical course. Successful treatment with either chloroquine or hydroxychloroquine and prolonged survival of children with SP-C mutations and ILD has been reported (Fig 5C).

**ABCA3 Deficiency**

The membrane transporter ABCA3 facilitates the translocation of phospholipids from the cytosol into lamellar bodies for the production of surfactant in type II alveolar epithelial cells. Mutations within ABCA3 are the most common genetic cause of respiratory failure in full-term infants. In fact, affected infants present in the neonatal period with severe and progressive RDS despite medical treatment. There is a genotype-phenotype correlation; patients homozygous for severe mutations invariably have a neonatal presentation and death in the first year of life, whereas milder mutations permit prolonged survival. However, ABCA3 mutations have been identified also in older children and even young adults with ILD, usually with DIP. Distinctive ultrastructural abnormalities observed in the alveolar type II cells of patients with ABCA3 mutations include small, markedly abnormal lamellar bodies with densely packed phospholipid membranes and electron-dense inclusions. Notably, the family history is usually negative, as the disease is inherited in an autosomal recessive fashion.

**NK2 Homeobox 1/TTF-1 Mutations**

NK2 homeobox 1 (NKX2.1)/TTF-1 is critical for lung development, surfactant homeostasis, and innate immune responses. It is a transcription factor for SP-B, SP-C, and ABCA3. Deletions or loss-of-function mutations on 1 copy (“haploinsufficiency”) of NKX2.1 gene can result in severe RDS and chronic ILD, classically in the form of “brain-thyroid-lung syndrome,” which is characterized by hypothyroidism, muscular hypotonia, developmental delay, and choreoathetosis, as the gene is also expressed in the thyroid gland and central nervous system. However, patients with NKX2.1 mutations also may present in the newborn period or during childhood with isolated lung involvement as well as with a spectrum of pulmonary manifestations, including alveolar proteinosis and severe neonatal RDS, pulmonary fibrosis, PH, and recurrent respiratory infections. Moreover, mutations within NKX2.1 may be associated with NEHI. Lung disease in this setting is thought to result from decreased amounts of several gene products in combination or reduced amounts of a key protein, particularly SP-B or ABCA3, below a critical level. Incidence and prevalence of lung disease due to NKX2.1 haploinsufficiency are unknown. As with other surfactant dysfunction disorders, histologic abnormalities include prominent alveolar type II epithelial cell hyperplasia, thickening of the interstitium by mesenchymal cells, and accumulation of foamy macrophages along with granular, eosinophilic proteinaceous material within the air spaces. Clinical availability of genetic testing and improved recognition of disease patterns on imaging studies have allowed many cases to be diagnosed noninvasively. No specific therapies have been demonstrated to be effective in these disorders.

**FIGURE 5**

A, SP-C deficiency in an 8-month-old girl presenting with RDS. CT scan shows extensive GGO. B, CT scan performed at the age of 18 months shows partial resolution of the ground glass abnormality. C, Follow-up CT scan performed at the age of 5 years shows further improvement of the parenchymal changes, although patchy GGO and fine septal thickening persist. All courtesy of Maurizio Zompatori, Bologna, Italy.
cytoskeleton. They are also involved in signal transduction, and cell survival, proliferation, and differentiation.\textsuperscript{73,74} Loss-of-function mutations within the integrin \(\alpha_3\) (\(ITGA3\)) gene have been associated with a fatal recessive multiorgan disorder consisting of congenital nephrotic syndrome, early-onset ILD, and skin fragility.\textsuperscript{75–77} Lung involvement was the primary cause of death in all cases, and lung biopsy revealed abnormal alveolarization, consistent with distorted morphogenesis. \(ITGA3\) mutations are probably underrecognized, as both the full spectrum of clinical manifestations and genotype-phenotype correlations are poorly characterized. Nevertheless, \(ITGA3\) gene sequencing is strongly recommended in newborns presenting with severe RDS and/or congenital nephrotic syndrome of unknown etiology.

Filamin A Mutations

Loss-of-function mutations in filamin A (\(FLNA\)), which encodes the actin cross-linking protein FLNA, cause X-linked periventricular nodular heterotopia, one of the most common brain malformations.\textsuperscript{78} However, \(FLNA\) mutations also have been associated with severe diffuse lung disease (characterized on HRCT by GGO, thickened interlobular septa, atelectasis, areas of hyperinflation, and cysts), tracheobronchomalacia, and severe PH.\textsuperscript{79–81} Lung pathology reveals abnormal alveolarization. \(FLNA\) mutations are inherited in an X-linked dominant manner, with high perinatal mortality in affected male patients, whereas in female patients the prognosis depends on the severity of the associated cardiovascular abnormalities.\textsuperscript{82} In premature infants with diffuse lung disease and respiratory course atypical for chronic neonatal lung disease in terms of timing, severity, and response to treatment, \(FLNA\) mutations should be suspected.

Humidifier Disinfectant–Associated chILD

Humidifier disinfectant–associated chILD is a unique chILD syndrome caused by inhalation of humidifier disinfectants in the home environment. Humidifier disinfectant–associated chILD, outbreaks of which were originally observed among Korean children in spring 2006,\textsuperscript{83–85} is characterized by spontaneous air leak, rapid progression, and high mortality.\textsuperscript{86,87} Radiologic abnormalities include diffuse or patchy GGO, dense consolidation, and diffuse centrilobular nodules. Lung biopsy reveals a temporally homogeneous pathologic process characterized by variable degrees of bronchiolar injury associated with bronchiocentric acute lung damage and relative sparing of the lobular periphery, consistent with an inhalation injury.\textsuperscript{86} Humidifier disinfectant–associated chILD has been eradicated on withdrawal of humidifier disinfectants from the market in November 2011. However, thousands of potentially toxic chemicals (to which children are far more vulnerable than adults) are used worldwide. Therefore, in cases of unusually acute and progressive disease, an environmental hazard should be suspected.

Parent Experiences and Perspectives

A broader understanding of the experiences and expectations of families of children diagnosed with ILD is crucial for improving current delivery and future planning of health care in this setting. A recent Web-based survey conducted in the United Kingdom identified a number of areas for development, which included feeding problems (an issue previously not fully appreciated), written information sharing, written communication between shared care hospitals, training for less-experienced hospitals, and psychological support.\textsuperscript{88} Some of these issues will be addressed by the currently ongoing FP-7 chILD program, a European project, which aims at increasing awareness of chILD across Europe, setting up a pan-European database and bio-bank compatible with others worldwide, increasing diagnostic accuracy through international panels of clinicians, radiologists, geneticists, and pathologists, and implementing evidence-based guidelines and treatment protocols.\textsuperscript{89}

American Thoracic Society Clinical Practice Guideline on chILD

The American Thoracic Society has recently published a clinical practice guideline that provides a comprehensive approach to the evaluation and management of chILD, focusing on neonates and infants <2 years of age.\textsuperscript{13} Some of the key messages of the guideline can be summarized as follows:

- Owing to their rarity, more common causes of diffuse lung diseases should be excluded before testing for specific forms of chILD;
- Achieving a specific diagnosis is critically important, as disease behavior, management, and outcomes are highly variable;
- Although many patients still require tissue sampling, in the appropriate clinical setting genetic testing may obviate the need for lung biopsy,\textsuperscript{90} although the guideline also emphasizes limitations of current sequencing modalities and challenges in interpretation of results. Nevertheless, as many as one-third of cases can be classifiable based on clinical, genetic, and/or radiographic criteria without histologic information\textsuperscript{91};
- Referral of patients to highly specialized centers is highly recommended, as multidisciplinary discussion among pediatric pulmonologists, radiologists, and pathologists with expertise
in chILD greatly enhances the likelihood of accurate diagnosis; 
- Because no controlled clinical trials of therapeutic interventions have been performed for chILD, recommendations on management derive from observational evidence and clinical experience. Accordingly, the guideline emphasizes the need for decisions to be made on a case-by-case basis.

The chILD-EU Collaboration
ILD in children is rare and it has been estimated that the average European hospital will see no more than 5 cases per year.92 The chILD-EU collaboration has brought together centers across Europe with the aim of (1) creating a pan-European registry, (2) peer reviewing all potential diagnoses of child, (3) collecting prospective longitudinal data from well-defined groups of patients, and (4) setting up and performing the first randomized controlled trial of treatment.29, 89 To achieve this, it is essential that diagnostic and therapeutic approaches be harmonized across Europe. To this end, a sequence of diagnostic procedures, along with standard operating procedures for performing such investigations, and therapeutic interventions and protocols have recently been proposed and agreed on by using the Delphi methodology, a consensus-building process among experts through a series of carefully designed questionnaires.29

SUMMARY AND CONCLUSIONS
Childhood ILD encompasses a large spectrum of rare and heterogeneous disorders, which differ substantially from adult ILD. In the past decade, genetic discoveries and multicenter collaborative efforts have resulted in the publication of a guideline document that provides systematic diagnostic approaches and standardized nomenclature. In addition, an increasing proportion of cases can be diagnosed without lung biopsy through chest CT patterns and genetic testing. Yet, much work remains to be done: relatively little is known about the epidemiology, natural history, and pathogenesis of many chILDs; morbidity and mortality associated with these disorders remain substantial, and treatment is often empirical and supportive. Ongoing research and collaborative efforts are expected to provide insights into the molecular basis of chILD and identify targets for therapeutic intervention, thus allowing the establishment of evidence-based therapies.

ABBREVIATIONS
ABCA3: adenosine triphosphate binding cassette family member 3
ACDMPV: alveolar capillary dysplasia associated with misalignment of pulmonary veins
BAL: bronchoalveolar lavage
chILD: childhood interstitial lung disease
CT: computed tomography
DIP: desquamative interstitial pneumonia
FLNA: filamin A
GGO: ground glass opacity
HRCT: high-resolution CT
ILD: interstitial lung disease
ITGA3: integrin α3
NEHI: neuroendocrine cell hyperplasia of infancy
NKX2.1: NK2 homeobox 1
NSIP: nonspecific interstitial pneumonia
PH: pulmonary hypertension
PIG: pulmonary interstitial glycogenosis
RDS: respiratory distress syndrome
SP-B: surfactant protein B
SP-C: surfactant protein C
TTF-1: thyroid-transcription-factor 1

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