



## Review Article

# Childhood Interstitial Lung Disease: Review on Diagnosis and Management

Enas Ahmed Hamed<sup>1</sup>, Moustafa M. Elsaeid<sup>2</sup>, Khaled Saad<sup>2, \*</sup>, Hazem Abo-Zeed<sup>3</sup>

<sup>1</sup>Physiology Department, Faculty of Medicine, Assiut University, Assiut, Egypt

<sup>2</sup>Pediatric Department, Faculty of Medicine, Assiut University, Assiut, Egypt

<sup>3</sup>Department of Radiology, Faculty of Medicine, Assiut University, Assiut, Egypt

### Email address:

ksaad8@yahoo.com (K. Saad), khaled.ali@med.au.edu.eg (K. Saad)

\*Corresponding author

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**Abstract:** Within the past few years, there is a rapid expansion in our understanding of childhood interstitial lung disease (chILD). chILD refers to a diverse group of rare chronic and complex respiratory disorders in children, mainly in infants under two years of age, which includes immunological and developmental abnormalities. These disorders involve the interstitium as well as the distal airspaces that result in restrictive lung physiology and significant impairment of gas exchange. chILD is clinically complex and associated with high morbidity and mortality. This review aimed to describe chILD classification, epidemiology, diagnostic approaches, morbidity, treatments, and the outcomes of chILD.

**Keywords:** Childhood Interstitial Lung Disease, chILD Syndrome, Diffuse Lung Disease

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## 1. Introduction

Childhood interstitial lung disease (chILD) refers to a diverse group of rare chronic and complex respiratory disorders in children, mainly in infants under two years of age, which includes immunological and developmental abnormalities. These disorders involve the interstitium as well as the distal airspaces that result in restrictive lung physiology and significant impairment of gas exchange. chILD is clinically complex and associated with high morbidity and mortality.<sup>1-3</sup> The term “diffuse lung disease” has often been used for interstitial lung disease (ILD), because the interstitial compartment is not always involved. Recently, the term “chILD syndrome” has been approved by the chILD Research Network and the American Thoracic Society Committee on chILD in order to aid the diagnosis of the uncommon causes of diffuse lung disease phenotypes in children.<sup>1,2</sup>

## 2. Epidemiology of chILD

In children, information on ILDs global epidemiology remains extremely limited because of a lack of systematic registries to collect data on these cases around the world. The few researches that estimated the incidence or prevalence of chILD used diverse methods to identify cases, different inclusion criteria, and different populations. Over the past 2 decades, the scope of chILD was initially described through the experience of large single-site referral centers and through national and international collaborative groups.<sup>2,4,5</sup> Few studies reported estimates of the frequency of chILD in populations.<sup>4,6,7</sup> Dinwiddie et al.,<sup>6</sup> conducted active surveillance of idiopathic ILD in UK and Ireland with reporting by respiratory pediatricians over a three-year period. The prevalence rate was 0.36 cases/100,000 in immune-competent children <17 years of age. Incidence estimates varied from 0.13 cases/100,000 children <17 years of age/year in Germany<sup>4</sup> to 10.8–16.2 cases/100,000 children <15 years of

age/year in Denmark.<sup>7</sup> In 2004, European Respiratory Society task force identified 185 cases of chILD in immune-competent children.<sup>8</sup> In 2007, Deutsch et al.,<sup>3</sup> reported 187 cases in children <2 years of age based solely on lung biopsy ascertainment from 11 pediatric centers over a 5-year time period.<sup>3</sup> In France, beginning in 2006, a National Reference Center for Rare Lung Diseases (RespiRare) was created to centralize data collection, and over 200 cases of ILD were identified over 3 years, however, a specific diagnosis could not be established for ~25% of cases.<sup>5</sup> Extrapolation from smaller studies had suggested an approximate incidence of 1 case per 100,000 populations.<sup>9</sup> The previous reported prevalence is likely to be considerably underestimated, particularly given the increased recognition of interstitial lung diseases in the pediatric population in recent years, due to (1) a recently developed classification system for classifying chILD; (2) increased recognition, particularly of the unique ILDs which occur in infants; and (3) increased use of thorascopic lung biopsy in pediatric patients for definitive diagnosis. Additionally, although the prevalence of any single specific ILD is low, the combination of the varied types of ILDs in the pediatric population may be sizable as a combined group.<sup>10</sup> Nowadays, we need a national registry or large prospective multicenter studies focusing on the evaluation of the true prevalence of interstitial lung disease in infants and children.

### 3. Pathophysiology of chILD

ILDs display a wide range of phenotypic expression that is influenced by the age of onset and instigating factors. However, in all situations, disease progression shares the common features of lung remodeling. For a long time, chronic ILD and pulmonary fibrosis were believed to result mainly from chronic inflammation following an initial injury to the alveolar epithelial lining.<sup>1</sup> In cases of limited injury, it was thought that the reparative effort could reverse the trend toward fibrosis. By contrast, in situations of enduring injury, the repair process driven by inflammatory molecules produced by the local cells will result in scarring and structural changes. Therefore, by targeting the inflammatory response, the belief was that fibrosis could be prevented or controlled. This theory explains the large use of anti-inflammatory therapy with, however, limited clinical efficacy. In addition, over-expression of pro-inflammatory mediators such as interleukin 8 (IL-8) in rodent lung was not found to be associated with marked progressive chronic fibrosis. Based on these observations, a hypothesis has emerged with evidence that inflammation may not be the prominent factor for development of the fibrotic response in ILDs.<sup>11,12</sup>

Based on clinical and experimental observations, a new paradigm has progressively emerged with the alveolar epithelium being viewed as a key factor in the development of ILD. Following injury, alveolar epithelial cells may actively participate in the restoration of a normal alveolar architecture through a coordinated process of re-epithelialization, or in the development of fibrosis through a process known as epithelial-mesenchymal transition (EMT). Repeated injuries

of “vulnerable” alveolar epithelial cells and the failure of the alveoli to correctly respond to injury lead to abnormal lung repair and progressive fibrosis. Prolonged denudation of the basement membrane adds to intense modifications of cell functions with imbalanced production of oxidants, proteases, and polypeptide mediators, including cytokines and growth factors such as TGF- $\beta$  and endothelin (ET)-1.<sup>13-16</sup> The local population of fibroblasts and myofibroblasts will progressively increase due to stimulation of proliferation by local mitogenic factors and reduction of apoptosis. This leads to progressive aberrant tissue remodeling by disorganization of extracellular matrix (ECM) component deposition, including fibrillar collagen, elastic fibers, fibronectin, and proteoglycans. Impairment of alveolar surface restoration contributes to the failure to replace damaged type 1 cells, abnormalities in pulmonary surfactant and alveolar collapse. In addition, the abnormal lung architecture observed in pulmonary fibrosis appears to be associated with the formation of new blood vessels. This process requires the secretion of angiogenic molecules to stimulate endothelial cell migration and neovascularization.<sup>11,13-16</sup>

The nature of provocative injury and following alveolar epithelium dysfunction includes genetic and epigenetic factors in addition to environmental and host comorbidity components.<sup>17</sup> From a number of reports, there is emerging evidence that the development of all forms of ILD is, at least in part, determined by genetic factors. In children, mutations are mainly reported in the genes encoding surfactant protein SP-C (SFTPC) and SP-B (SFTPB).<sup>18</sup> Other surfactant system defects include mutations in the genes encoding the thyroid transcription factor 1 (TTF-1) and the member A3 of the ABCA3.<sup>19</sup> In addition to genetic causes, there is convincing evidence that environmental factors affect the disease expression and progression. Existing data points out the role of tobacco smoke, exposure to aero contaminants, and viruses. To this point, several studies have shown the presence of numerous virus proteins in lung tissues from patients with ILD and lung fibrosis, with an expression localized to alveolar epithelial cells.<sup>20</sup> Much progress has been made recently in the identification of the pathological processes associated with ILD development and progression. This should help define new therapeutic strategies, including those capable of interfering with the pathways that lead to myofibroblast expansion and alveolar epithelial cell apoptosis. Such therapeutic interventions may be particularly promising in children, who usually experience a less devastating disease with a potential for significant regeneration of the alveolar structure.<sup>20</sup>

### 4. Classification of chILD

Two main factors led to the development of a new classification for chILD. First, there has been substantial confusion and difficulty associated with the description and classification of specific ILD in infants and young children with multiple terms used for similar abnormalities and sometimes the same term used for differing conditions; and

there has been a tendency to attempt to fit these pediatric disorders into the diagnostic schema used for adults. Using the adult classification was both suboptimal and limiting as conditions common in adults are rare or absent in infants and children and recently recognized infant conditions have no place in the adult classification. Second, the adult ILD classification system didn't acknowledge the important role of heritable and genetic disorders that widely recognized as an important component of chILD.<sup>10</sup> The European Respiratory Society (ERS) Taskforce defined subgroups according to etiology and histopathology.<sup>11</sup> The ERS review divided the diagnoses made clinically into four categories based on a proposal by Fan and Langston<sup>21</sup>: (1) Diffuse lung parenchymal disease of unknown association (drug reaction, aspiration, connective tissue disorders, infection, environmental disorders); (2) idiopathic interstitial pneumonias (NSIP), cellular/fibrotic, desquamative interstitial pneumonitis (DIP), lymphocytic interstitial pneumonia (LIP), diffuse alveolar damage (DAD)/acute interstitial pneumonia, organizing pneumonia (OP), usual interstitial pneumonia (UIP) to include familial cryptogenic fibrosing alveolitis, and chronic pneumonitis of infancy (CPI); (3) other forms of interstitial pneumonia to include lymphangioleiomyomatosis, Langerhans cell granulomatosis,

pulmonary alveolar proteinosis (PAP), sarcoidosis, eosinophilic pneumonia, idiopathic/infantile pulmonary hemosiderosis; and (4) congenital disorders (DIP, lymphoid interstitial pneumonia (LIP), lipoid pneumonia, nonspecific interstitial pneumonia / UIP, and surfactant deficiencies). Although this concept was an important step toward improved understanding and diagnosis of chILD, there was clearly a need for further refinement, particularly as diagnostic criteria were not provided for these entities, disorders of immunocompromised children were not addressed, and the requirement for chronicity excluded severe and rapidly progressive conditions. Additionally, adult terminology continued to be used in large part for quite different entities, including interstitial pulmonary fibrosis (IPF) and UIP, conditions that are common in adults, but rare in children.<sup>21</sup> chILD classification system, proposed by the American Thoracic Society Committee on Childhood interstitial lung disease and the Childhood interstitial lung disease Research Network, the term "Childhood interstitial lung disease syndrome" was used to exclude common causes of diffuse lung disease such as cystic fibrosis, congenital heart disease, bronchopulmonary dysplasia, and pulmonary infection; it recognized that some chILD conditions may be asymptomatic when identified.<sup>2</sup>

**Table 1.** Clinicopathologic classification of diffuse lung disease in childhood<sup>3</sup>.

I. Disorders of infancy
A. Diffuse developmental disorders
1. Acinar dysplasia
2. Congenital alveolar dysplasia
3. Alveolar capillary dysplasia with misalignment of pulmonary veins
B. Growth abnormalities
1. Prenatal conditions – secondary pulmonary hypoplasia of varying degree
2. Postnatal conditions – chronic neonatal lung disease
a. Prematurity-related chronic lung disease (also known as BPD)
b. Term infants with chronic lung disease
3. Associated with chromosomal abnormalities
a. Trisomy 21
b. Others
4. Associated with congenital heart disease in chromosomally normal children
C. Surfactant dysfunction disorders and related abnormalities
1. Surfactant dysfunction disorders
a. Sp-B genetic mutations (pulmonary alveolar proteinosis and variant histologies)
b. Sp-C genetic mutations (chronic pneumonitis of infancy is the dominant histologic pattern, others include pulmonary alveolar proteinosis, DIP, NSIP)
c. ABCA3 genetic mutations (pulmonary alveolar proteinosis –dominant histologic pattern, others include CPI, DIP, NSIP)
d. Congenital GMCSF receptor deficiency (PAP histologic pattern)
e. TTF-1 genetic mutations
f. Others with histology consistent with surfactant dysfunction disorder without an as yet recognized genetic disorder
2. Lysinuric protein intolerance (PAP histologic pattern)
D. Specific conditions of unknown/poorly understood etiology
1. NEHI
2. Pulmonary interstitial glycogenosis
a. Primary
b. Associated with other pulmonary conditions
II. Disorders of the normal host
A. Infectious and post-infectious processes
1. Post-infectious airway injury ranging from mild airway fibrosis to constrictive/ obliterative bronchiolitis with and without preceding history of viral respiratory infection
2. Specific infections identified
a. Bacterial
b. Fungal
c. Mycobacterial
d. Viral

*B. Disorders related to environmental agents*

1. Hypersensitivity pneumonia

2. Toxic inhalation

*C. Aspiration syndromes**D. Eosinophilic pneumonias**E. Acute interstitial pneumonia/ Hamman–Rich syndrome/idiopathic diffuse alveolar damage**F. Non-specific interstitial pneumonia**G. Idiopathic pulmonary hemosiderosis**H. Others*

## III. Disorders related to systemic disease processes

*A. Immune-mediated disorders*

1. Specific pulmonary manifestations

a. Goodpasture's syndrome

b. Acquired pulmonary alveolar proteinosis/ autoantibody to GMCSF

c. Pulmonary vasculitis syndromes

2. Nonspecific pulmonary manifestations

a. Nonspecific interstitial pneumonia

b. Pulmonary hemorrhage syndromes

c. Lymphoproliferative disease

d. Organizing pneumonia

e. Non-specific airway changes including lymphocytic bronchiolitis, lymphoid hyperplasia, and mild constrictive changes

3. Other manifestations of collagen-vascular disease

*B. Non-immune-mediated systemic disorders*

1. Storage disease

2. Sarcoidosis

3. Langerhans cell histiocytosis

4. Malignant infiltrates

5. Others

## IV. Disorders of the immuno-compromised host

*A. Opportunistic infections*

1. PCP

2. Fungal/yeast

3. Bacterial

4. Mycobacterial

5. Viral

6. Suspected

*B. Disorders related to therapeutic intervention – chemotherapeutic drug and radiation injury*

1. Chemotherapeutic drug injury

2. Radiation injury

3. Combined

4. Drug hypersensitivity

*C. Disorders related to solid organ, lung and bone marrow transplantation, and rejection syndromes*

1. Rejection

2. Graft-versus-host disease

3. Post-transplant lympho-proliferative disorder

*D. Diffuse alveolar damage of undetermined etiology**E. Lymphoid infiltrates related to immune compromise (for non-transplanted patients)*

1. Nonspecific lymphoproliferation

2. With lymphoid hyperplasia

3. With poorly formed granulomas

4. Malignant

## V. Disorders masquerading as interstitial disease

*A. Arterial hypertensive vasculopathy**B. Congestive vasculopathy including veno-occlusive disease**C. Lymphatic disorders*

1. Lymphangiectasis

2. Lymphangiomatosis

*D. Pulmonary edema**E. Thromboembolic*

## VI. Unclassified

*End-stage disease**Nondiagnostic**Inadequate tissue**Insufficient information*

*ABCA3* ATP-binding cassette transport proteins (ABC), *BPD* bronchopulmonary dysplasia, *CPI* chronic pneumonitis of infancy, *DIP* desquamative interstitial pneumonitis, *GMCSF* granulocyte-macrophage colony-stimulating factor, *NSIP* nonspecific interstitial pneumonia, *NEHI* neuroendocrine cell hyperplasia of infancy, *PCP* pneumocystis pneumonia, *Sp* surfactant protein, *TTF1* thyroid transcription factor 1.

## 5. Diagnostic Approach to chILD

After excluding or treating more common causes of lung disease (e.g., infection, recurrent aspiration, cystic fibrosis, immunodeficiency and congenital heart), the term ‘childhood interstitial lung diseases syndrome’ is then used to refer to children who meet three out of four of the following criteria<sup>22</sup>:

- 1) Respiratory symptoms (e.g. cough, rapid and difficult breathing, or exercise intolerance);
- 2) Respiratory signs (e.g. resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure);
- 3) Hypoxemia; and
- 4) Diffuse parenchymal abnormalities on chest imaging.

The first step in the diagnosis of chILD involves preparing a careful clinical history and performing a thorough clinical examination, followed by noninvasive tests (NITs) {Pulmonary function tests (PFTs), chest X-ray (CXR), high-resolution computed tomography (HRCT) scan and echocardiography} and also invasive tests (bronchoalveolar lavage {BAL} and lung biopsy) if the less-invasive diagnostic procedures are unable to arrive at a specific diagnosis. Generally, the evaluation proceeds from the least to the most invasive procedures, although the sequence depends on the context, acuity, and severity of the patient’s condition.

### 5.1. History and Physical Examination

A thorough medical history and physical exam remain useful in providing clues to the primary or underlying diagnosis. A patient’s age at presentation is important because different diagnoses are more common in the neonate and those who are younger than 2 years. The prevalence of chILD is higher in the younger patients: more than 30% of patients are less than 2 years at diagnosis. 7% have parental consanguinity and nearly 10% of case siblings were affected by similar conditions.<sup>1,9,23,24</sup> A history of prematurity, cardiac disease or Down syndrome is associated with alveolar simplification or growth abnormality.<sup>9</sup> Exposure to birds or other environmental antigens could point to hypersensitivity pneumonitis. The use of mineral oil for constipation in a healthy infant or an older child with neurologic impairment would strongly support the diagnosis of lipoid pneumonia. Hemoptysis and a history of renal disease would suggest a pulmonary-renal syndrome. A history of recurrent or unusual infections would be consistent with an immunodeficiency.<sup>1,9</sup> The presenting manifestations are often subtle and nonspecific. At the most severe, respiratory distress and failure soon after birth are associated with SP-B deficiency, ABCA3 mutations and TTF-1 mutations.<sup>1</sup> The onset of chILD is usually insidious and many children may have had symptoms for years before the diagnosis of ILD is established. However, the majority of patients have symptoms for less than one year at the time of initial evaluation. The clinical manifestations vary from asymptomatic presentation with radiological features suggestive of ILD to more characteristic presence of respiratory symptoms and signs such as cough, tachypnea and

exercise intolerance.<sup>22,24</sup> Chronic dry cough, tachypnea, dyspnea, retractions, cyanosis, clubbing, failure to thrive can be consequent to the respiratory deficiency or related to the primary disease, exercise intolerance, dry crepitation at the lung bases, loud second heart sound due to pulmonary hypertension and frequent respiratory infections are all common presentations in chILD. Observed cyanosis is less common, but hypoxemia is common. Extrapulmonary manifestations such as arthritis and rash suggest an immune-mediated connective tissue disease.<sup>9,11,12</sup>

### 5.2. Clinical Symptoms Are Predictive of Outcome in chILD

The course of ILD in pediatric patients is variable. It is, therefore, important to have predictors of outcome in these patients. Fan and Kozinetz<sup>25</sup> collected the data on 99 children with chILD with a duration of illness >1 month without any associated pathological condition. A severity-of-illness score derived from findings in the initial evaluation was assigned to each patient (table 2). The only factor associated with decreased survival was a higher severity of illness score. All the other clinical features, such as weight below the fifth percentile for age, crepitations, clubbing, family history of chILD and symptom duration at initial evaluation, did not influence survival. However, because of the retrospective design of the study, the authors were unable to determine if changes in severity-of-illness score over time could correlate with disease progression or response to therapy.<sup>25</sup>

**Table 2. Severity-of-illness score<sup>25</sup>.**

1	Asymptomatic
2	Symptomatic with normal oxygen saturation under all conditions
3	Symptomatic with normal oxygen saturation at rest but with abnormal oxygen saturation (SaO <sub>2</sub> < 90%) with sleep or exercise
4	Symptomatic and with abnormal oxygen saturation at rest (<90%)
5	Symptomatic with pulmonary hypertension

### 5.3. Physiological Testing

#### 5.3.1. Pulmonary Function Tests (PFT)

ILDs are usually characterized by a restrictive lung function, together with a reduction in diffusing capacity of the lungs for carbon monoxide (D<sub>LCO</sub>). However, in early disease, lung volumes, and D<sub>LCO</sub> may be within the normal range. Furthermore, in sarcoidosis and in histiocytosis X evidence of airflow obstruction is also found. This suggests that the using restrictive lung functions as an exclusive diagnostic biomarker for ILD is neither sensitive nor specific enough. Serial lung function testing is used to monitor disease clinical course. There is, however, little agreement about how frequently these lung function measurements must be obtained in the follow-up of the different forms of ILDs as the clinical course of the diverse ILDs shows wide variation.<sup>26</sup>

#### 5.3.2. Imaging Studies of chILD

Chest radiographs (CXR) are usually the first imaging study performed in chILD syndrome. They rarely provide a specific diagnosis, but they are frequently abnormal and may identify

diseases that mimic chILD.<sup>2,27</sup>

HRCT scan is considered the main tool for confirming chILD and for defining the specific diagnosis. The correct interpretation of the imaging results needs more eyes, or at least, a recheck of the images by a radiologist with special interest in ILD. Also, a better communication between the clinician and the radiologist is needed to improve the understanding of the patient's condition. HRCT defines the presence, extent, and pattern of lung disease. This may aid diagnosis, identify a site for biopsy, and help monitor the disease. Radiation dosing tailored to neonates and infants permits dramatic reductions in radiation exposure. CT scanning is superior to CXR at identifying ILD, and is superior to MRI in resolution, detecting characteristics of chILD diseases, and correlating with histological findings.<sup>2,27-29</sup> The purpose of chest HRCT is to evaluate the presence and extent of disease. In some cases, it can be diagnostic, but is more usually supportive of a diagnosis that takes account of clinical history, blood results and sometimes bronchoalveolar lavage and/or biopsy material. The general principles of scanning are to minimize radiation dosage to the child while maximizing the information obtained.<sup>27</sup> The administration of contrast medium will make the assessment of ground glass shadowing almost impossible, and so careful consideration should be given as to the risk/benefit of using a contrast medium based on the expected diagnosis.<sup>28</sup> It is recognized that although faster CT scanners may enable chest CT without the need for anesthetic, however, it is not recommended, as (1) the technique frequently provides suboptimal results from respiratory movements made by the child and (2) the variance in lung volumes during an uncontrolled respiratory cycle will reduce the value of the scans obtained and the reliability of CT to provide the supportive evidence for a diagnosis of chILD.<sup>28</sup> In rapidly-breathing infants, high-quality scans can be obtained by controlled ventilation that employs either sedation and mask ventilation or endotracheal intubation and general anesthesia. Both inspiratory images as close to full lung inflation and selected expiratory images are desirable.<sup>29</sup> Controlled ventilation HRCT (CVHRCT) is a technique that (1) facilitates assessment of the extent of air trapping and ground glass opacities, (2) prevents dependent atelectasis from masking pathologic abnormalities, and (3) eliminates motion artifact by controlling both motion and lung volume.<sup>30</sup> Mask ventilation is used to deliver deep breaths to a sedated child, resulting in a short period of apnea during which the lungs are imaged. The sedation may consist of general anesthesia, with the prone position if necessary to evaluate dependent opacities that frequently occur in sedated children. If sedation or anesthesia cannot be administered, a less invasive approach is lateral decubitus imaging but image quality and reproducibility are usually poorer.<sup>31</sup> At least two independent readers scored ground-glass opacity (GGO) (ground glass score) and honeycombing (fibrosis score) for ILD. On a scale of 0–5 in the three lobes of both lungs as follows: 0– no GGO, 1– GGO involving up to <5% of the lobe, 2– GGO involving 5–24% of the lobe, 3– GGO involving 25–49% of the lobe, 4–

GGO involving 50–75% of the lobe, 5– GGO involving >75% of the lobe for ground glass score; 0– no interstitial disease, 1– septal thickening without honeycombing, 2– honeycombing involving up to 25% of the lobe, 3– honeycombing involving 25–49% of the lobe, 4– honeycombing involving 50–75% of the lobe, 5– honeycombing involving >75% of the lobe for fibrosis score. Each observer assessed the extent of involvement in each of three defined regions: above aortic arch, between the arch and inferior pulmonary veins, and between inferior pulmonary veins and lung base. The mean estimate of the two readers was used to define the fibrosis and ground glass score for each lobe.<sup>32,33</sup> Research on the ability of HRCT scans to differentiate between active and inactive disease has been mainly confined to ILD associated with systemic sclerosis.<sup>33</sup> There is evidence that a predominant ground glass pattern is more likely to represent active inflammatory disease and to respond to appropriate therapy, particularly in fibrocytic alveolitis, extrinsic allergic alveolitis, and desquamative interstitial pneumonia.<sup>33,34</sup> It is still unproven that a ground glass pattern precedes a reticular or honeycomb pattern, although this seems likely.<sup>33</sup> The association of a ground glass pattern with traction bronchiectasis or bronchiolectasis is likely to indicate some associated fibrosis, whereas ground glass change without traction bronchiectasis usually indicates active inflammation.<sup>26</sup> Reticular and honeycomb patterns on HRCT scans correlate well with histological evidence of fibrosis. HRCT is reasonably accurate in the separation between a group of patients in which disease is clearly irreversible and a group of patients in whom responsiveness is reasonably likely.<sup>26,33,34</sup> Can HRCT predict response to therapy in IPF? Gay et al.,<sup>35</sup> set up a study with 38 biopsies proven IPF patients. The study patients received 1 mg/kg prednisone daily during 3 months. The HRCT before treatment was scored (score from 0 to 5 for each lobe) for ground glass and fibrosis by 4 radiologists independently. They demonstrated that a fibrosis score of 2 or more has 80% sensitivity and 85% specificity in predicting survival. However, it is not clear how many drop outs were present during the survival follow-up and how long the time of follow-up was. Thomeer et al.,<sup>26</sup> studied 155 IPF patients with a median follow-up of 2.5 years (SD 1.8). Only the fibrosis score at baseline was predictive of survival (HR 1.58, 95% CI 1.15–2.17), whereas a ground glass score or changes in ground glass score or fibrosis score over 6 and 12 months were not predictive of survival. A HRCT fibrosis score of more than 2 had a relative risk for death of 2.31 (95% CI 1.40–3.80). However, the area under the curve for the fibrosis score was only 0.61 (95% CI 0.52–0.70), which means that the score had only a moderate to low sensitivity and specificity for survival.<sup>26</sup>

ILDs are characterized by an acute or chronic inflammation of the interstitium, also called the alveolar capillary membrane. A possible way to measure the alveolar-capillary membrane permeability is by radionuclide aerosol lung imaging. The rate of the clearance of the aerosol is inversely related to the integrity of the alveolar-capillary barrier. Perthechnegas and 99m Tc-diethylenetriamine pentacetate (DTPA) have been

studied as disease activity measure in different forms of ILDs.<sup>26,36</sup> Positron emission tomography imaging has appeared on the scene of biomarkers of ILD.<sup>18,26</sup> F–FDG PET imaging may serve as a sensitive tool for the evaluation of disease activity in sarcoidosis, with higher sensitivity and interobserver agreement compared to the classical Gallium scintigraphy. The potential value of F–FDG PET as a biomarker for disease activity in other ILDs is less clear.<sup>18</sup> In IPF, the magnitude of F–FDG uptake in the lungs is usually low.<sup>18</sup> As F–FDG is thought to assess the inflammatory burden and not the fibrosis,<sup>18</sup> the finding of relatively low survival in IPF can be regarded as confirmative for the concept that inflammation does not play a major role in the pathogenesis of this disease. No studies are present that correlates rate of <sup>18</sup>F–FDG uptake with survival in specific forms of interstitial lung diseases.<sup>26</sup>

The echocardiogram should be an early investigation to estimate pulmonary artery pressure, and exclude cardiac mimics of interstitial lung disease, such as cor triatrium leading to pulmonary edema. Pulmonary hypertension, where present, should be diagnosed and treated accordingly in liaison with pediatric cardiologist.<sup>28</sup>

**5.4. Laboratory Studies**

ILD and lung fibrosis are caused by repeated subclinical injuries of a “susceptible” lung parenchyma. Consequently, phenotypic manifestations progress from the onset of symptoms and mild disease to severe respiratory impairment precipitated by acute exacerbations. Based on this current understanding, relevant biomarkers should include molecules

that will help the physician predicting disease progression and designing clinical trials. Several research studies for the identification of biomarkers in ILD have been performed so far. Despite insufficient evidence to validate their translation into clinical practice, recent developments provide perspective for some of these molecules to serve as markers for disease susceptibility, activity, and prognosis. Tests can be grouped into (a) genetic abnormalities; (b) immune function (especially if the follicular bronchiolitis-lymphoid interstitial pneumonia spectrum is suspected); (c) autoantibody studies (cases of pulmonary hemorrhage, alveolar proteinosis, or if there is evidence of a systemic disease); (d) environmental organic dust exposures (hypersensitivity pneumonitis); (e) miscellaneous, that is, ACE inhibitors in cases of suspected sarcoidosis. The younger the child is, the more carefully new or established genetic diagnoses are sought. In all cases of chILD, DNA of the patient and parents should be stored for future analyses. The clinical situation will dictate which tests are performed and whether it is realistic to await results before proceeding to a CT or lung biopsy.<sup>28</sup> Identification of biomarkers, which could be used for diagnosis, measurements of disease severity and progression, and responsiveness to treatments, is a major challenge in the ILD field for both pediatric and adult patients. In the coming years, the rapidly evolving field of biotechnologies will certainly allow us to discover a number of novel biomarkers. A critical issue will be the validation and translation of these findings into patient care, and this will require investigations in populations of individuals with very careful and longitudinal phenotyping.<sup>20</sup>

*Table 3. Initial diagnostic approach for ILD.<sup>22</sup>*

Possible diagnoses to exclude before evaluating for childhood ILD <sup>a</sup>	Diagnostic approaches
Infection	Appropriate cultures Consider bronchoscopy and bronchoalveolar lavage
Cystic fibrosis	Sweat chloride test
Immunodeficiency (primary vs. secondary) <sup>b</sup>	Complete blood count and differential, HIV, immunoglobulin, vaccine response, others as indicated
Recurrent aspiration	Barium swallow study
Congenital heart disease or pulmonary hypertension	Echocardiogram, cardiac catheterization (select cases)

ILD: interstitial lung disease.

<sup>a</sup>Note that identification of these diagnoses does not completely preclude the diagnosis of ILD. If respiratory symptoms persist despite treatment of the identified abnormalities or severity is out of proportion to the identified causes, additional ILD evaluations may be further considered.

<sup>b</sup>Certain forms of ILD also occur in children with immunodeficiency and immune dysfunction.

**5.5. Genetic Testing**

The availability of clinical genetic testing now allows for noninvasive definitive diagnosis in some cases. The currently known genetic causes of chILD include abnormalities in the genes encoding SFTPB, SFTPC, ABCA3, GM–CSF receptors  $\alpha$  and  $\beta$  (CSFRA and CSFRB), and thyroid transcription factor–1 (NKX2.1/TTF1).<sup>2</sup> The choice of specific genetic tests should be guided by the family history and clinical context. A specific diagnosis provides clinically useful information for the great majority of cases as, it informs management, prognosis, and genetic counseling. Currently, only a subset of types of chILD has a defined genetic basis. However, it is likely that additional disease–associated genes will be

identified in the future.<sup>22</sup>

**5.6. Invasive Investigations**

**5.6.1. Bronchoscopy with Bronchoalveolar Lavage**

Bronchoscopy with BAL is the most commonly used invasive technique in patients with ILD because it is relatively safe, easily performed, and readily available. In addition to enabling evaluation of airway anatomy and physiology, airway and alveolar samples are obtained by BAL for cytology and microbiologic diagnosis.<sup>2</sup> The possibility of performing mucosal or carinal biopsy to evaluate epithelial histology and ciliary structure is an added benefit. Bronchoscopy is relatively well tolerated, widely available, and may help

diagnosis of infection, aspiration, hemorrhage, or PAP.<sup>2,22,37</sup> If BAL is to be performed during the same anaesthetic as CT, then it should follow the imaging; where it is to be performed at the time of lung biopsy, the lobe designated for a lung biopsy should be avoided. Where possible flexible bronchoscopy should be performed via endotracheal or laryngeal mask to reduce suction channel contamination from the upper airway. The first bronchoalveolar lavage fluid aliquot should be unfiltered and used for microbiological studies, and the other aliquots should be pooled, filtered through sterile gauze only if a lot of mucus is present, which is unlikely in chILD, and used for analysis of cellular and non-cellular components.<sup>28,37</sup> Although the diagnostic yield is low in pediatric diffuse lung disease, BAL can be used to diagnose specific disorders: infection, aspiration, alveolar hemorrhage, alveolar proteinosis, and histiocytosis, sarcoidosis, lysosomal storage disorders (Gaucher or Niemann–Pick cells) and *SFTPC* mutations (pro–surfactant protein C protein).<sup>2,28,37</sup> BAL cell differentials can be useful in narrowing the differential diagnosis with neutrophilia suggesting aspiration or infection; eosinophilia suggesting eosinophilic pneumonia, drug–induced lung disease, or parasitic disease and lymphocytosis suggesting hypersensitivity pneumonitis, sarcoidosis, or lymphocytic interstitial pneumonia.<sup>37</sup>

### 5.6.2. Lung Biopsy

The timing and need for lung biopsy is controversial. chILD patients who are well and thriving may not merit biopsy even if the CT scan appearances are not typical. Some would consider that an oxygen requirement warrants a diagnostic lung biopsy, while others would wait and see. There is clearly merit in performing an invasive procedure only if treatment will be changed as a result. Steroids are a mainstay of treatment for chILD and the timing of biopsy related to their initiation is often dictated by circumstance. Where possible, biopsy prior to steroid treatment is recommended (to minimize risk to wound healing and to expedite specific chILD treatments, i.e., TNF- $\alpha$  antagonist infliximab combined with methotrexate for sarcoidosis, and cyclophosphamide for angiitis with granulomatosis).<sup>28</sup> The dilemma posed by the sick patient with chILD who is on the verge of ventilation (and biopsy would most likely tip to requiring ventilation) or is unstable on a ventilator often dictates that a steroid trial before a biopsy may be appropriate. If the child is already ventilated, unless the ventilator requirements are very high, a biopsy can safely be performed.<sup>28</sup>

The site of biopsy should be guided by a recent CT chest. There should be the liaison between the surgeon, pathologist, and pediatrician. Any other procedures which may merit general anesthesia (e.g., bronchoalveolar lavage, mucosal biopsy, placement of a vascular access device or gastrostomy) should be carefully planned. The tip of the middle lobe and lingula should be avoided, and biopsy should preferably be from two sites, and sample areas of varying disease severity. Increasingly, a biopsy is using video-assisted thoracoscopic surgery (VATS) rather than a minithoracotomy. Whatever

technique is used, the procedure must only be undertaken by an experienced surgeon, who is confident of obtaining adequate biopsies (at least 10×10×10 mm); a very superficial biopsy, which does not contain distal airways, may result in a diagnostic error.<sup>28</sup> Different methods may be used to obtain lung tissue. The major difference between individual methods lies mainly in balancing invasiveness against the potential for obtaining adequate and sufficient tissue for diagnosis. Surgical approaches to lung biopsy include limited open–lung biopsy (OLB) (i.e., open thoracotomy), VATS, and trans bronchial and percutaneous needle biopsy.<sup>8</sup> Biopsies should be taken from areas of differing severity, avoiding the tips of the middle lobe and lingula. The biopsy should ideally be a wedge at least 10 mm depth and 20 mm along the pleural axis unless precluded by the size of the patient (i.e. a neonate). The biopsy should be fixed in inflation for histology and a piece should be saved in glutaraldehyde for electron microscopy especially, in cases of suspected *SFTPB* or *ABCA3* mutations, where lamellar bodies are abnormal.<sup>38</sup>

## 6. Prognosis of chILD

### 6.1. Morbidity Associated with chILD

Among studies that reported outcomes of chILD, the duration of follow–up varied or was not reported, restricting comparisons between studies. Furthermore, no study has reported outcomes beyond 6 years follow–up. In many studies, definitions of outcomes were limited to imprecise descriptions such as “improved” or “stable” making them difficult to interpret.<sup>1,2,6</sup> Since each individual chILD disorder is rare, and therefore rarely encountered by pediatricians, diagnosis may be difficult. Diagnostic delay may have a negative impact on outcome, especially in chILD disorders that progress rapidly.<sup>2,4,5,8</sup> Response to treatment and outcome can be evaluated in children based on several criteria such as decrease in cough and dyspnea, increase in oxygenation at rest and sleep, and changes in pulmonary function tests. Improvement on thoracic HRCT may also be seen, but tends to occur over a much longer period of time. Reports in pediatric ILD had not shown a good correlation between histological findings and outcome. Some children with relatively severe fibrosis on lung biopsy make good progress, whereas others with mild desquamation have a poor outcome. This is probably due to the variable severity of the disease in different parts of the lung, especially in relation to the particular area biopsied, despite HRCT guidance. Overall a favorable response to corticosteroid therapy can be expected to 40–65% of cases, although the significant squeal such as limited exercise tolerance or the need for long–term oxygen therapy is often observed.<sup>2,4,5,8</sup>

The outcome of children with ILD in terms of death and disease–free survival is reported to be 15– 60%<sup>3,25</sup> and 50%, respectively.<sup>3</sup> The available data on the clinical profile of children with ILD mostly come from small case series that included less than 30 children. Also, many of these reports had focused on one or more specific conditions such as fibrosing



alveolitis or DIP rather than looking at the complete spectrum of ILD.<sup>1-3</sup> Fan and Kozinetz<sup>25</sup> reported a 64% 5-year survival rate among children with diffused lung diseases who were 1 month to 18 years old and 38% 5-year survival rate among those who presented with Pulmonary hypertension (PHT). A European Respiratory Society task force study reported a mortality rate of only 6%, with clinical improvement in 74% of patients, from birth until 16 years of age. This study included only patients who had symptoms of at least 3-month duration, thereby excluding many of the more rapidly progressive cases of neonatal diffused lung diseases.<sup>8</sup>

ILD are often associated with PHT. Echocardiographic measurements have revealed PHT in up to one-quarter of patients with ILD and in IPF. PHT secondary to ILD (PHT-ILD) is generally classified as pulmonary hypertension due to lung diseases and hypoxia. The presence of PHT is associated with a poor prognosis and is a strong predictor of mortality. The mechanisms of pulmonary hypertension in ILD have not been sufficiently elucidated. It has been suggested that pulmonary fibrosis leads to vasoconstriction due to hypoxia (Euler-Liljestrand reflex). Elevated endothelin-1 levels can be found in pulmonary fibrosis and may cause pulmonary vasoconstriction. Additionally, progressive fibrosis leads to irreversible changes of the pulmonary vasculature and *in situ* thrombosis.<sup>39</sup>

## 6.2. Mortality Associated with *chILD*

For *chILD* disorders, overall mortality ranged from 6% to 30% (1). Studies from developed countries that reported mortality included patient groups with variable periods of follow-up, extending to 17 or 18 years of age. For studies conducted in developed countries with cohorts spanning childhood and adolescence, mortality ranged from 6% to 19% (median, 13%). Among these studies the longest follow-up periods were five<sup>25</sup> and six years<sup>40</sup>. For specific *chILD* disorders, mortality was highest for surfactant protein B deficiency (100% without a lung transplant) and ABCA3 mutations (42–100%). Mortality was also associated with surfactant protein C deficiency, TTF-1 mutations, IPF, DIP and chronic pneumonitis of infancy. Mean duration of follow-up after diagnosis ranged from 1 to 9.8 years.<sup>1</sup>

## 7. Treatment of *chILD*

### 7.1. General Measures

Neonates and infants with severe, progressive disease may be referred for lung transplantation evaluation after discussion with their family. All patients with *chILD* should receive supportiveness and preventive care including nutritional support and monitoring, supplemental nocturnal or continuous oxygen when needed and interventions to prevent serious infections such as immunizations with pneumococcal vaccine, an annual influenza vaccination, and routine childhood immunizations, with the exception of live-virus vaccines in immunosuppressed patients. Oxygen therapy was used in 28–88% of ILD cases.<sup>4,6,8,25</sup> Aggressive treatment of

intercurrent infections and strict avoidance of tobacco smoke and other air pollutants are strongly recommended.<sup>12,41</sup> Families should receive education and support from care providers. Additionally, genetic counseling should be available to family members of patients with identified genetic disorders to address future reproductive planning and follow-up, especially if asymptomatic family members carry dominant mutations in SFTPC or NKX2-1/TTF1.<sup>19</sup>

### 7.2. Pharmacologic Therapy

Very few children do not require any treatment and recover spontaneously. In the majority of cases, treatment with anti-inflammatory, immunosuppressive, or anti-fibrotic drugs is required for weeks, months or even years.<sup>6,11</sup> Various drugs discussed below can be used, but no guidelines for treatment of *chILD* have been proposed so far. The major reason is the very limited number of pediatric patients available for a prospective clinical trial. In addition, controlled studies with a placebo arm are unacceptable because of the poor prognosis of untreated cases and the reported efficacy of anti-inflammatory therapies in a number of *chILD*. At the present time, the main therapeutic strategy is based on the concept that suppressing inflammation may most likely prevent progression to fibrosis. Although currently, no randomized controlled trials exist in children with ILD, pharmacologic treatment includes corticosteroids which remain the first-line drugs for a number of these disorders and steroid-sparing agents with anti-inflammatory properties, such as hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, and intravenous immunoglobulin.<sup>42</sup>

Steroids administered orally and/or intravenously. This has been well illustrated by the results of the ERS Task Force on pediatric ILD.<sup>11</sup> Oral prednisolone is most commonly administered at a dose of 1–2 mg/kg/day. Children with significant disease are best treated with pulsed methylprednisolone at least initially.<sup>6,43</sup> This is usually given at a dose of 10–30 mg/kg/day for 3 days consecutively at monthly intervals. The minimum number of cycles recommended is 3 but treatment may need to be continued for 6 months or more depending on response. When the disease is under control, the dosage of methylprednisolone can be reduced or the time between cycles can be spaced out. The disease may then be controlled with oral prednisolone preferably given as an alternate day regime. In few cases oral prednisolone is used from the beginning simultaneously with intravenous methylprednisolone but this is only recommended in those with very severe disease. Methylprednisolone may be effective when other forms of steroids administration fail without significant side effects.<sup>6,9,43</sup> Although data are lacking, the pulse intravenous therapy is at least as effective as oral therapy and has fewer side effects. The mechanism by which high-dose pulse corticosteroid treatment may be more effective than continuous prednisone therapy at lower doses is still unknown. It has been suggested that pulse treatment may induce stronger immunosuppressive effects with lower long-term toxicity.<sup>6,9</sup> An alternative to steroids is hydroxychloroquine with a recommended dose of 6–10

mg/kg/day. Hydroxychloroquine was used in 5–50% of cases with ILDs.<sup>4,6,8</sup> Individual case reports have described a response to hydroxychloroquine even in the presence of steroid resistance.<sup>6</sup> Hydroxychloroquine has been used for the treatment of surfactant protein C mutations, pulmonary interstitial glycogenosis, desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, idiopathic pulmonary hemosiderosis, sarcoidosis, and many connective tissue diseases with pulmonary involvement.<sup>42</sup> Eye exams must be routinely performed to look for retinal toxicity, although this complication is extremely rare in children.<sup>42</sup> Some groups have proposed to base the decision as to which agent to use on the lung biopsy findings, with a preference for steroids in case of large amount of desquamation and inflammation and for hydroxychloroquine if increased amounts of collagen representing pre-fibrotic change are found. However, as documented in the ERS Task Force on pediatric ILD, the preferred choice between steroids or hydroxychloroquine in children is highly dependent on the expertise of the center in charge of the patient, and does not seem to be oriented by the histopathological pattern.<sup>8,11</sup> In 38 cases of diffuse lung disease in Germany, hydroxychloroquine was used twice – in one of two cases of SP-C deficiency, with a good response and, in one of four cases of *ABCA3* mutations, with no response.<sup>4</sup>

In situations of inefficiency of steroids and hydroxychloroquine, other immunosuppressive or cytotoxic agents such as azathioprine (2–3 mg/kg/day, maximum dose 150 mg/day), cyclophosphamide (1–1.5 mg/kg/day) and cyclosporine (4 mg/kg/day in two divided doses) may be used. These treatments have been used mainly in situation of autoimmune disorders.<sup>9,44</sup> Cyclophosphamide is the treatment of choice in immune-mediated alveolar hemorrhage syndromes that are not controlled with corticosteroids. Cyclophosphamide has also been shown to be effective in scleroderma, with improvement in lung function, dyspnea, skin thickness and quality of life one year after initiation compared with placebo; however, when therapy was stopped at one year, most of the beneficial effects were lost one year later.<sup>9</sup> The use of cyclophosphamide must be weighed against potentially serious complications such as hemorrhagic cystitis, pulmonary toxicity, malignancy, gonadal toxicity, and hematologic toxicity.<sup>9</sup> Promising therapeutic options of chILD include macrolides e.g. Sirolimus. Indeed, these antibiotics have been shown to display a number of anti-inflammatory and immunomodulatory actions. Although the mechanisms and cellular targets specific to macrolide activity remain to be elucidated, beneficial effects in several chronic lung diseases have been reported.<sup>9</sup> Macrolides such as erythromycin, clarithromycin and azithromycin, possess anti-inflammatory properties and have been used to treat airway disorders such as bronchiectasis (both idiopathic and cystic fibrosis-related), diffuse panbronchiolitis, post-lung transplant bronchiolitis obliterans syndrome, and severe asthma.<sup>45</sup> Of interest is the ability of macrolides to accumulate in host cells including epithelial cells and phagocytes. A favorable response to treatment with clarithromycin has been described in an adult

patient with DIP.<sup>46</sup>

The TNF- $\alpha$  blocker etanercept has been used for refractory pediatric sarcoidosis, in combination with methotrexate. Other causes of ILD which have been successfully treated with etanercept include polyarteritis nodosa, and other rare vasculitis diseases. If etanercept fails, the anti-TNF- $\alpha$  monoclonal infliximab may be worth trying.<sup>41</sup> There are no reports on the use of these novel therapies in chILD. Finally, in the coming years, it is likely that an expanding number of molecules aimed at favoring alveolar surface regeneration and repair through activation and proliferation of tissue-resident (progenitor) cells will come out.<sup>9</sup>

### 7.3. Other Specific Treatment Strategies

Depending on the underlying diseases, several specific treatment strategies need to be considered. These include whole lung lavage for pulmonary alveolar proteinosis, which has been reported to be effective by removing the material from the alveolar space. Other strategies such as interferon- $\gamma$  for pulmonary haemangiomas, anti-infective therapy for chronic respiratory infections (e.g. cytomegalovirus or Epstein-Barr virus infection) and pulsed cyclophosphamide for Wegener's granulomatosis are effective. In patients with hypersensitivity pneumonitis, avoidance of the causative environmental antigen is of fundamental importance. Many patients with chILD also have secondary pulmonary artery hypertension. Sildenafil is a phosphodiesterase-5 inhibitor that dilates pulmonary vasculature. Due to the devastating prognosis of PH-ILD, targeted therapy of pulmonary hypertension could offer an additional therapeutic option for those patients who are not candidates for lung transplantation, and could serve as a bridge to transplantation for patients at risk of clinical deterioration or death on the transplant waiting list.<sup>47</sup>

In recent years, lung transplantation has emerged as a possible option in chILD of all ages, even in young infants, and lung or heart-lung transplantation may be offered as an ultimate therapy for end-stage chILD. The outcome and survival do not seem to be different from those reported in other diseases, although comparisons are difficult to establish due to the small number of cases.<sup>9,12</sup> Lung transplantation may be used in cases of surfactant protein B deficiency, surfactant protein C deficiency, *ABCA3* mutations, TTF-1 mutation, chronic pneumonitis of infancy and idiopathic pulmonary fibrosis. Among 187 children aged less than 2 years with diffuse lung disease only 2% had a lung transplant.<sup>3,9,12</sup>

### 7.4. Monitoring of Response to Treatment

The variety of chILD diagnoses makes a single common monitoring plan of little value. chILD-EU collaboration<sup>28</sup> has looked to enable reference across diagnoses by the development of an observational trial protocol focused on the first year of diagnosis. Monitoring is at months 1, 2, 3, 6 and 12 and annually thereafter. Key observations are clinical

(respiratory rate, heart rate, weight, oxygen saturation in air awake, oxygen saturation including overnight while asleep and on exercise, evidence of pulmonary hypertension) and radiological monitoring (CXR at diagnosis, 6 and 12 months; CT not recommended, however, if considered justifiable, a limited cut thin-section HRCT of areas of interest should provide sufficient information). In older children spirometry at each observational monitoring visit should be recorded, with  $D_{LCO}$  and body plethysmography recommended as indicated but at least once per year.<sup>28</sup> In infants and small children decrease in tachypnea, return of weight gain and growth to normal levels, improved exercise tolerance, routinely employ overnight pulse oximetry monitoring and an increase in resting oxygen saturation levels of 3–4% are considered to indicate a favorable response. As improvements on HRCT scans tend to occur only over longer periods of time and radiation exposure should be minimized, imaging plays a limited role.<sup>41</sup>

The evidence base for chILD treatments is limited because the disorders are so rare and there have been no clinical trials. The general principle of treatment is that minimising inflammation may prevent progression to fibrosis. Corticosteroids and hydroxychloroquine are widely used in the treatment of chILD, not always with success. Both have anti-inflammatory properties but they also may have other effects, for example hydroxychloroquine may inhibit the intracellular processing of the precursor protein of surfactant protein C. As chILD disorders are generally incurable, supportive care (nutritional supplementation, influenza vaccination, oxygen supplementation) is important.<sup>41</sup> chILD disorders have a diverse range of etiologies and pulmonary pathologies, thus a common treatment strategy is unlikely to be effective for all chILD disorders. Current treatments are not based on rigorous scientific evidence but on the experience of individual health professionals and the preferences of individual centers. There is an impetus to standardize treatment, follow-up, and collection of biological samples in observational studies with a view to providing evidence to support the first randomized controlled trial of treatment for child. It is hoped that the establishment of the United States chILD Research Network (chILDRN) will help to achieve that aim.<sup>1</sup>

## Conflict of Interest

All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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