American Thoracic Society Documents

An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy

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Contents

Background: **There is growing recognition and understanding of the entities that cause interstitial lung disease (ILD) in infants. These entities are distinct from those that cause ILD in older children and adults.**

Methods: **A multidisciplinary panel was convened to develop evidence-based guidelines on the classification, diagnosis, and management of ILD in children, focusing on neonates and infants under 2 years of age. Recommendations were formulated using a systematic approach. Outcomes considered important included the accuracy of the diagnostic evaluation, complications of delayed or incorrect diagnosis, psychosocial complications affecting the patient's or family's quality of life, and death.**

Results: **No controlled clinical trials were identified. Therefore, observational evidence and clinical experience informed judgments. These guidelines: (*1*) describe the clinical characteristics of neonates and infants (<2 yr of age) with diffuse lung disease (DLD); (*2*) list the common causes of DLD that should be eliminated during the evaluation of neonates and infants with DLD; (*3*) recommend methods for further clinical investigation of the remaining infants, who are regarded as having "childhood ILD syndrome"; (*4*) describe a new pathologic classification scheme of DLD in infants; (*5*) outline supportive and continuing care; and (*6*) suggest areas for future research.**

Conclusions: **After common causes of DLD are excluded, neonates and infants with childhood ILD syndrome should be evaluated by a knowledgeable subspecialist. The evaluation may include echocardiography, controlled ventilation high-resolution computed tomography, infant pulmonary function testing, bronchoscopy with bronchoalveolar lavage, genetic testing, and/or lung biopsy. Preventive care, family education, and support are essential.**

Keywords: diffuse lung disease; lung growth abnormalities; surfactant proteins; neuroendocrine cells

EXECUTIVE SUMMARY

Interstitial lung disease (ILD) in infants is caused by entities that are distinct from those that cause ILD in older children and adults. Growing recognition and understanding of the various entities that cause ILD in children has led to the need for improved classification and evaluation. A committee was convened by the American Thoracic Society (ATS) to develop guidelines to inform clinicians, patients, and organizations regarding the classification, evaluation, and management of childhood ILD (chILD).

Diagnosis

- All neonates and infants (<2 yr of age) with diffuse lung disease (DLD) should have common diseases that can cause DLD excluded as the primary diagnosis. These include cystic fibrosis, congenital or acquired immunodeficiency, congenital heart disease, bronchopulmonary dysplasia, pulmonary infection, primary ciliary dyskinesia presenting with newborn respiratory distress, and recurrent aspiration.
- Once the common diseases that can cause DLD have been eliminated, a neonate or infant with DLD is regarded as having "chILD syndrome" if at least three of the following four criteria are present: (*1*) Respiratory symptoms (cough, rapid and/or difficult breathing, or exercise intolerance); (*2*) respiratory signs (tachypnea, adventitious sounds, retractions,

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digital clubbing, failure to thrive, or respiratory failure); (*3*) hypoxemia; and (*4*) diffuse abnormalities on a chest radiograph (CXR) or computed tomography (CT) scan.

- Neonates and infants who are diagnosed with one of the common diseases that can cause DLD, but whose severity of illness is out of proportion to that diagnosis, require further evaluation for coexisting chILD syndrome.
- For patients with chILD syndrome:
  - We recommend diagnostic testing to determine the exact chILD diagnosis (*strong recommendation*).
  - We recommend echocardiography as part of the initial evaluation to rule out structural cardiovascular disease and pulmonary hypertension (*strong recommendation*).
  - We suggest thin section CT scanning of the chest to optimally characterize the nature and distribution of the lung disease (*weak recommendation*).
  - We suggest that thin-section CT scans be performed at centers with expertise in performing pediatric chest CT, if possible (*weak recommendation*).
  - For all patients, we recommend performing thin-section CT using the lowest radiation dose that provides adequate diagnostic information (*strong recommendation*).
  - We suggest infant pulmonary function testing (iPFT) to better characterize physiologic alterations (*weak recommendation*).
  - We suggest flexible bronchoscopy with bronchoalveolar lavage (BAL) to exclude infection or airway abnormalities as possible causes of DLD (*weak recommendation*).
- For neonates and infants with chILD syndrome in whom other diagnostic investigations have not identified the precise chILD disease, or in whom there is clinical urgency to identify the precise chILD disease, we recommend surgical lung biopsy (*strong recommendation*).
  - For patients with chILD syndrome who undergo surgical lung biopsy, we recommend that the biopsy be performed using video-assisted thoracoscopy (VATS) rather than open thoracotomy, if expertise is available (*strong recommendation*).
  - Lung biopsy specimens should be handled as suggested by published protocols, with separate portions of the biopsy undergoing formalin fixation for histopathology and immunohistochemistry, microbiologic culture, freezing for possible immunofluorescence or other special studies, and fixation for electron microscopy.

Special Considerations

- For newborns who present with chILD syndrome and severe disease, rapidly progressive disease, or a family history of adult ILD or chILD, we recommend testing for genetic abnormalities associated with neonatal DLD (i.e., mutations in the genes *SFTPB*, *SFTPC*, and *ABCA3*, which respectively encode the proteins SP-B, SP-C, and ABCA3) (*strong recommendation*). All such testing should be performed by Clinical Laboratory Improvement Amendments–approved laboratories.
- For newborns who present with chILD syndrome, congenital hypothyroidism, and hypotonia, we recommend genetic testing for *NKX2.1* (i.e., thyroid transcription factor [TTF]) mutations or deletions (*strong recommendation*).
- For newborns who present with chILD syndrome leading to respiratory failure and refractory pulmonary hypertension, we suggest testing for *FOXF1* deletions or mutations (*weak recommendation*).
- For infants beyond the neonatal period who have chILD syndrome, we recommend testing for *SFTPC* and *ABCA3* mutations if initial studies do not provide a diagnosis (*strong recommendation*).
- For infants beyond the neonatal period who have chILD syndrome with alveolar proteinosis and whose genetic testing for *SFTPC* and *ABCA3* are negative, we suggest genetic testing for *CSF2RA* and *CSF2RB* (i.e., colony-stimulating factor receptor 2 [CSF2R] α and β chains), if available, and obtaining serum levels of granulocyte-macrophage colony–stimulating factor (GM-CSF) (*weak recommendation*). Genetic testing for *CSF2RA* and *CSF2RB* is currently only available in the context of research studies, but it is expected to become more available in the near future.
- For infants beyond the neonatal period who have chILD syndrome with hypothyroidism and/or neurologic abnormalities (e.g., hypotonia or choreoathetosis), or those with severe disease, a family history of adult ILD or chILD, or other features of surfactant dysfunction mutations and negative testing for ABCA3 and SFTPC, we recommend genetic testing for *NKX2.1* (i.e., TTF-1) mutations or deletions (*strong recommendation*).

Management

- There have been no controlled trials of any therapeutic interventions in chILD syndrome. Therefore, management is based upon indirect evidence, case reports, and unsystematic observations (i.e., clinical experience).
- For infants with severe, life-threatening chILD diseases, we recommend referral to a pediatric lung transplantation center after discussion with the family (*strong recommendation*).
- Given the limited evidence of a beneficial effect on clinical outcomes and the well known side effects of immunosuppressive medications, the decision about whether or not to initiate a trial of immunosuppressive therapy must be made on a case-by-case basis. Considerations include the severity of disease, rate of progression, prognosis without treatment, comorbidities, and family values and preferences. All patients with chILD syndrome who receive a trial of pharmacological therapy should be closely monitored for side effects.
- All patients with chILD syndrome should receive supportive and preventive care. This may include treatment of hypoxemia, nutritional failure, and comorbidities, as well as interventions to prevent infection.
- Families of patients with chILD syndrome should receive education and support from care providers.
- Genetic counseling should be made available to the family members of patients with chILD syndrome, particularly if asymptomatic family members may be carriers of a dominant gene mutation, such as *SFTPC* or *NKX2.1*.

Research Priorities

Limited knowledge exists in the field of chILD, despite the significant impact these diseases have on children, families, health care economics, and, potentially, subsequent adult disease. It is

essential that research be conducted and funding opportunities be developed for children with these disorders. The goals of research include the following:

- Establish accurate incidence and prevalence rates of specific chILD diagnoses.
- Determine the natural history and clinical phenotypes of specific chILD diagnoses and their relationships to adult pulmonary disease through international databases.
- Further delineate mechanisms of normal lung development and growth and their alteration in DLD and specific chILD diagnoses.
- Determine the genetic, epigenetic, cellular, and molecular basis of chILD diagnoses, incorporating animal and tissue culture models, as well as clinical biomarkers and systems biology ("-omics") approaches.
- Conduct multicenter studies of protocol-driven diagnostic, therapeutic, and quality approaches to chILD syndrome to ascertain the optimal methods of clinical evaluation and management.
- Create high-quality, accessible tissue repositories and biobanks to enhance research efforts
- Promote common terminology for chILD diagnoses and their continued inclusion in future revisions of *The International Classification of Diseases.* This will increase recognition of specific entities, enable studies of their incidence and prevalence, and improve and track health care utilization for these entities.

INTRODUCTION

ILD is a nonspecific term referring to disorders that feature remodeling of the lung interstitium and distal airspaces, with resultant abnormal gas exchange. In childhood, the term "interstitial" lung disease may be misleading, because some diseases are considered ILD based upon similarities in the clinical presentation and diagnostic evaluation, even though the primary pathology may occur outside of the interstitium. For this reason, we refer to these diseases as DLD, rather than ILD. A historical perspective of chILD is provided in the online supplement.

Recent developments highlight the need for a new approach to the classification, diagnosis, and management of childhood DLD. These developments include: (*1*) the recognition that the natural history of ILD among children is significantly different from that among adults; (*2*) the recognition of unique phenotypes, especially in infants and younger children; (*3*) the discovery of genetic abnormalities that cause pediatric ILD; and (*4*) advances in diagnostic techniques.

These *Guidelines* provide a comprehensive and critical review of the evidence, as well as advice regarding the classification, diagnostic evaluation, and management of an entity herein defined as chILD syndrome. The focus of these *Guidelines* is on the neonate and infant (<2 yr old), because most of the recently described novel diagnostic entities disproportionately affect infants. The online supplement provides a historical perspective of chILD syndrome, as well as additional details related to classification, interpretation of imaging studies, genetic testing, typical findings on PFT, and handling the lung biopsy specimen.

METHODS

These Clinical Practice Guidelines were prepared using the methods of ATS (Table 1). The methods are described in detail in the online supplement.

TABLE 1. SUMMARY OF THE METHODOLOGY EMPLOYED IN THE PREPARATION OF THIS GUIDELINE STATEMENT FOR THE AMERICAN THORACIC SOCIETY

Method	Yes	No
Panel assembly		
Included experts for relevant clinical and nonclinical disciplines	X	
Included individual who represents the views of patients and society at large	X	
Included a methodologist with appropriate expertise (documented expertise in conducting systematic reviews to identify the evidence base and the development of evidence-based recommendations)		X
Literature review		
Performed in collaboration with librarian		X
Searched multiple electronic databases	X	
Reviewed reference lists of retrieved articles	X	
Evidence synthesis		
Applied prespecified inclusion and exclusion criteria	X	
Evaluated included studies for sources of bias	X	
Explicitly summarized benefits and harms	X	
Used PRISMA1 to report systematic review		X
Used GRADE to describe quality of evidence		X
Generation of recommendations		
Used GRADE to rate the strength of recommendations		X

Definition of abbreviations: GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; PRISMA1 = Preferred Reporting Items for Systematic Reviews and Meta-Analyses 1.

CLASSIFICATION

ILD in infants and children has been previously categorized in ways that lack a coherent organizing principle (1–3). However, a more organized classification scheme for DLD in children less than 2 years of age was recently published by the chILD Research Network (chILDRN; Table 2) (4–6). We believe that this classification scheme should be used routinely to categorize pediatric DLD.

The chILDRN classification scheme is broadly divided into two categories: "Disorders More Prevalent in Infancy" and "Disorders not Specific to Infancy." An advantage of this classification strategy is that the first category recognizes that some disorders present largely in infancy, but may also develop later in childhood or even adulthood, whereas the second category acknowledges that infants can develop conditions that are more common in older children and adults. The second category is further divided into important subgroups (often according to clinical associations). The chILDRN classification scheme is described further in the online supplement.

DEFINITIONS

There is considerable overlap in the way chILD disorders present (6–10). In children with DLD, tachypnea is consistently the most prevalent sign, occurring in 75–93% of patients (4, 11–13). Hypoxemia is also common, as are crackles and cough (4, 11, 12). Some children present with wheezing or with normal lung sounds (12). Failure to thrive is also common in young children with DLD (4, 11, 12).

The term chILD syndrome has been adopted in an effort to identify a phenotype that requires prompt diagnostic evaluation, from among children with DLD and the nonspecific respiratory signs described previously here (14). The chILD syndrome exists when an infant (<2 yr old) with DLD has had the common causes of DLD excluded as the primary diagnosis and has at least three of the following four criteria: (*1*) respiratory symptoms (e.g., cough, rapid and/or difficult breathing, or exercise intolerance);

TABLE 2. PROPOSED CLASSIFICATION SCHEME FOR PEDIATRIC DIFFUSE LUNG DISEASE

I. Disorders more prevalent in infancy
  A. Diffuse developmental disorders
    1. Acinar dysplasia
    2. Congenital alveolar dysplasia
    3. Alveolar–capillary dysplasia with pulmonary vein misalignment
  B. Growth abnormalities
    1. Pulmonary hypoplasia
    2. Chronic neonatal lung disease
      A. Prematurity-related chronic lung disease (bronchopulmonary dysplasia)
      B. Acquired chronic lung disease in term infants
    3. Structural pulmonary changes with chromosomal abnormalities
      A. Trisomy 21
      B. Others
    4. Associated with congenital heart disease in chromosomally normal children
  C. Specific conditions of undefined etiology
    1. Pulmonary interstitial glycogenosis
    2. Neuroendocrine cell hyperplasia of infancy
  D. Surfactant dysfunction mutations and related disorders
    1. *SPFTB* genetic mutations—PAP and variant dominant histologic pattern
    2. *SPFTC* genetic mutations—CPI dominant histologic pattern; also DIP and NSIP
    3. *ABCA3* genetic mutations—PAP variant dominant pattern; also CPI, DIP, NSIP
    4. Others with histology consistent with surfactant dysfunction disorder without a yet recognized genetic disorder
II. Disorders not specific to infancy
  A. Disorders of the normal host
    1. Infectious and postinfectious processes
    2. Disorders related to environmental agents: hypersensitivity pneumonia, toxic inhalation.
    3. Aspiration syndromes
    4. Eosinophilic pneumonia
  B. Disorders related to systemic disease processes
    1. Immune-related disorders
    2. Storage disease
    3. Sarcoidosis
    4. Langerhans cell histiocytosis
    5. Malignant infiltrates
  C. Disorders of the immunocompromised host
    1. Opportunistic infection
    2. Disorders related to therapeutic intervention
    3. Disorders related to transplantation and rejection syndromes
    4. Diffuse alveolar damage of unknown etiology
  D. Disorders masquerading as interstitial disease
    1. Arterial hypertensive vasculopathy
    2. Congestive vasculopathy, including veno-occlusive disease
    3. Lymphatic disorders
    4. Congestive changes related to cardiac dysfunction
III. Unclassified—includes end-stage disease, nondiagnostic biopsies, and those with inadequate material

Definition of abbreviations: CPI = chronic pneumonitis of infancy; DIP = desquamative cell interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; PAP = pulmonary alveolar proteinosis.

Many of these entities may present as child interstitial lung disease syndrome. This classification scheme was initially proposed in Reference 6.

(*2*) respiratory signs (e.g., resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure); (*3*) hypoxemia; and (*4*) diffuse abnormalities on CXR or a CT scan. Abnormalities in pulmonary function are not included, because PFT may not be available, particularly in younger children. This definition is sensitive for detecting the presence of a chILD disease, but its specificity has not been determined. The definition also has not been studied prospectively (14).

The chILD syndrome requires that more common causes of DLD have been excluded. These include cystic fibrosis, congenital or acquired immunodeficiency, congenital heart disease, bronchopulmonary dysplasia, pulmonary infection, primary ciliary dyskinesia presenting with newborn respiratory distress, and recurrent aspiration. The relationship between DLD, chILD syndrome, specific chILD diagnoses, and potential "masqueraders" are depicted in Figure 1.

***Recommendation: For patients with chILD syndrome, we recommend diagnostic testing to determine the exact chILD diagnosis* (strong recommendation).**

RATIONALE. This recommendation is based upon the observation that diagnostic testing provides either clinically useful information or a specific diagnosis for the vast majority of infants with chILD syndrome. It reflects the committee's judgment that the benefits of confirming an exact chILD diagnosis (i.e., initiating appropriate treatment, avoiding unnecessary or potentially harmful empiric treatment, identifying precipitants, and informing decisions regarding appropriate goals of care and genetic counseling) outweigh the costs, burdens, and harms of diagnostic testing (i.e., initiating inappropriate treatment for false-positive results and foregoing necessary treatment for false-negative results; *see* Table E1 in the online supplement).

The observation that diagnostic testing provides a specific diagnosis for more than 50% of patients suspected of having ILD derives from three multicenter retrospective studies (6, 11, 15) and two single-center prospective case series (13, 16) that described the occurrence of ILDs and DLDs in children and the utility of diagnostic testing, as well as four diagnostic accuracy studies for high-resolution CT (HRCT) in DLDs (17–20). Our confidence in the results of these studies is diminished by the study design, the absence of studies using the current chILD syndrome definition in a general pediatric pulmonary patient population, and the small numbers of patients with some forms of DLD, particularly the more recently recognized entities. Despite these limitations, the recommendation is strong, because we are certain that the importance of the benefits described previously here exceed the importance of the costs, burdens,

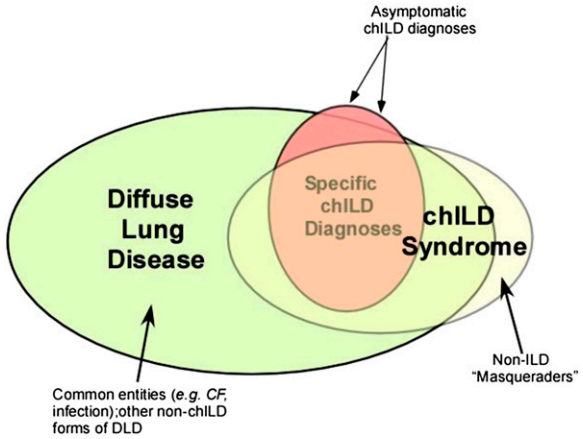

Figure 1. Venn diagram depicting a conceptual framework, which demonstrates the relationships among diffuse lung disease (DLD), childhood interstitial lung disease (chILD) syndrome, and specific chILD diagnoses. Note that chILD syndrome is a subset of DLD, and more common causes of respiratory disease, such as cystic fibrosis and infection, must be excluded before proceeding with investigations directed at diagnosing specific chILD entities. In addition, there are "masqueraders" of DLD, including cardiac, pulmonary vascular, and lymphatic disorders. Although there are recognized specific chILD diagnoses, some may be asymptomatic when identified, such as in certain individuals with known *SFTPC* mutations. Specific chILD diagnoses comprise only a portion of chILD syndrome, as some cases remain unclassified. Future discovery of additional specific diagnostic entities will more fully define chILD syndrome.

and potential harms and, therefore, the vast majority of well informed families would choose additional diagnostic testing.

EPIDEMIOLOGY

There are few data regarding the prevalence of chILD syndrome (12), although it appears that chILD syndrome is rare. Studies that have evaluated the epidemiology of childhood DLD or chILD syndrome are described in the online supplement.

DIAGNOSTIC EVALUATION

Overview

The urgency of the diagnostic evaluation, the choice of diagnostic tests, and the decisions about whether to perform genetic testing and/or to proceed to lung biopsy depend upon numerous factors. These include the clinical context and disease severity, acuity, and duration (Figures 2–4). The trend toward worsening or improvement, age at presentation, immunocompetence, and family history (i.e., whether there are other family members with adult ILD, chILD diagnoses, or a history of neonatal respiratory failure) are also important factors (10, 21–24). Regarding disease severity, this judgment may be based upon the degree of symptoms (25) and gas exchange abnormalities, or the presence of echocardiographic evidence of pulmonary hypertension (26). Imaging studies can demonstrate the distribution and extent of disease, but may not correlate with functional severity, response to therapy, or prognosis.

Diagnostic Tests

Echocardiography. Pulmonary vascular disease and structural heart disease may masquerade as pediatric DLD (15). In addition,

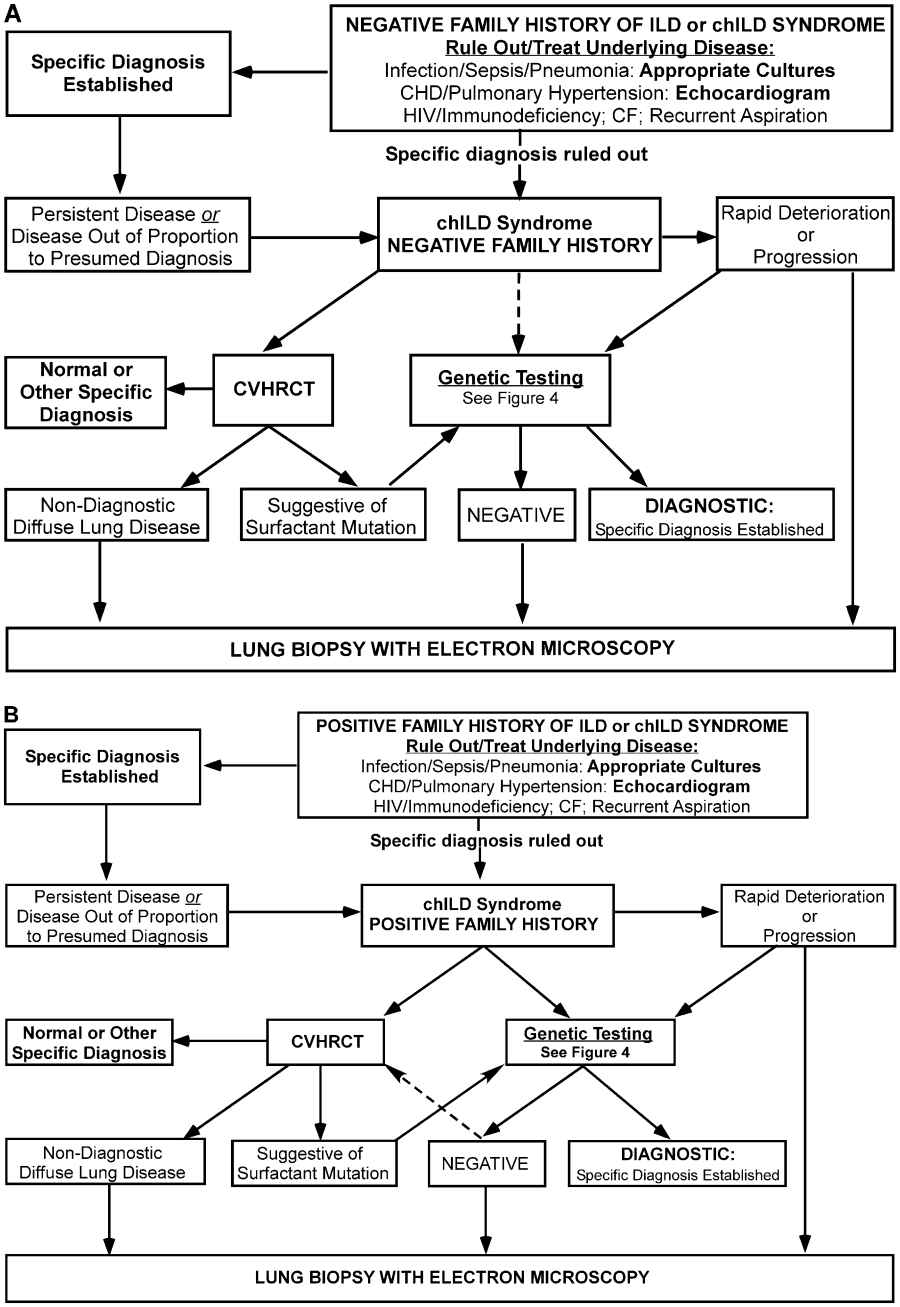

Figure 2. Proposed general diagnostic approach for childhood interstitial lung disease (chILD) syndrome: neonatal onset of severe respiratory disease. (*A*) Negative family history of specific chILD entities or other ILD (including adult ILD). *Dotted lines* indicate paths that may be considered depending on clinical context. (*B*) Positive family history of specific chILD entities or other ILD (including adult ILD; note: genetic analysis of surfactant proteins may take several weeks; lung biopsy may be necessary to guide clinical decision making in rapidly progressive cases). In this and subsequent figures, controlled ventilation high-resolution computed tomography (CVHRCT) is included as the preferred method of CT imaging. However, *see text* for discussion of CVHRCT versus HRCT. CF = cystic fibrosis; CHD = congenital heart disease; EM = electron microscopy; HIV = human immunodeficiency virus.

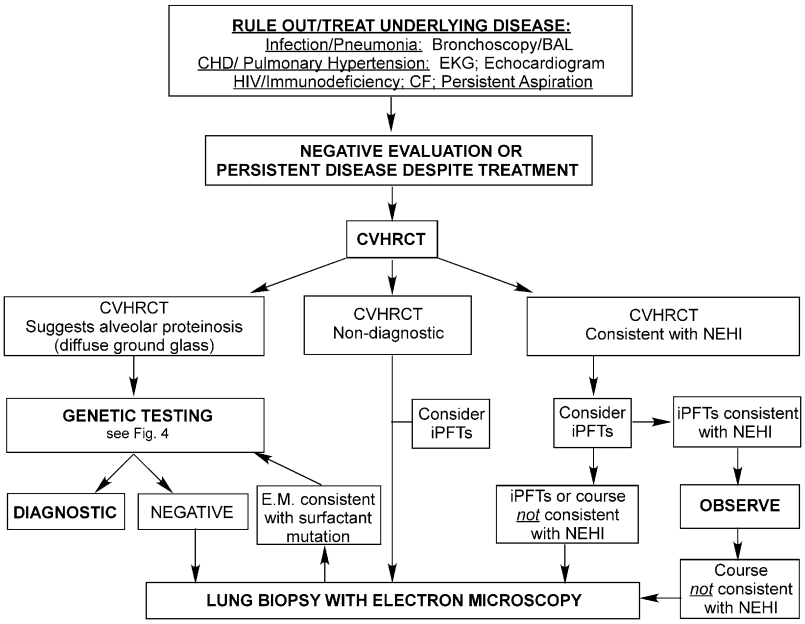

Figure 3. Proposed general diagnostic approach for childhood interstitial lung disease (chILD) syndrome. Evaluation of chronic/persistent symptoms in infants presenting at over 1 month of age. In this and subsequent figures, controlled ventilation high-resolution computed tomography (CVHRCT) is included as the preferred method of CT imaging. However, *see text* for discussion of CVHRCT versus HRCT. BAL = bronchoalveolar lavage; CF = cystic fibrosis; CHD = congenital heart disease; EKG = electrocardiogram; EM = electron microscopy; iPFT = infant pulmonary function test; NEHI = neuroendocrine cell hyperplasia of infancy.

pulmonary hypertension in patients with pediatric DLD is associated with a worse prognosis (25). Thus, an echocardiographic study to estimate right ventricular pressure and to visualize the pulmonary veins is a safe, noninvasive diagnostic test for all infants with suspected chILD syndrome.

***Recommendation: For patients with chILD syndrome, we recommend echocardiography as part of the initial evaluation to rule out structural cardiovascular disease and pulmonary hypertension* (strong recommendation).**

RATIONALE. This recommendation is based upon the observations that cardiac and vascular anomalies are detected by echocardiography in up to 9% of children suspected of having ILD, that echocardiography improves the detection of pulmonary hypertension in the setting of DLD, and that cardiac and vascular anomalies may be treatable. It reflects the committee's judgment that the desirable consequences of identifying cardiac anomalies, vascular anomalies, or pulmonary hypertension (i.e., initiation of appropriate treatment, avoidance of unnecessary or potentially harmful empiric therapies, and ability to provide information to inform decisions regarding the appropriate goals of care) outweigh the undesirable consequences of echocardiography (i.e., the cost and burden of echocardiography, inappropriate reassurance if there is a false-negative result, and unnecessary concern if there is a false-positive result; Table E1).

The observations described here derive from a multicenter retrospective study (6), one single-center retrospective case series study (25), and two single-center prospective case series (13, 26) that evaluated the prevalence of congenital cardiac and vascular disorders in children suspected of having ILD, as well as two diagnostic accuracy studies for echocardiographic evaluation of pulmonary hypertension in adults with DLDs (27, 28). The studies also reported that pulmonary vascular disease negatively affects survival in children with ILD, a finding that is comparable to the negative prognosis of adults with pulmonary hypertension and ILD (29–32).

Our confidence in these results is diminished by the study design, risk of bias (e.g., single-center studies, lack of blinding, lack of a gold standard), small study sizes with few events, indirectness (i.e., the recommendation is intended for children who meet the current chILD syndrome definition, but it is based upon studies conducted in children who did not meet the current definition and adults with advanced lung disease), and inconsistency (i.e., although many studies in children and adults suggested that echocardiography accurately identifies pulmonary hypertension in ILD, others demonstrated that the estimation of systolic pulmonary artery pressure by echocardiography was inaccurate, particularly in adults with advanced lung disease (33)). Despite these limitations, our recommendation is strong, because we are certain that, for the vast majority of patients, the importance of detecting and treating cardiac anomalies, vascular anomalies, and pulmonary hypertension exceeds the costs, burdens, and harms of echocardiography.

Imaging studies. CXRs are usually the first imaging study performed in chILD syndrome. They rarely provide a specific chILD diagnosis, but they are frequently abnormal, and may identify diseases that mimic chILD syndrome (34, 35). CT 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 (36, 37). HRCT further reduces

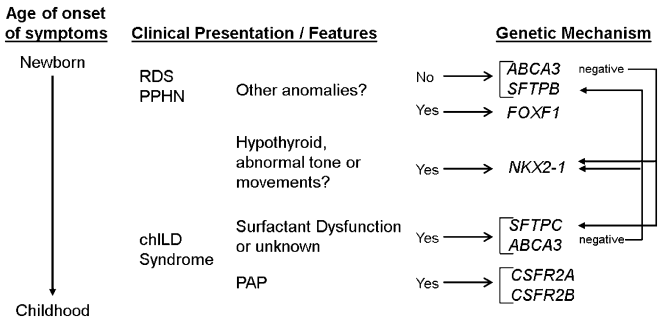

Figure 4. Genetic approach to childhood interstitial lung disease (chILD) diagnosis. Possible genetic mechanisms are listed at *right,* ordered depending upon age of the patient at presentation (*top* to *bottom*), as well as selected phenotypic characteristics. *Arrows* point to initial gene(s) to be analyzed; if results of initial studies were negative, *arrows* on *right* indicate additional genetic studies to be considered. PAP = pulmonary alveolar proteinosis; PPHN = persistent pulmonary hypertension of the newborn; RDS = respiratory distress syndrome.

radiation exposure, while providing higher spatial resolution. In very ill neonates, CT scanning may be more difficult to accomplish. Distinct CT findings for all chILD disorders are not well defined.

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 (38). 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 at TLC or FRC. The sedation may consist of general anesthesia, with prone position if necessary to evaluate dependent opacities that frequently occur in sedated children (39). If sedation or anesthesia cannot be administered, a less invasive approach is lateral decubitus imaging (40), but image quality and reproducibility are usually poorer. No studies have compared CVHRCT to either HRCT or conventional CT in chILD syndrome, and some clinicians question whether the increased risk of anesthesia or sedation is justified (41).

The interpretation of imaging studies is addressed in the online supplement.

Recommendation: For patients with chILD syndrome, we suggest thin-section CT scanning of the chest to optimally characterize the nature and distribution of the lung disease **(weak recommendation).**

RATIONALE. Three modalities are available to evaluate DLD in children: CXR, CT scanning, and magnetic resonance imaging (MRI). This recommendation for thin-section CT is based upon the observations that CT scanning is superior to CXR at identifying DLD, and that CT scanning is superior to MRI in resolution, detecting characteristics of chILD diseases, and correlating with histological findings. The recommendation reflects the committee's belief that the upsides of CT scanning (i.e., potentially achieving a definitive diagnosis without lung biopsy, guiding further diagnostic evaluations, and avoiding unnecessary or potentially harmful empiric treatment) outweigh the downsides (i.e., radiation exposure, cost, and burden; Table E1).

The observations described here derive from two observational studies that found that CT scanning is more likely than CXR to accurately identify DLD in children (17, 35), numerous case series that reported a strong correlation between histologic findings and the thin-section CT scan appearance in children with surfactant protein C mutation (42), neuroendocrine cell hyperplasia of infancy (NEHI) (Figure 5) (20) and other DLDs (17, 19, 35), and two studies that demonstrated that CT scanning is superior to MRI in resolution and in identifying ground glass opacity, normal peripheral bronchi, and air trapping in patients with cystic fibrosis (43, 44). Although cystic fibrosis is not a chILD disorder, resolution is an important determinant of image quality, and the findings of air trapping and ground glass opacity are key observations in chILD. It is important to recognize that MRI techniques for lung imaging are improving rapidly, and, therefore, ongoing comparison of CT scanning and MRI will be necessary.

Our confidence in these findings is tempered by the study design, small studies with few events, and indirectness (i.e., the recommendation is for patients with chILD syndrome in general, but many of the studies enrolled patients with a specific type of DLD). The weak strength of the recommendation reflects our uncertainty about the balance of upsides and downsides, which derives from the poor quality of the evidence and our inability to estimate the absolute benefits, because the prevalence of some forms of DLD are unknown, particularly more recently recognized entities.

Recommendation: For patients with chILD syndrome, we suggest that thin-section CT scans be performed at centers with expertise in performing pediatric chest CT, if possible **(weak recommendation).**

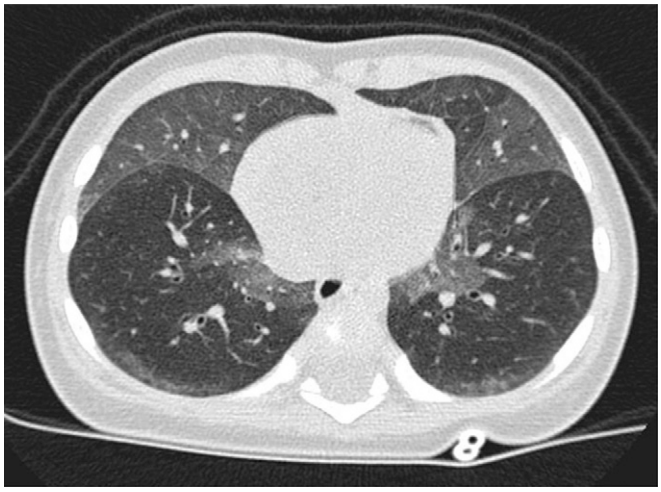

Figure 5. Neuroendocrine cell hyperplasia of infancy (NEHI). Single controlled ventilation high-resolution computed tomography image (at TLC) of the lower chest of a 4-month-old with tachypnea and hypoxemia. The scan demonstrates sharply defined areas of ground glass opacity most marked in the right middle lobe and lingula. Diffuse air trapping was seen on expiratory images, affecting both the ground glass areas and the remaining lung. No additional abnormalities were identified. NEHI was confirmed by lung biopsy.

RATIONALE. This recommendation is based upon our recognition that the techniques used in pediatric imaging can be challenging and require experience to obtain high-quality images that lead to an accurate diagnosis. These techniques include controlling lung inflation for inspiratory and expiratory imaging (45), the use of high-pitch CT technique to minimize imaging time, thus decreasing image blurring due to motion (46), the use of pediatric sedative medication (47, 48) when appropriate, and the use of ventilation support to minimize atelectasis that can obscure areas of the lung parenchyma (49). Each of these techniques appears to improve diagnostic accuracy, although our confidence in such estimates is limited by the study design and small studies with few events.

The recommendation for testing at a center capable of using such techniques indicates our belief that the upsides of these techniques (i.e., improved diagnostic accuracy) outweigh the downsides (i.e., cost and potential need for sedation; Table E1). However, the weak strength of the recommendation reflects our uncertainty about this balance, which is attributable to the poor quality of evidence.

Recommendation: For all patients, we recommend performing thin-section CT using the lowest radiation dose that provides adequate diagnostic information **(strong recommendation).**

RATIONALE. This recommendation is based upon an observational study that found that children who have had CT scans have an increased risk of leukemia and brain tumors (50), as well as observational studies of atomic bomb survivors that suggest a small increase in later cancer risk (51). Although our confidence in the estimates of effect is limited due to the study design, small studies with few events, and indirectness (i.e., some supporting data is extrapolated from atomic bomb survivors rather than CT scan recipients), our recommendation is strong, because of the relative importance of the benefit (i.e., reduction in cancer risk) compared with the harm (i.e., slightly diminished image resolution; Table E1).

PFT. Using the raised-volume rapid thoracic compression (RVRTC) method, spirometry and plethysmographic lung volumes can be performed in sedated infants (52, 53), including those requiring supplemental oxygen therapy. The technique is now performed at a large number of pediatric centers in the United States and Canada. Standard procedures for RVRTC have been published (54), as well as normal reference values for RVRTC forced flows (55), fractional lung volumes (52), and bronchodilator responsiveness (56). Other measurements (e.g., diffusing capacity) have not been standardized for routine use in infants.

Typical PFT findings in chILD syndrome are described in the online supplement.

***Recommendation: For infants with chILD syndrome, we suggest infant PFT to better characterize physiologic alterations* (weak recommendation).**

RATIONALE. This recommendation for infant PFT is based upon the observation that infant PFT reliably identifies physiologic alterations in patients with chILD syndrome. It reflects our belief that the desirable consequences of obtaining accurate information about physiologic abnormalities (i.e., informing judgments about disease severity and prognosis that can guide clinical decisions) exceed the undesirable consequences of infant PFT (i.e., side effects of sedation, burden, and cost; Table E1).

The observations described above derive from two case series (57, 58) and one single-center retrospective cohort study (59–62). These studies demonstrated that infant PFT reliably identifies physiologic alterations in patients with chILD syndrome, especially in NEHI. Studies also suggested that infant pulmonary function may correlate with bombesin immunostaining of neuroendocrine cells found on lung biopsy tissue (58), as well as future pulmonary function and oxygen need (62).

Our confidence in these results is limited by the study design, risk of bias (i.e., only single-center studies), and selection bias (i.e., failure to enroll consecutive patients). The recommendation is weak, because our certainty that the desirable consequences outweigh the undesirable consequences is diminished by our low confidence in the supporting evidence.

Bronchoscopy with BAL. Bronchoscopy with BAL is used to assess and sample the airways and alveoli (63, 64). Bronchoscopy with BAL is the most commonly used invasive technique in patients with DLD, because it is relatively safe, easily performed, and readily available (65). A European Respiratory Society (ERS) task force report outlined the technical aspects, normal values, and indications for BAL in children (66). A modification of the diagnostic considerations for BAL findings in children is in Table 3. However, the cellular constituents of BAL do not exactly reflect the cellular composition of the interstitial space (67). As a result, it has limited value in identifying the specific ILD, assessing disease progression, or guiding therapy in adults with ILD (67, 68), as well as in children with chILD syndrome (69). A single study has suggested that pro–surfactant protein (SP) C protein is increased in BAL effluent of patients with known *SFTPC* mutations (70); however, the use of BAL as a sensitive and specific diagnostic tool in these patients requires further investigation. Recent reports of analysis of individual cytokines (71) or broader proteomics (72) in BAL of infants with chILD syndrome suggest that some of these entities, particularly NEHI, may have specific "biometric signatures," although further investigation is necessary to corroborate these findings.

The primary benefit of bronchoscopy with BAL in chILD syndrome is to obtain specimens for microbiologic studies to exclude infection (73, 74). The possibility of performing mucosal or carinal biopsy to evaluate epithelial histology and ciliary structure is an added benefit, although there are only limited reports of this procedure in older children (75, 76).

TABLE 3. DIAGNOSTIC BRONCHOALVEOLAR LAVAGE FINDINGS

Diagnostic BAL findings
Patients with suspected infections
Positive cultures or microbiological testing in the appropriate clinical setting:
Positive viral cytopathologic findings in the appropriate clinical setting:
In all patients
Hemosiderin-laden macrophages: alveolar hemorrhage syndromes
PAS-positive granular material with hypocellularity: aveolar proteinosis (consider surfactant dysfunction mutation or GM-CSF–related disorders)
Intracytoplasmic pentalaminar inclusion bodies (EM) or positive CD1a staining: pulmonary histiocytosis
Suggestive BAL findings
BAL neutrophilia
Infectious lower airway disease (pneumonia, bronchitis, bronchiectasis)
Aspiration syndromes
Diffuse alveolar damage/ARDS
BAL eosinophilia
Drug-induced DLD
Eosinophilic lung disease
Churg-Strauss syndrome
Asthma
Allergic bronchopulmonary mycosis
Parasitic disease
Fungal infection
Lipid-laden macrophages
Suggestive, but not diagnostic, of aspiration
BAL lymphocytosis
Predominant CD-4$^+$ cells*
Sarcoidosis
Predominant CD-8$^+$ cells*
Pulmonary histiocytosis
Hypersensitivity pneumonitis
Drug-induced ILD
Collagen-vascular disease
Miscellaneous findings
Storage cells typical of Niemann-Pick disease

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; DLD = diffuse lung disease; EM = electron microscopy; GM-CSF = granulocyte-macrophage colony–stimulating factor; ILD = interstitial lung disease; PAS = periodic acid-Schiff.

Data from Reference 66.

* This is only applicable if flow cytometry is carried out on BAL specimen; this is not widely applied in pediatric clinical practice.

Cytologic studies may be useful for excluding alternative causes of DLD, such as pulmonary hemorrhage syndromes (77, 78), pulmonary alveolar proteinosis (79–81), pulmonary histiocytosis (82–84), sarcoidosis (85), Niemann-Pick disease (86), and aspiration (87). Findings consistent with pulmonary alveolar proteinosis should lead to an investigation of surfactant dysfunction mutations, GM-CSF pathway abnormalities, and lysinuric protein intolerance (80, 88–95). Evidence of aspiration may be obtained by lipid staining of alveolar macrophages (96), although the sensitivity and specificity of the finding is questionable (97, 98). Measuring gastric pepsin levels (99) and/or determining alveolar macrophage localization of milk proteins (100, 101) are more recently developed techniques, which are still undergoing study.

A recent ATS *Clinical Practice Guideline* on the clinical utility of BAL cellular analysis in ILD discussed the combined use of BAL cellular analysis, HRCT scanning, and clinical information to better diagnose ILD (102). Although directed at ILD in adults, rather than pediatric patients, this *Guideline* underscores the lack of specificity of BAL cellular constituents, as well as the inability to use BAL cellular results as predictive of the course of an individual patient's illness.

***Recommendation: For patients with chILD syndrome, we suggest flexible bronchoscopy with BAL to exclude infection or airway abnormalities as possible causes of DLD* (weak recommendation).**

RATIONALE. This recommendation is based upon evidence that infectious etiologies are detected in the airways of a significant

proportion of immunosuppressed infants with DLD or immunocompetent infants with diffuse pulmonary infiltrates, and that, occasionally, a specific diagnosis is made. It reflects our judgment that the upsides of excluding infection, excluding airway abnormalities, and/or potentially making a specific diagnosis (i.e., initiation of appropriate treatment, avoidance of unnecessary or potentially harmful empiric therapies, and provision of information to inform decisions regarding the appropriate goals of care) outweigh the risks (i.e., hypoxemia, bronchospasm), burden, and cost of flexible bronchoscopy in most patients (Table E1).

There is a plethora of literature concerning BAL in children (*see* Ref. 66), but only a few studies have addressed BAL findings in specific chILD entities, such as *SFTPC* mutations (70). The evidence that informed our recommendation was from several case series in which BAL found an infectious etiology in approximately one-half of infants with DLD who were immunosuppressed due to the treatment of malignancy (64) and roughly one-third of immunocompetent infants with diffuse pulmonary infiltrates (64, 73, 87). These series found that an infectious etiology was the most common finding, and that specific diagnoses were determined by BAL in a minority of patients. Our confidence in these estimates is limited by the study design (i.e., case series), small sample sizes, and indirectness (i.e., the series included many immunosuppressed patients who had received chemotherapy, but our recommendation is for patients with chILD syndrome). The recommendation is weak because our certainty that the desirable consequences of flexible bronchoscopy outweigh the undesirable consequences is diminished by our low confidence in the supporting evidence.

Although our recommendation was driven by the ability of BAL to exclude infection and to make a specific chILD diagnosis, we recognize that BAL may detect other abnormalities in patients with DLD. BAL may be useful for documenting the presence of blood or hemosiderin-laden macrophages in the lower respiratory tract (78), although this does not provide a specific explanatory diagnosis (103). The accuracy of BAL for the diagnosis of gastroesophageal reflux is the subject of debate, and several studies suggest that it is neither sensitive nor specific (97, 98). Investigators have used BAL histologic studies to confirm abnormal cell markers in patients previously diagnosed with Langerhans histiocytosis (82, 84), and inflammatory cytokine levels have been investigated in BAL fluid from patients previously diagnosed with sarcoidosis (85).

Genetic testing. Several single-gene disorders have been identified that can result in chILD syndrome (104–106). Patients are generally selected for genetic testing if the clinician recognizes that the patient has the clinical, radiographic, and/or histopathologic characteristics of a genetic disorder. The phenotypic manifestations of single-gene disorders overlap considerably; therefore, more than one gene is often analyzed in a patient. Prioritization of the genes to be analyzed depends upon features such as the age of presentation, mode of inheritance, or presence of extrapulmonary manifestations.

In newborns, the clinical phenotype of severe hypoxemic respiratory failure and pulmonary hypertension may result from alveolar–capillary dysplasia with misalignment of the pulmonary veins (ACD-MPV) and mutations in *SFTPB*, *ABCA3*, and possibly *SFTPC*. Newborns with ACD-MPV also have cardiac, gastrointestinal, or genitourinary malformations (107).

Another clinical phenotype that may present as either diffuse neonatal disease or nonspecific chronic respiratory symptoms later in life manifests with hypothyroidism and/or neurological findings—specifically, chorea (108). The neurological manifestations may not be apparent in the neonatal period (109). This phenotype may be due to loss-of-function mutations in or gene deletions of one *NKX2.1* allele (110–115).

In infants and young children, the constellation of DLD, failure to thrive, and pathological findings of alveolar proteinosis may be due to loss-of-function mutations or deletions of both alleles in the genes (*CSF2RA* and *CSF2RB*) that encode the α and β subunits of the receptor for GM-CSF (91, 92).

Single-gene disorders associated with chILD syndrome, their clinical manifestations, and genetic testing are described in greater detail in the online supplement. Although genetic testing may be relatively expensive, it is rarely harmful, and can provide a definitive diagnosis, obviate unnecessary procedures and interventions, and potentially provide important prognostic information for families and physicians. These considerations factor strongly in the strength of the recommendations stated subsequently here. However, we should note that the sensitivity and specificity of genetic testing for chILD disorders has not been formally evaluated and, therefore, the frequency of false-positive and false-negative results cannot be estimated. During our deliberations regarding genetic testing, we assumed that the frequency of false-positive and false-negative results is low. Limitations of genetic testing are discussed further in the online supplement.

Our specific recommendations with rationales concerning the use of genetic testing are addressed subsequently here in the sections entitled AGE-SPECIFIC CONSIDERATIONS: NEWBORNS WITH SEVERE CHILD SYNDROME and AGE-SPECIFIC CONSIDERATIONS: INFANTS WITH SLOWLY PROGRESSIVE CHILD SYNDROME.

Lung biopsy. Few studies have addressed the indications or diagnostic utility of lung biopsy in chILD syndrome (Figure 6). Nevertheless, it is widely accepted that the potential benefits of lung biopsy outweigh the risks in most children with acute respiratory deterioration, prolonged lung disease, or unresolved lung disease (116–123), particularly infants and young children on extracorporeal membrane oxygenation (124–126).

Surgical approaches to lung biopsy include limited open-lung biopsy (OLB) (i.e., open thoracotomy) (127), VATS (128), and transbronchial and percutaneous needle biopsy (129–131). OLB has been the primary surgical approach in young children (120, 121, 132, 133). However, VATS visualizes a greater percentage of the lung and permits the sampling of different lobes with the same incision sites (a consensus statement recommends multiple biopsy sites [134], even though there are limited data to support this approach [58]). Studies that have evaluated pediatric lung biopsy using VATS found less postoperative and long-term morbidity compared with OLB (16, 135, 136). VATS also appears to be associated with less postoperative pain, shorter recovery time, and superior cosmetic results compared with a large thoracotomy incision. For these reasons, VATS is replacing OLB as the primary lung biopsy technique in pediatric patients. Transbronchial and percutaneous needle biopsies are limited by the small amount of tissue obtained.

Genetic testing has obviated the need for biopsy in some patients (137), but many patients still require tissue sampling. As an example, critically ill newborns receiving aggressive pulmonary support (e.g., mechanical ventilation, supplemental oxygen, inhaled nitric oxide, and/or extracorporeal membrane oxygenation) may require a lung biopsy to obtain the diagnosis in a timely manner. Because many conditions that manifest this way have a high early mortality (e.g., ACD-MPV or presumptive *ABCA3* mutation–related lung disease), timely diagnostic information could significantly alter treatment options (e.g., lung transplantation, withdrawal of support) (138). Figure 6 shows the typical microscopic appearance of three entities included in the differential diagnosis of DLD in infancy: pulmonary interstitial glycogenosis, NEHI, and *SFTPC* mutation.

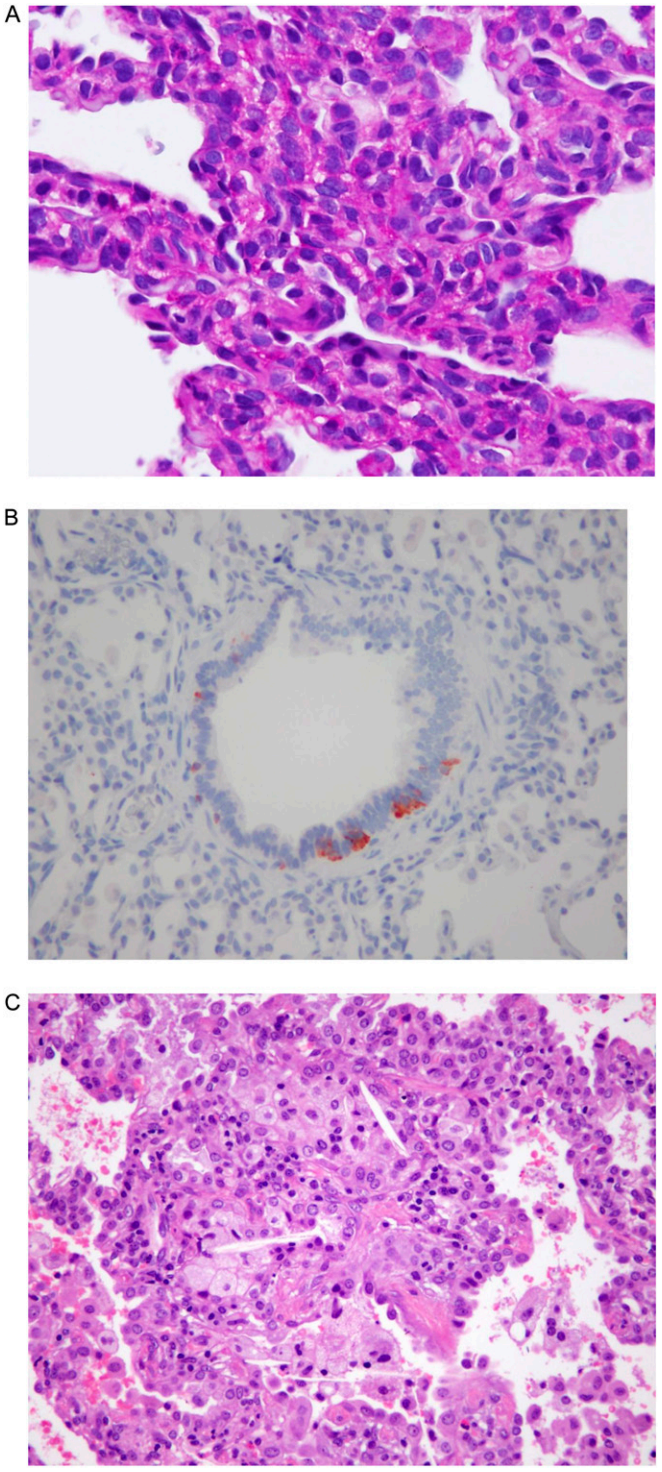

Figure 6. (*A*) Pulmonary interstitial glycogenosis. The alveolar interstitium is widened by bland-appearing vacuolated foamy cells that contain glycogen. Due to loss of glycogen during tissue processing, only rare biopsies, such as this one, will have periodic acid-Schiff (PAS)–positive material within the interstitial cells. For most biopsies, intracellular glycogen is best demonstrated by ultrastructural (i.e., electron microscopic) examination (PAS stain). (*B*) Neuroendocrine cell hyperplasia of infancy (NEHI). In a normal-appearing background, this bronchiole contains multiple clusters of Bombesin-immunopositive neuroepithelial cells, a characteristic finding in NEHI (Bombesin immunohistochemistry [197]). (*C*) Surfactant protein (SP)-C mutation. This biopsy from a patient with an SpC mutation shows a chronic pneumonitis of infancy pattern with uniform alveolar epithelial hyperplasia, mild interstitial widening with small numbers of lymphocytes, and patchy intra-alveolar accumulation of foamy macrophages and cholesterol clefts. No proteinaceous material is evident in this region, but it is typically a minor feature in this pattern (hematoxylin and eosin).

Portions of the biopsy should undergo formalin fixation for histopathology and immunohistochemistry, be sent for microbiologic culture, be frozen for possible immunofluorescence or other special studies, and be appropriately fixed for electron microscopy. Handling the lung biopsy specimen is described in the online supplement.

***Recommendation: For neonates and infants with chILD syndrome in whom other diagnostic investigations have not identified the precise chILD disease, or in whom there is clinical urgency to identify the precise chILD disease, we recommend surgical lung biopsy* (strong recommendation).**

Rationale. This recommendation is based upon the finding that lung biopsy is more likely to determine a specific chILD disease than less invasive procedures. It reflects our belief that performing a surgical lung biopsy rather than a less invasive procedure has more upsides (i.e., a higher likelihood of obtaining information that affects treatment decisions, prognosis, family planning, and other therapeutic choices) than downsides (i.e., potential surgical complications, longer recovery time, and more pain) (Table E1).

The finding that lung biopsy is more likely to determine a specific chILD disease than less invasive procedures derives from a single-center prospective case series (13), two large multicenter retrospective studies (6, 65), and 13 small, single-center retrospective studies (12, 16, 118, 120–124, 126, 133, 135, 139, 140). Moreover, numerous retrospective studies found that the lung biopsy results frequently changed treatment decisions (117, 118, 120, 125, 133, 139, 141).

Our confidence in these results is limited due to the study design, risk of bias (i.e., nonconsecutive patient selection and single-center enrollment), and small sample size with few events. The recommendation is strong despite these limitations, because we are certain that the likelihood of confirming a diagnosis (and, therefore, obtaining information necessary to guide decision making) is greater with a surgical lung biopsy than a less invasive procedure, and that the magnitude of this difference outweighs both the likelihood of a surgical complication and the additional recovery time and pain.

***Recommendation: For patients with chILD syndrome who undergo surgical lung biopsy, we recommend that the biopsy be performed using VATS rather than open thoracotomy, if expertise is available* (strong recommendation).**

Rationale. This recommendation is based upon evidence that lung biopsy via VATS has fewer surgical complications, a shorter operative time, and less pain than lung biopsy via open thoracotomy, while providing a similar diagnostic yield. It reflects the committee's judgment that the importance of these benefits of VATS exceeds the importance of better access to the lung that is provided by open thoracotomy (Table E1).

The evidence described here derives from four single-center observational studies (16, 135, 142, 143) that compared the safety, diagnostic yield, operative time, and postoperative course of lung biopsy via VATS with lung biopsy via open thoracotomy in patients with chILD syndrome. Our confidence in the findings is limited by the study design, risk for bias (i.e., nonconsecutive patient selection and single-center enrollment), and small sample size with few events. Despite the limitations of the evidence, the recommendation is strong, because the benefits of VATS described here far exceed those of open

thoracotomy in terms of importance, and, therefore, we are certain that the vast majority of well informed families would choose VATS over open thoracotomy.

Recommendation: Lung biopsy specimens should be handled as suggested by published protocols, with separate portions of the biopsy undergoing formalin fixation for histopathology and immunohistochemistry, microbiologic culture, freezing for possible immunofluorescence or other special studies, and fixation for electron microscopy.

Age-Specific Considerations: Newborns with Severe chILD Syndrome

Initial evaluation of the newborn with chILD syndrome focuses on the severity and rate of progression of the disease, pregnancy and birth histories, and any family history of chILD syndrome, adult ILD, or early infant deaths. Evidence of congenital heart disease (e.g., pulmonary venous abnormalities) is also sought.

CVHRCT is usually the first diagnostic test (Figure 2). In newborns with severe disease, rapidly progressive disease, or a family history, genetic testing and early lung biopsy are often warranted, because such disease has a poor prognosis. These tests are performed early, because the results may influence management choices (Table 4, Figures 2 and 4).

Potential chILD diagnoses in newborns with severe or rapidly progressive DLD that can be diagnosed with genetic testing include the following: surfactant disorders due to ABCA3 or SP-B deficiency, which may resemble respiratory distress syndrome; surfactant disorder due to mutation or deletion of one *NKX2.1* allele, which manifests with respiratory disease, congenital hypothyroidism, and neurological manifestations (e.g., hypotonia, chorea); and abnormalities in lung development (e.g., ACD-MPV due to *FOXF1* mutation or deletion), which manifests as hypoxemic respiratory failure with refractory pulmonary hypertension.

Recommendation: For newborns who present with chILD syndrome and severe disease, rapidly progressive disease, or a family history of adult ILD or chILD, we recommend testing for genetic abnormalities associated with neonatal DLD (e.g., the SFTPB, SFTPC, and ABCA3 mutations)* (strong recommendation). *All such testing should be performed by Clinical Laboratory Improvement Amendments–approved laboratories.

RATIONALE. This recommendation is based upon the observation that approximately 25% of infants with severe refractory DLD have a mutation in *SFTPB*, *SFTPC*, or *ABCA3*. The recommendation reflects our judgment that the benefits of identifying patients with such mutations (i.e., avoiding the risks and burdens of surgical lung biopsy, facilitating decision making regarding lung transplantation and/or palliative care, and counseling for subsequent pregnancies [144–146]) exceed the cost of genetic testing (Table E1). The observation described here is based upon more than 40 case reports (8, 147, 148), case series (149–157), and genetic epidemiology studies (158–160) that estimated the prevalence of *SFTPB*, *SFTPC*, or *ABCA3* mutations among infants with severe refractory DLD. Our confidence in these estimates is limited, because most studies enrolled highly selected patients, which could have biased the results toward a higher estimated prevalence.

Despite the possibility that the prevalence of *SFTPB*, *SFTPC*, and *ABCA3* mutations has been overestimated, our recommendation is strong, because we are certain that the benefits of genetic testing described here exceed the cost in terms of importance, and, therefore, that the vast majority of well informed families would choose genetic testing.

***Recommendation: For newborns who present with chILD syndrome, congenital hypothyroidism, and hypotonia, we recommend genetic testing for NKX2.1 (i.e., TTF) mutations or deletions* (strong recommendation).**

RATIONALE. This recommendation is based upon evidence that newborns and children with mutations in the TTF gene (*NKX2.1*) may present with various combinations of respiratory disease in the newborn period, congenital hypothyroidism, and/or hypotonia. The recommendation reflects our impression that the benefits of identifying patients with such mutations (i.e., avoiding the risks and burdens of surgical lung biopsy, patient and family preferences, information to counsel about the potential for familial disease, and anticipatory monitoring for neurological symptoms) exceed the cost of genetic testing (Table E1).

The evidence described here is from more than 10 case reports (111, 114, 115, 161–163) and case series (110, 113, 164). The major limitations of the evidence are the study design and that the prevalence of the mutation in patients with this triad of findings has never been estimated; therefore, the yield of testing is uncertain. Even if the prevalence of the mutation is low, our recommendation is strong, because we are certain that the benefits of genetic testing described here outweigh the cost in terms of importance, and, therefore, that the vast majority of well informed families would choose genetic testing.

***Recommendation: For newborns who present with chILD syndrome leading to respiratory failure and refractory pulmonary hypertension, we suggest testing for FOXF1 deletions or mutations* (weak recommendation).**

RATIONALE. This recommendation is based upon the observation that up to 40% of newborns with hypoxemia and severe pulmonary hypertension due to ACD-MPV have *FOXF1* deletions or mutations, according to two case reports (165, 166) and a case series (107). The recommendation reflects our judgment that the benefits of identifying patients with such mutations (i.e., avoiding the risks and burdens of surgical lung biopsy, patient and family preferences) exceed the cost of genetic testing (Table E1).

Our confidence in this estimated prevalence of the mutation is limited, because the study enrolled highly selected patients, which could have biased the studies toward a higher estimated prevalence. The recommendation is weak for two reasons. First, the turnaround of results may not coincide with the urgency of establishing a diagnosis for clinical decision making. Second, we are uncertain that the deletions and mutations are sufficiently common among such patients to justify the cost of genetic testing. This uncertainty is due to our lack of confidence in the estimated prevalence of the deletions and mutations, as well as our recognition that most cases of hypoxemia and severe pulmonary hypertension in newborns have other etiologic causes.

TABLE 4. DISORDERS CAUSING SEVERE NEONATAL CHILDHOOD INTERSTITIAL LUNG DISEASE SYNDROME

Acinar dysplasia
Pulmonary hypoplasia/alveolar simplification
Alveolar–capillary dysplasia with misalignment of the pulmonary veins (*FOXF1* mutations)
PIG
Surfactant protein B deficiency (homozygous *SFTPB* mutations)
ABCA3 gene mutations
TTF-1 (*NKX2.1*) mutations
Pulmonary hemorrhage syndromes
Pulmonary lymphangiectasia

Definition of abbreviations: PIG = pulmonary interstitial glycogenosis; TTF = thyroid transcription factor.

Age-Specific Considerations: Infants with Slowly Progressive chILD Syndrome

Infants with chILD syndrome who are more than 1 month of age and have slowly progressive disease can be evaluated in a step-

wise fashion, with noninvasive testing initially and then selective invasive techniques. This approach minimizes unnecessary procedures (Figure 3) (12, 13).

An infant's history may suggest the cause of their DLD. Examples include cystic fibrosis, immunodeficiency, and recurrent aspiration. Gastroesophageal reflux disease with recurrent aspiration has been hypothesized to be a cause of chILD syndrome, because it is present in 26–49% of children with a chILD diagnosis, but this is unproven and requires further investigation (6, 12). CVHRCT may suggest specific chILD diagnoses, most importantly NEHI (Figure 6), and PFTs may be useful (Figure 3), but many infants require genetic testing or lung biopsy for definitive diagnosis.

Potential chILD diagnoses in infants with slowly progressive DLD that can be diagnosed with genetic testing include surfactant disorders due to: ABCA3 or SP-C deficiency; mutations or deletions of both alleles of the genes (*CSF2RA* and *CSF2RB*) encoding the subunits of the receptor for GM-CSF, which manifests with chILD syndrome and alveolar proteinosis; and, mutation or deletion of one *NKX2.1* allele, which manifests with chILD syndrome, congenital hypothyroidism, and neurological manifestations (e.g., hypotonia, chorea).

Recommendation: For infants beyond the neonatal period who have chILD syndrome, we recommend testing for SFTPC and ABCA3 mutations if initial studies do not provide a diagnosis **(strong recommendation).**

RATIONALE. This recommendation is based upon the observation that, among children who present with DLD beyond the neonatal period, the prevalence of mutations in *SFTPC* may be up to 17% (167), and the prevalence of mutations in *ABCA3* may be between 5 and 22% (152, 168). The recommendation reflects our belief that the benefits of identifying a mutation in *SFTPC* or *ABCA3* (i.e., avoiding the need for more invasive evaluation and identifying a disease mechanism that has implications for other family members) outweigh the cost of genetic testing (Table E1).

The prevalence of mutations in *SFTPC* or *ABCA3* are estimated from more than 20 case reports (169–172) and case series (42, 70, 151, 152, 157, 167, 168, 171, 173–177). Our confidence in the estimates is limited by the potential selection bias inherent in some of these studies, which could have biased the results toward a higher estimated prevalence. The recommendation is strong despite our limited confidence in the estimates, because we are certain that the benefits of identifying a mutation in *SFTPC* or *ABCA3* described here outweigh the cost of genetic testing in terms of importance, and, therefore, that the vast majority of well informed families would choose genetic testing.

Recommendation: For infants beyond the neonatal period who have chILD syndrome with alveolar proteinosis and whose genetic testing for SFTPC and ABCA3 are negative, we suggest genetic testing for CSF2RA and CSF2RB (i.e., CSF2R α and β chains), if available, and obtaining serum levels of GM-CSF **(weak recommendation).**

RATIONALE. This recommendation is based upon six case reports of patients with chILD syndrome who had lung pathology findings similar to those observed in adults with alveolar proteinosis due to autoimmune disease. The patients had circulating neutralizing antibodies to GM-CSF, mutations in the genes encoding the α or β subunits of GM-CSF receptor (*CSF2RA* or *CSF2RB*) (91, 92, 178–181), and elevated circulating GM-CSF levels (180). The recommendation reflects our judgment that the benefits of identifying a mutation in *CSF2RA* or *CSF2RB* plus elevated circulating GM-CSF levels testing (i.e., understanding more about the disease, the potential for avoiding lung biopsy, or the possibility of obtaining information that will be of importance to the family) justify the cost of genetic testing (Table E1). The major limitation of the evidence is that the prevalence and spectrum of disease due to such mutations are unknown. The recommendation is weak, because testing is only available under research protocols (but may become more available in the near future), and we are uncertain that the genetic and biochemical abnormalities are sufficiently common among such patients to justify the cost of genetic testing. Current information on the availability of such testing may be found at www.genetests.org.

Recommendation: For infants beyond the neonatal period who have chILD syndrome with hypothyroidism and/or neurologic abnormalities (e.g., hypotonia or choreoathetosis), or those with severe disease, a family history of adult ILD or chILD, or other features of surfactant dysfunction mutations and negative testing for ABCA3 and SFTPC, we recommend genetic testing for NKX2.1 (i.e., TTF-1) mutations or deletions **(strong recommendation).**

RATIONALE. This recommendation is based on case reports and a small case series (115, 164) that described children and young adults with mutations in *NKX2.1*, hypothyroidism, neurologic abnormalities, and pulmonary findings. The recommendation reflects our belief that the benefits of identifying mutations in *NKX2.1* (i.e., avoiding the risks and burdens of surgical lung biopsy, patient and family preferences, information to counsel about the potential for familial disease, and anticipatory monitoring for neurological symptoms) justify the cost of genetic testing (Table E1). The evidence is limited by the study design, lack of detailed information on pulmonary findings and pathology (110, 182), and insufficient numbers of patients to determine prevalence or test characteristics. Despite the poor evidence, the recommendation is strong, because we are certain that the benefits of identifying mutations in *NKX2.1* described here outweigh the cost of genetic testing in terms of importance, and, therefore, that the vast majority of well informed families would choose genetic testing.

Special Considerations: Immunodeficiency

All patients with DLD should be evaluated for immunodeficiency, because infections can cause DLD (116, 128, 183–186). Categorizing any detected immunodeficiency as primary (e.g., severe combined immunodeficiency) (187–190), acquired (e.g., human immunodeficiency virus) (191), or due to immunosuppressive medication may help guide evaluation and treatment.

Identifying an underlying immunodeficiency does not exclude a chILD diagnosis. Many chILD diagnoses are associated with immunologic dysfunction, such as follicular bronchiolitis, lymphocytic interstitial pneumonitis, and constrictive/obliterative bronchiolitis (6, 192–196).

PROGNOSIS

The morbidity and mortality associated with chILD syndrome (and other types of pediatric DLD) is uncertain due to conflicting data. Fan and Kozinetz (25) reported a 64% 5-year survival rate among children with DLD who were 1 month to 18 years old and a 38% 5-year survival rate among those who presented with pulmonary hypertension. In contrast, 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 (11). 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 DLD. The North American chILDRN study (4) included children under 2 years of age who had been diagnosed by lung biopsy, and found a mortality rate of 30%, with 50% of patients experiencing on-going morbidity.

It has become clear that some chILD entities are associated with very high mortality, whereas others have a favorable outcome. As an examples, SP-B deficiency (9, 156) and ACD-MPV (107) have a bleak prognosis, mutations in *ABCA3* (10) and *STFPC* (147, 173, 177) lead to more variable disease, and NEHI has a more favorable prognosis (58, 197).

TREATMENT

There have been no controlled trials of any therapeutic interventions in chILD syndrome. Therefore, management is based upon uncontrolled studies, case series, case reports, and unsystematic observations (i.e., clinical experience), as well as indirect evidence from other patient populations (198).

Interdisciplinary longitudinal care directed by specialists at centers with expertise in the diagnosis and management of chILD syndrome is optimal. Such centers should have multidisciplinary services, including pediatric pulmonology, radiology, surgery, and pathology. The center's staff should include other healthcare professionals, such as social workers, nutritionists, genetic counselors, and respiratory therapists.

Pharmacological Therapy

Immunosuppressive pharmacotherapy (e.g., systemic corticosteroids, hydroxychloroquine) has been reported to be useful in isolated cases of DLD in children, but it has not been well studied in the chILD entities. If a clinician elects to initiate a trial of immunosuppressive therapy, the patient should be closely monitored for side effects. This may include bone density scanning, serial growth measurements, and ophthalmologic screening in children receiving chronic corticosteroids (199, 200), or periodic complete blood counts and ophthalmologic evaluations in children receiving chronic hydroxychloroquine (201, 202).

Recommendation: Given the limited evidence of a beneficial effect on clinical outcomes and the well known side effects of immunosuppressive medications, the decision about whether or not to initiate a trial of immunosuppressive therapy must be made on a case-by-case basis. Considerations include the severity of disease, rate of progression, prognosis without treatment, comorbidities, and family values and preferences. All patients with chILD syndrome who receive a trial of pharmacological therapy should be closely monitored for side effects.

Lung Transplantation

Lung transplantation is an option for infants and children with end-stage lung disease (203–207). There are several reports of the successful transplantation in infants with chILD syndrome (144, 145, 208), although the number of patients reported is small. Infants with chILD syndrome, diagnosis for whom a poor outcome is likely and effective treatment is unavailable (e.g., SP-B deficiency, ACD-MPV, or severely affected infants with mutations in *ABCA3*), should be referred to a center with experience in lung transplantation of infants to be considered for transplantation (145, 146).

Recommendation: For infants with severe, life-threatening chILD diseases, we recommend referral to a pediatric lung transplantation center after discussions with the family (strong recommendation).

RATIONALE. This recommendation is based on the observation that lung transplantation is associated with 5- and 7-year survival rates of 51 and 45%, respectively, in children (209). It reflects the committee's recognition that the potential benefits of lung transplantation referral (i.e., availability of appropriate and knowledgeable counseling for families of such patients and survival among patients who undergo transplantation) outweigh the risks (i.e., perioperative complications and infections or malignancies due to long-term immunosuppression among patients who undergo transplantation), burdens, and costs (Table E1).

The survival data cited here are derived from the 2011 Pediatric Lung and Heart–Lung report from the *Registry of the International Society for Heart and Lung Transplantation*, which encompassed lung transplantations for all causes between 1990 and 2010 (209). The report included only 15 patients under 1 year of age with SFTPB mutations. We found an additional three case series, all from a single institution, that described lung transplantation for mutations of *SFTPB*, *SFTPC*, and *ABCA3* (144–146). The total number of patients transplanted in these series was 25 of the 29 accepted as candidates for the procedure. The long-term survival, as well as complications of transplantation, was not significantly different from infants transplanted for other underlying causes.

Our confidence in the estimated survival and complication rates due to lung transplantation in children is limited by study design (i.e., case series), indirectness (much of the data are from children transplanted for any reason, whereas the recommendation is for children with a chILD disease), and small sample sizes. The recommendation for referral of patients with a severe, life-threatening chILD disease to a lung transplantation center is strong despite the limited quality of the evidence, because the importance of the potential benefits described here far exceed the importance of the risks and costs; thus, we are certain that the vast majority of well informed families would choose referral to a lung transplantation center in this situation.

Supportive and Preventive Care

Patients with chILD syndrome routinely have their pulse oximetry measured to determine whether supplemental oxygen is indicated during the day, during the night, with exercise, and/or during feeding (infants only). Children with severe respiratory impairment due to chILD syndrome may benefit from invasive or noninvasive ventilation.

Many patients with chILD syndrome have poor somatic growth that requires nutritional intervention. Nutritional support has not been studied in chILD syndrome, but evidence of its importance in bronchopulmonary dysplasia and cystic fibrosis lung disease (210–212) suggests that growth should be closely monitored and that nutritional supplementation may be beneficial.

Patients with chILD syndrome should avoid harmful environmental exposures, such as second-hand smoke. They may benefit from the pneumococcal vaccine (213), an annual influenza vaccination (213), and routine childhood immunizations, with the exception of live-virus vaccines in immunosuppressed patients. Respiratory syncytial virus can increase the morbidity and mortality of infants and young children with chronic lung diseases, such as chILD syndrome (214); a recent study found significantly increased risk for respiratory syncytial virus hospitalization in children with chILD (215). For this reason, palivizumab is usually considered in significantly compromised infants and young children, even though there have been no related studies to confirm the theoretical benefits of palivizumab. Immunosuppressed children are routinely given prophylaxis for *Pneumocystis jiroveci*.

Families may benefit from genetic counseling when undergoing genetic testing. This is particularly true if a genetic basis for the patient's disease is revealed or the disease is associated with the development of adult ILD (e.g., *SFTPC* mutations) (177).

Quality of life, family stress, and parental grief have not been studied in patients with chILD syndrome or their families. However, it seems likely that interpersonal stresses adversely affect

the quality of life for patients with chILD syndrome and their families, because this occurs with other chronic pediatric illnesses, such as cystic fibrosis (216). Thus, supportive services and social work assistance should be regularly offered to patients and families. Early involvement in family support groups may help with the stress of a diagnostic workup, even before a specific diagnosis is made. Additional information is available from the chILD Foundation (available online at www.childfoundation.us).

Recommendation: All patients with chILD syndrome should receive supportive and preventive care. This may include treatment of hypoxemia, nutritional failure, and comorbidities, as well as interventions to prevent infection.

Recommendation: Families of patients with chILD syndrome should receive education and support from care providers.

Recommendation: Genetic counseling should be made available to the family members of patients with chILD syndrome, particularly if asymptomatic family members may be carriers of a dominant gene mutation, such as* SFTPC *or NKX2.1.

RESEARCH PRIORITIES

Relatively little is known about many of the entities comprising chILD syndrome, even though they may cause severe disease and there are few therapeutic options. For this reason, future research is essential. Research priorities for chILD syndrome are described in detail in the online supplement.

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