

**An Official ATS Clinical Practice Guideline: Classification, Evaluation, and
Management of Childhood Interstitial Lung Disease (chILD) in Infancy**

Authors: Geoffrey Kurland ^{1,2}, Robin R Deterding ^{1,3}, James S Hagood ^{1,4}, Lisa R
Young ^{1, 5}, Alan S Brody ⁶, Robert G Castile ⁷, Sharon Dell ⁸, Leland L Fan ⁹,
,Aaron Hamvas ¹⁰, Bettina C Hilman ¹¹, Claire Langston ¹², Lawrence M
Nogee ¹³, Gregory J Redding; on behalf of the chILD Research Network

Key words: diffuse lung disease, lung growth abnormalities, surfactant proteins,
neuroendocrine cells (5 key words not in title)

TABLE OF CONTENTS:

Executive Summary

Introduction

Methods

Classification

Definitions

Epidemiology

Diagnostic Evaluation

 Overview

 Diagnostic tests

 Echocardiography

 Imaging studies

 Pulmonary function tests

 Bronchoscopy

 Genetic testing

 Lung biopsy

 Age-specific considerations: Newborns with severe chILD Syndrome

 Age-specific considerations: Infants with slowly progressive chILD

Syndrome

 Special considerations: Immunodeficiency

Prognosis

Treatment

Pharmacological therapy
Lung transplantation
Supportive and preventive care
Research priorities

Abbreviations

ABCA3: ATP Binding Cassette A3

ABCA3: Gene locus encoding for ABCA3

ACD-MPV: Alveolar-Capillary Dysplasia with Misalignment of the Pulmonary Veins

ARDS: Acute Respiratory Distress Syndrome

BAL: Bronchoalveolar lavage

CFA: Cryptogenic Fibrosing Alveolitis

chILD: Childhood Interstitial Lung Disease

CLIA: Clinical Laboratory Improvement Amendments

CPI: Chronic Pneumonitis of Infancy

chILDRN: chILD Research Network

CVHRCT: Controlled ventilation high resolution computed tomography

CXR: Chest radiograph

DLD: Diffuse Lung Disease

DIP: Desquamative Cell Interstitial Pneumonia

ECMO: Extracorporeal Membrane Oxygenation

EM: Electron microscopy

ERS: European Respiratory Society

FRC: Functional residual capacity

GERD: Gastroesophageal reflux disease

GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor

HIV: Human Immunodeficiency Virus

HRCT: High resolution computed tomography

iPFT: Infant Pulmonary Function Test(ing)

ILD: Interstitial Lung Disease

IPF: Interstitial Pulmonary Fibrosis

LIP: Lymphocytic Interstitial Pneumonitis

NEHI: Neuroendocrine Cell Hyperplasia of Infancy

NHLBI: National Heart, Lung, and Blood Institute

NIH: The National Institutes of Health

NKX2.1: gene encoding for Thyroid Transcription Factor-1

OLB: Open Lung Biopsy

PAS: Periodic Acid-Schiff

PFT: Pulmonary Function Test(ing)

PIG: Pulmonary Interstitial Glycogenosis

RLDC: Rare Lung Diseases Consortium

RSV: Respiratory Syncytial Virus

RVRTC: Raised Volume Rapid Thoracic Compression

SCID: Severe Combined Immunodeficiency

SP-B; SP-C: Surfactant Protein-B, -C

SFTPB, *SFTPC*: genes encoding SP-B and SP-C, respectively

TLC: Total Lung Capacity

TTF-1: Thyroid Transcription Factor-1

UIP: “Usual” type Interstitial Pneumonia

VATS: Video-Assisted Thoracoscopic Surgery

VEGF: Vascular Endothelial Growth Factor

ABSTRACT

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 <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.

RESULT: 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 years 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 "chILD 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.

CONCLUSION: After common causes of DLD are excluded, neonates and infants with chILD 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.

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 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 years 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, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse abnormalities on a chest radiograph 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 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 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., *SFTPB*, *SFTPC*, and *ABCA3* mutations) (strong recommendation). All such testing should be performed by CLIA-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) (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-alpha and beta 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), we recommend genetic testing for *NKX2.1* (i.e., Thyroid Transcription Factor-1) (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, co-morbidities, 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. Examples include treatment of co-morbidities and prevention of infection.
- Families of patients with chILD Syndrome should receive education and support from care providers.

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 Diffuse Lung Disease 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 (ICD). 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

Interstitial lung disease (ILD) is a non-specific 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 diffuse lung disease (DLD), rather than ILD. A historical perspective of childhood ILD 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 Childhood Interstitial Lung Disease (chILD) Syndrome. The focus of these guidelines is on the neonate and infant (< 2 years old), since 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 pulmonary function testing, and handling the lung biopsy specimen.

METHODS

These clinical practice guidelines were prepared using the methods of the American Thoracic Society (Table 1). The methods are described in detail in the online supplement.

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 two 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, while 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 above (14). The chILD

Syndrome exists when an infant (<2 years) 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), **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 chest radiograph or a computed tomographic (CT) scan. Abnormalities in pulmonary function are not included because pulmonary function testing 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
ATS chILD Statement

Revision R2

10/13/2012

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 percent 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 interstitial and diffuse lung diseases in children and the utility of diagnostic testing, as well as four diagnostic accuracy studies for high resolution CT (HRCT) in diffuse lung diseases (17-20). Our confidence in the results of these studies is diminished by the study design, the absence of studies utilizing 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 above exceed the importance of the costs, burdens, 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, 3, and 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, 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 non-invasive 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 percent of children suspected of having ILD, that echocardiography improves the detection of pulmonary hypertension in the setting of diffuse lung disease, 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) (see Table E1 in the online supplement).

The observations described above 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 diffuse lung diseases (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., while 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 detecting and treating cardiac anomalies, vascular anomalies, and pulmonary hypertension exceeds the costs, burdens, and harms of echocardiography.

Imaging studies

Chest radiographs (CXR) 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). Computed tomography (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 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 high resolution computed tomography (CVHRT) is a technique that a) facilitates assessment of the extent of air trapping and ground glass opacities, b) prevents dependent atelectasis from masking pathologic abnormalities, and c) 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 Total Lung Capacity (TLC) or Functional Residual Capacity (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 diffuse lung disease in children: chest radiography, CT scanning, and magnetic resonance imaging (MRI). This recommendation for thin section CT is based upon the observations that CT scanning is superior to chest radiography at identifying diffuse lung disease 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) (see Table E1 in the online supplement).

The observations described above derive from two observational studies that found that CT scanning is more likely than chest radiography to accurately identify diffuse lung disease 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), NEHI (20) and other diffuse lung diseases (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 diffuse lung disease). 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).

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) (see Table E1 in the online supplement). 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) (see Table E1 in the online supplement).

Pulmonary Function Testing

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 pulmonary function test findings in chILD Syndrome are described in the online supplement.

Recommendation: For infants with chILD Syndrome, we suggest infant pulmonary function testing to better characterize physiologic alterations (weak recommendation).

Rationale: This recommendation for infant pulmonary function testing is based upon the observation that infant pulmonary function testing 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 pulmonary function testing (i.e., side effects of sedation, burden, and cost) (see Table E1 in the online supplement).

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 pulmonary function testing reliably identifies physiologic alterations in patients with chILD syndrome, especially in Neuroendocrine Cell Hyperplasia of Infancy (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 bronchoalveolar Lavage

Bronchoscopy with bronchoalveolar lavage (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). An ERS task force report outlined the technical aspects, normal values, and indications for BAL in children (66). 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-SPC 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).

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 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 American Thoracic Society (ATS) Clinical Practice Guideline on the clinical utility of bronchoalveolar lavage cellular analysis in ILD discussed the combined use of BAL cellular analysis, high resolution CT 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 bronchoalveolar lavage (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 provide 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 (see Table E1 in the online supplement).

There is a plethora of literature concerning BAL in children (see (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 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.

While 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 extra-pulmonary 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 diffuse lung disease, 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 alpha and beta-subunits of the receptor for Granulocyte-Macrophage Colony Stimulating Factor (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 below. 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 below 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 5). 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 ECMO (124-126).

Surgical approaches to lung biopsy include limited open lung biopsy (OLB) (i.e., open thoracotomy) (127), video-assisted thoracoscopic surgery (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 post-operative and long-term morbidity compared to OLB (16, 135, 136). VATS also appears to be associated with less post-operative 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 [ECMO]) may require a lung biopsy to obtain the diagnosis in a timely manner. Since 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 5 shows the typical microscopic appearance of three entities included in the differential diagnosis of DLD in infancy: Pulmonary Interstitial Glycogenosis (PIG), Neuroendocrine Cell Hyperplasia of Infancy (NEHI), and Surfactant Protein-C mutation.

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) (see Table E1 in the online supplement).

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., non-consecutive 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 video-assisted thoracoscopy rather than open thoracotomy, if expertise is available (strong recommendation).

Rationale: This recommendation is based upon evidence that lung biopsy via video-assisted thoracoscopic surgery (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 (see Table E1 in the online supplement).

The evidence described above derives from four single center observational studies (16, 135, 142, 143) that compared the safety, diagnostic yield, operative time, and post-operative 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, non-consecutive 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 above 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 3, 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 CLIA-approved laboratories.

Rationale: This recommendation is based upon the observation that approximately 25 percent 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 (see Table E1 in the online supplement). The observation described above 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 above 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 neurological findings, we recommend genetic testing for NKX2.1 (i.e., Thyroid Transcription Factor) (strong recommendation).

Rationale: This recommendation is based upon evidence that newborns and children with mutations in the thyroid transcription factor 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 (see Table E1 in the online supplement).

The evidence described above is from more than ten 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 above 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 percent of newborns with hypoxemia and severe pulmonary hypertension due to alveolar capillary dysplasia /misalignment of the pulmonary veins (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 (see Table E1 in the online supplement).

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.

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 non-invasive 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 (GERD) with recurrent aspiration has been hypothesized to be a cause of chILD Syndrome because it is present in 26 to 49% of children with a chILD diagnosis, but this is unproven and requires further investigation (6, 12). CVHRCT may suggest specific chILD diagnoses 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* *CSF2RB*) encoding the subunits of the receptor for granulocyte-monocyte colony stimulating factor (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 (see Table E1 in the online supplement).

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 above 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., Colony Stimulating Factor Receptor 2-alpha and beta chains), if available, and obtaining serum levels of granulocyte-macrophage colony stimulating factor (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 alpha or beta 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 (see Table E1 in the online supplement). 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), we recommend genetic testing for NKX2.1 (i.e., Thyroid Transcription Factor-1) (strong recommendation).*

Rationale: This recommendation is based upon 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 (see Table E1 in the online supplement). 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 above 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 (LIP), 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 et. al (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 (ERS) task force study reported a mortality rate of only 6%, with clinical improvement in 74% of patients, from birth until 16 years old (11). This study included only patients who had symptoms of at least 3 months duration, thereby excluding many of the more rapidly progressive cases of neonatal DLD. The North American chILDRN study (4) included children less than 2 years old 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, while others have a favorable outcome. As 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 (145, 208) (144), 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. Surfactant protein B deficiency, Alveolar-capillary dysplasia with misalignment of pulmonary veins, 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 upon 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; survival among patients who undergo transplantation) outweigh the risks (i.e., perioperative complications; infections or malignancies due to long-term immunosuppression among patients who undergo transplantation), burdens, and costs (see Table E1 in the online supplement).

The survival data cited above derives 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 less than 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 above 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 in order 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 non-invasive 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 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 (RSV) can increase the morbidity and mortality of infants and young children with chronic lung diseases such as chILD Syndrome (214); a recent study found significant increased risk for RSV 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 since 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 (www.childfoundation.us).

Recommendation: All patients with chILD Syndrome should receive supportive and preventive care. This may include treatment of hypoxemia, nutritional failure, and co-morbidities, 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.

ACKNOWLEDGEMENTS

This Statement was supported by Assembly Project Grants from the American Thoracic Society and in part by the Rare Lung Diseases Consortium, National Institutes of Health RR019498 (to B. Trapnell). The authors wish to acknowledge the editorial assistance and advice of Kevin Wilson, MD.

CONTRIBUTIONS

This ATS Guideline was prepared by an ad hoc central writing committee consisting of members of the chILD Research Network. The full list of the chILD Research Network as well as a Conflict of Interest statement follows.

Members of the Central Writing Committee for the chILD Research Network

Alan S. Brody, MD. Division of Pediatric Radiology, Cincinnati Children's Hospital Medical Center; Cincinnati, OH

Robert G. Castile, MD. Center for Perinatal Research, Nationwide Children's Hospital; Columbus, OH

Sharon Dell, MD. Division of Respiratory Medicine, The Hospital for Sick Children; Toronto, Ontario, Canada

Robin R. Deterding, MD. Division of Pediatric Pulmonology, Children's Hospital Colorado and University of Colorado, Aurora, CO

Leland L. Fan, MD. Division of Pediatric Pulmonology, Children's Hospital Colorado and University of Colorado, Aurora, CO

James S. Hagood, MD. Division of Pediatric Respiratory Medicine, Rady Children's Hospital of San Diego; and the University of California – San Diego, La Jolla, CA

Aaron Hamvas, MD. Division of Neonatology, Children's Hospital of St. Louis; St. Louis, MO.

Bettina C. Hilman, MD. Professor Emeritus of Pediatrics, Louisiana State University School of Medicine, Shreveport, LA (Currently in Winchester, VA)

Geoffrey Kurland, MD. Division of Pediatric Pulmonology, Children's Hospital of Pittsburgh; Pittsburgh, PA

Claire Langston, MD. Division of Pediatric Pathology, Texas Children's Hospital; Houston, TX

Lawrence M. Nogee, MD. Division of Neonatology, Johns Hopkins University School of Medicine; Baltimore, MD

Gregory J. Redding, MD. Division of Pediatric Pulmonology, Children's Hospital Medical Center; Seattle, WA

Lisa R. Young, MD. Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, and Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN.

Final editing of this Statement was done by:

Robin R. Deterding, MD, James S. Hagood, MD, Geoffrey Kurland, MD,
and Lisa R. Young, MD

Other Members of the chILD Research Network

<u>Name</u>	<u>Location (City, State or Country if not U.S.)</u>
Daniel W. Young, MD	Birmingham AL
Alejandro J. Colom, MD	Buenos Aires, Argentina
Alejandro M. Teper, MD	Buenos Aires, Argentina
Adam Jaffe, MD	Sydney; Australia
Ernst Cutz MD	Toronto, Canada
Felix Ratjen, MD	Toronto; Canada
John D. Mark, MD	Stanford, CA
Beverly Newman, MD	Stanford, CA
Carlyne Cool, MD	Denver, CO
Steven Abman, MD	Denver, CO
Margaret Anthony, MD	Denver, CO
Csaba Galambos, MD	Denver, CO
Gwen Kerby, MD	Denver, CO
Marzena Krawiec, MD	Denver, CO
David Lynch, MD	Denver, CO
Megan Dishop, MD	Denver, CO
Annick Clement, MD	Paris, France
Jonathan Popler, MD	Atlanta, GA
Pauline Chou, MD	Chicago, IL

Susanna McColley, MD	Chicago, IL
Adrienne Prestridge, MD	Chicago, IL
Young-Jee Kim, MD	Indianapolis IN
Susan C. Coventry, MD	Louisville, KY
Ronald L. Morton, MD	Louisville, KY
Fred Askin, MD	Baltimore, MD
Pamela Zeitlin, MD	Baltimore, MD
Alicia Casey, MD	Boston, MA
Martha Fishman, MD	Boston, MA
T. Bernard Kinane, MD	Boston, MA
Sze Man Tse, MD	Boston, MA
Stuart Sweet, MD	St. Louis, MO
Herman Thomas, MD	St. Louis, MO
Frances White, MD	St. Louis, MO
Pierre Barker, MD	Chapel Hill, NC
W. Adam Gower, MD	Winston-Salem, NC
Daniel Sheehan, MD	Buffalo, NY
William Travis, MD	New York City, NY
Clement Ren, MD	Rochester, NY
Susan Wert, MD	Cincinnati, OH
Bruce Trapnell, MD	Cincinnati, OH
Peter B. Baker, MD	Columbus, OH
Frederick Long, MD	Columbus, OH

Samuel Goldfarb, MD	Philadelphia, PA
Robert P. Guillerman, MD	Houston, TX
George Mallory, MD	Houston, TX
Timothy Vece, MD	Houston, TX
Gail Deutsch, MD	Seattle, WA
Eric L. Effman, MD	Seattle, WA
Theresa Guilbert, MD	Madison, WI
Andrew Bush, MD	London, U.K.

Conflicts of Interest TK

FIGURE AND TABLE LEGENDS

Table 1: Summary of the methodology employed in the preparation of this Guideline Statement for the American Thoracic Society.

Table 2. Proposed Classification Scheme for Pediatric Diffuse Lung Disease (From (6)). Many of these entities may present as chILD Syndrome.

Table 3. Disorders Causing Severe Neonatal chILD Syndrome

Table 4. Diagnostic Bronchoalveolar Lavage (BAL) Findings, modified from DeBlic (66)

Table 5. Areas for Future Research in chILD Syndrome

Figure 1. Venn diagram depicting a conceptual framework, which demonstrates the relationships among Diffuse Lung Disease (DLD), chILD Syndrome, and Specific hILD 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. While there are recognized Specific chILD Diagnoses, some may be asymptomatic when identified, such as 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.

Figure 2. Proposed General Diagnostic Approach for 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, CVHRCT is included as the preferred method of CT imaging. However, see text for discussion of CVHRCT vs HRCT.

Figure 3. Proposed General Diagnostic Approach for chILD Syndrome.

Evaluation of Chronic/Persistent Symptoms in Infants presenting at >1 month of age. In this and subsequent figures, CVHRCT is included as the preferred method of CT imaging. However, see text for discussion of CVHRCT vs HRCT.

Figure 4. Genetic Approach 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 are negative, arrows on right indicate additional genetic studies to be considered. RDS: Respiratory Distress Syndrome PPHN: Persistent Pulmonary Hypertension of the Newborn; PAP:

Pulmonary Alveolar Proteinosis.

ATS chILD Statement

Revision R2

10/13/2012

Figure 5. **5A:** 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)

5B: 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 Neuroendocrine Cell Hyperplasia of Infancy. (Bombesin immunohistochemistry (197))

5C: Surfactant Protein 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 intralveolar 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)

Figure 6: Neuroendocrine Cell Hyperplasia of Infancy (NEHI): Single CVHRCT 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.

TABLE 1

Panel assembly	Yes	No
<ul style="list-style-type: none"> Included experts for relevant clinical and non-clinical disciplines 	X	
<ul style="list-style-type: none"> Included individual who represents the views of patients and society at large 	X	
<ul style="list-style-type: none"> 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	Yes	No
<ul style="list-style-type: none"> Performed in collaboration with librarian 		X
<ul style="list-style-type: none"> Searched multiple electronic databases 	X	
<ul style="list-style-type: none"> Reviewed reference lists of retrieved articles 	X	
Evidence synthesis	Yes	No
<ul style="list-style-type: none"> Applied pre-specified inclusion and exclusion criteria 	X	
<ul style="list-style-type: none"> Evaluated included studies for sources of bias 	X	
<ul style="list-style-type: none"> Explicitly summarized benefits and harms 	X	
<ul style="list-style-type: none"> Used PRISMA1 to report systematic review 		X
<ul style="list-style-type: none"> Used GRADE to describe quality of evidence 		X
Generation of recommendations	Yes	No
<ul style="list-style-type: none"> Used GRADE to rate the strength of recommendations 		X

TABLE 2

Proposed Classification Scheme for Pediatric Diffuse Lung Disease (6).

- 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 Post-infectious 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, non-diagnostic biopsies and those with inadequate material

TABLE 3

Disorders Causing Severe Neonatal chILD Syndrome

Acinar Dysplasia

Pulmonary Hypoplasia / Alveolar Simplification

Alveolar Capillary Dysplasia with misalignment of the pulmonary veins (*FOXF1* mutations)

Pulmonary Interstitial Glycogenosis (PIG)

Surfactant Protein B deficiency (Homozygous *SFTPB* mutations)

ABCA3 gene mutations

TTF-1 (*NKX2.1*) mutations

Pulmonary Hemorrhage Syndromes

Pulmonary Lymphangiectasia

TABLE 4
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: Alveolar 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

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

FIGURE 1.

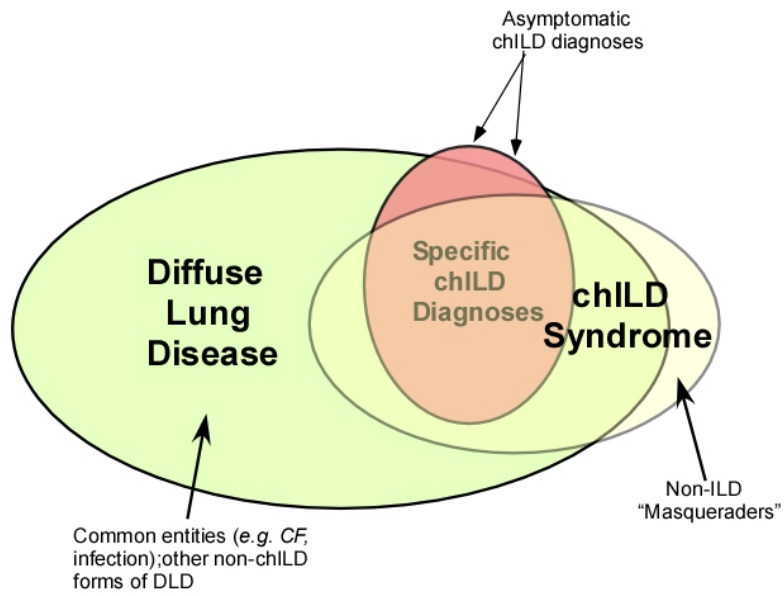


FIGURE 2a.

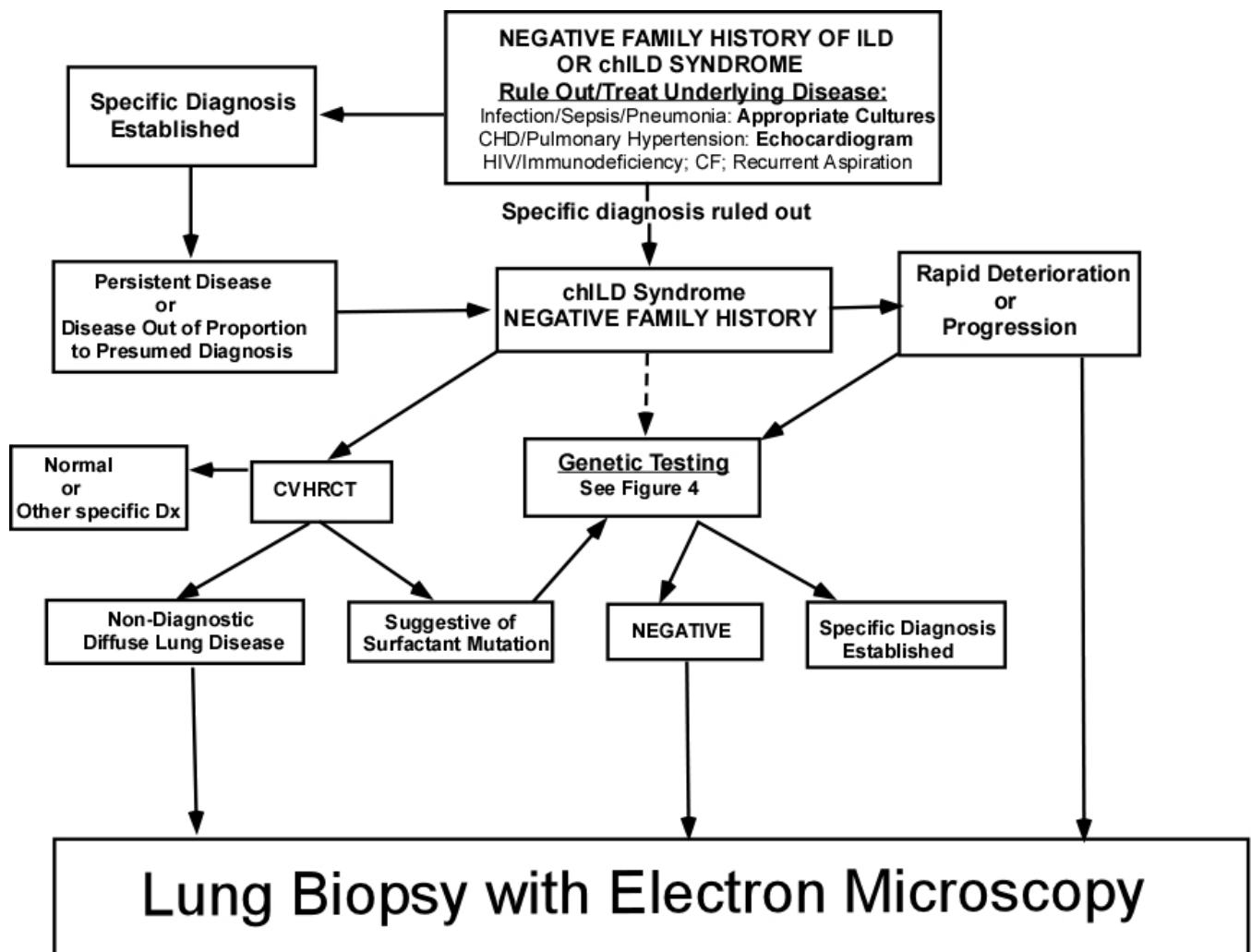


FIGURE 2b.

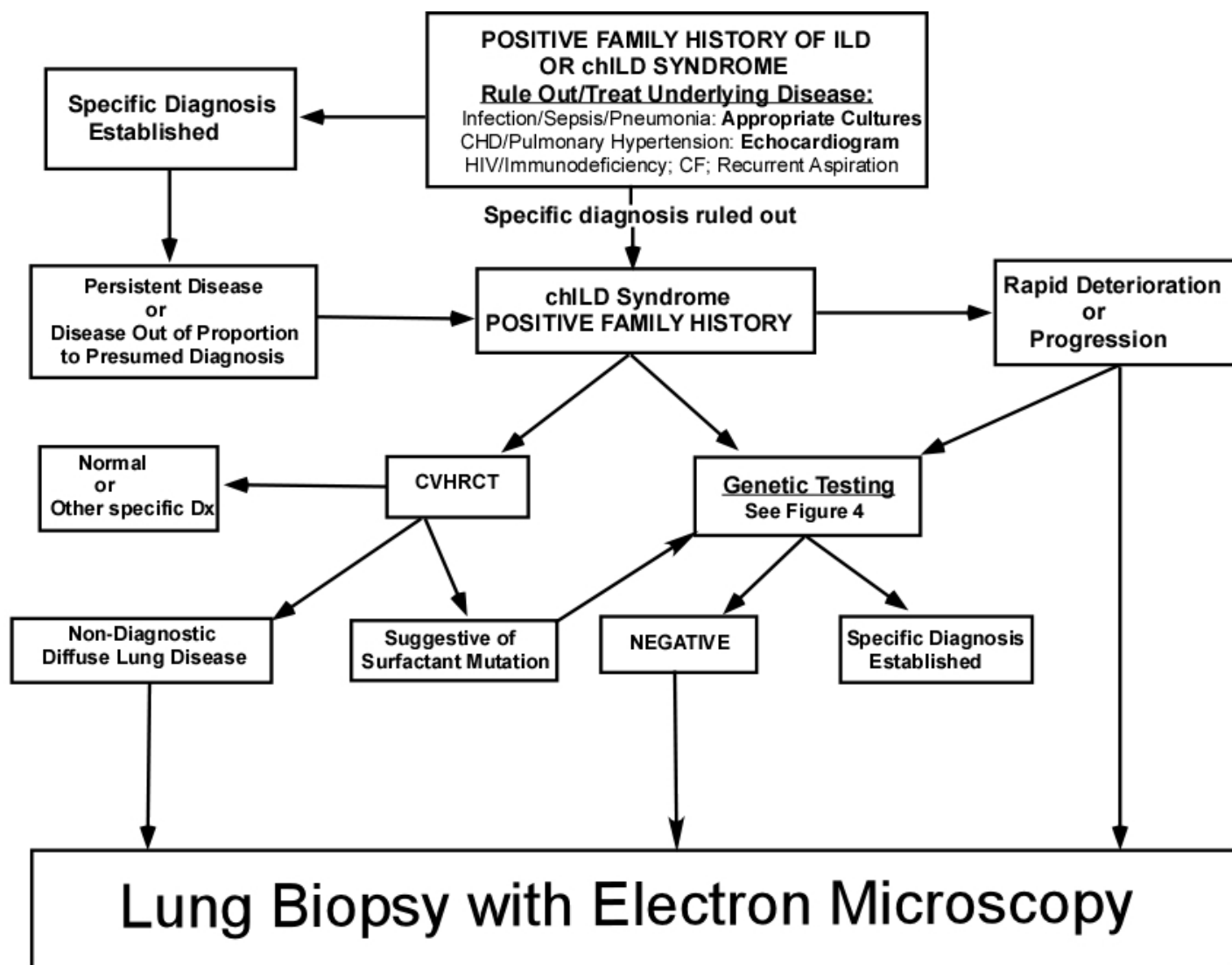


FIGURE 3

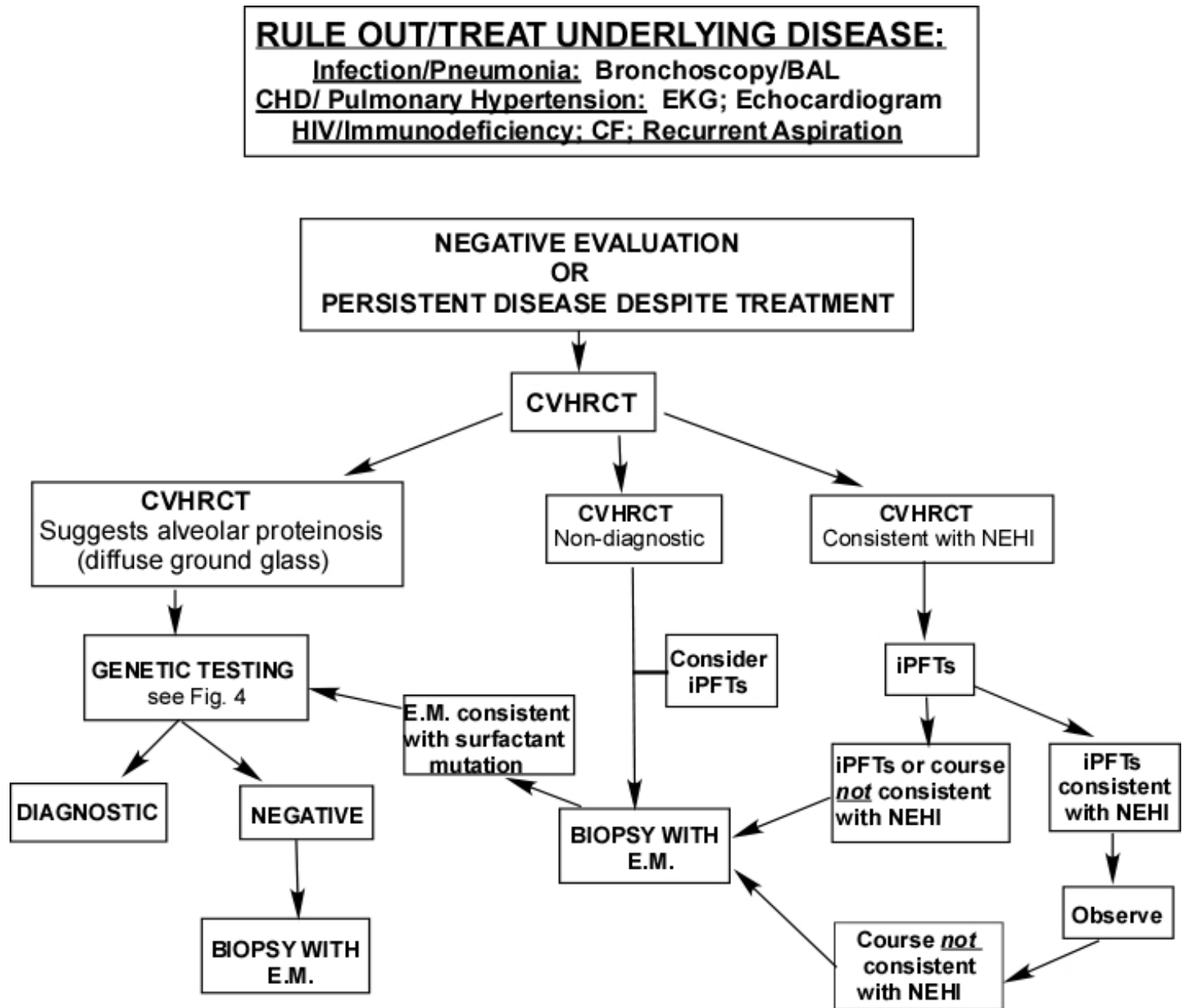


FIGURE 4

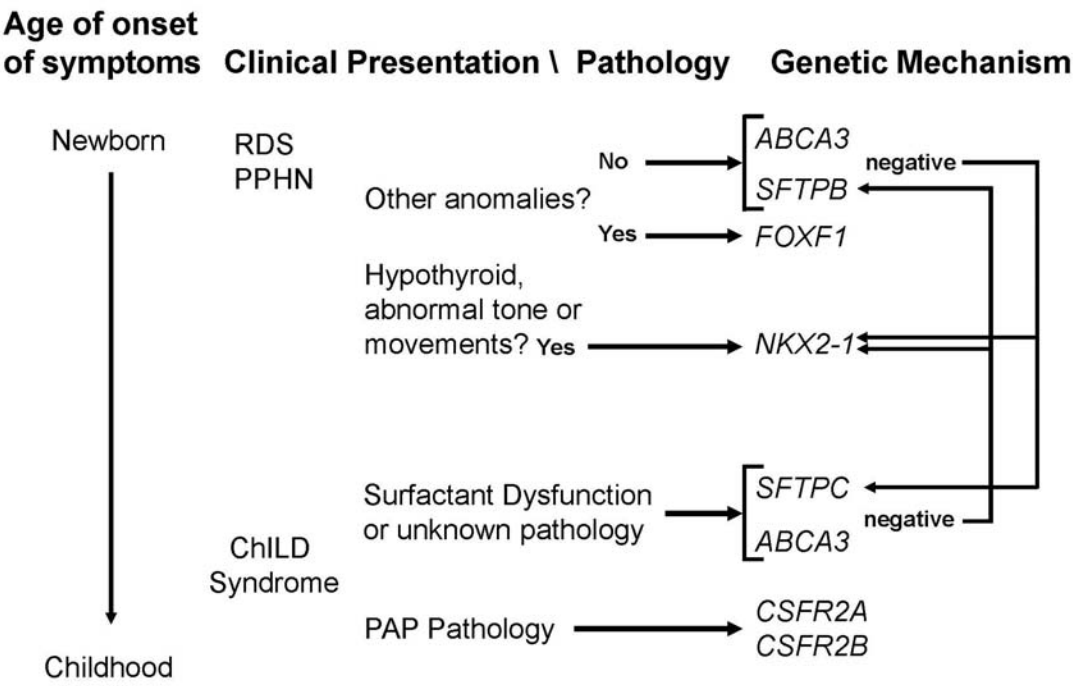
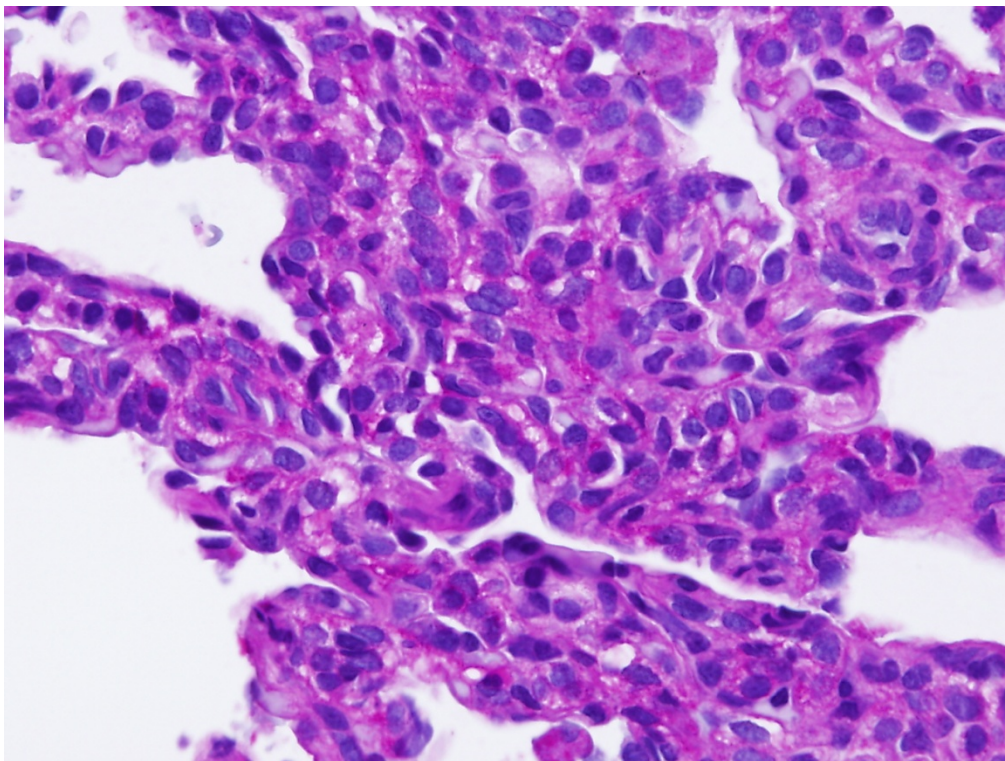
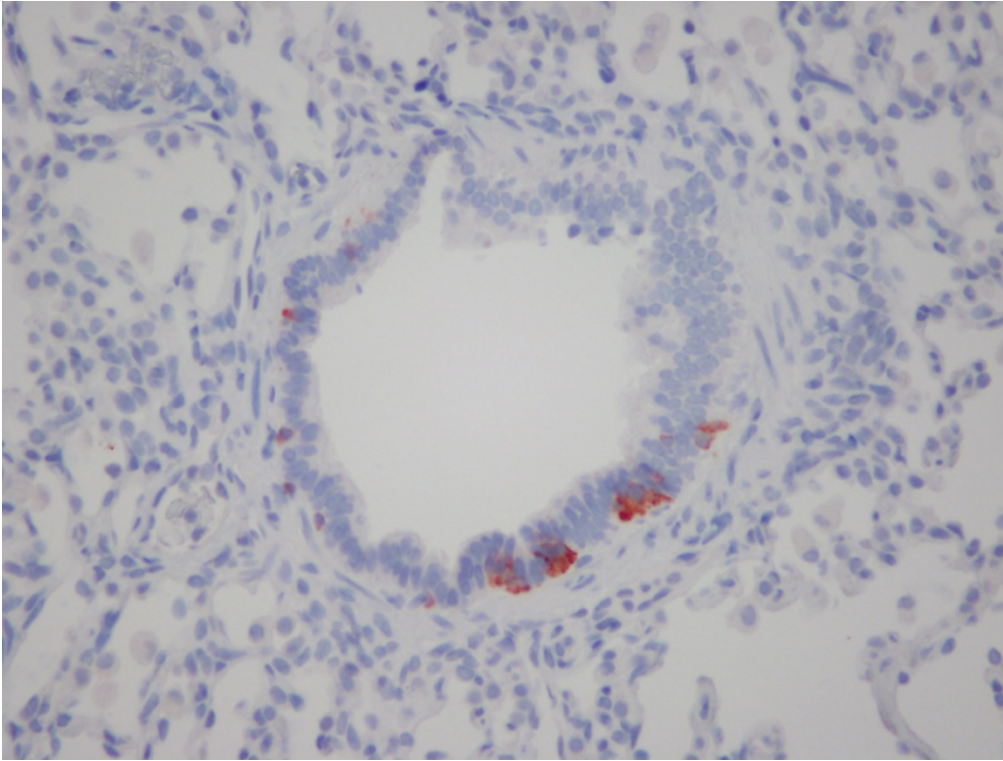


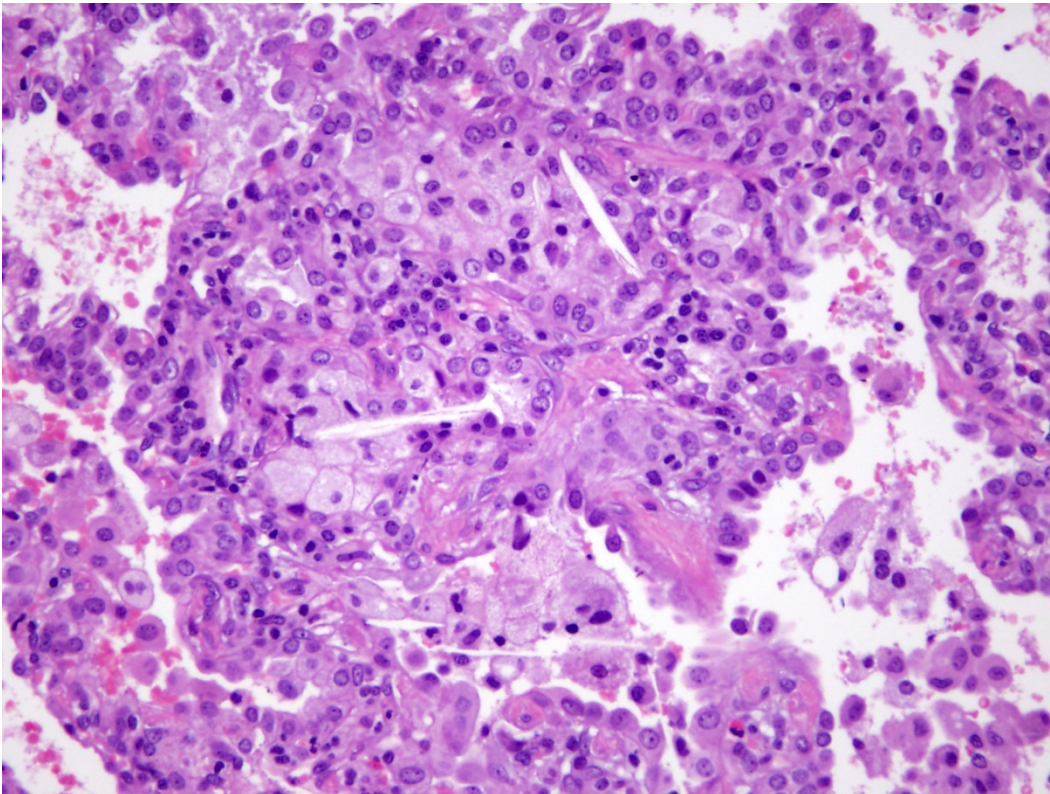
FIG 5



5A.

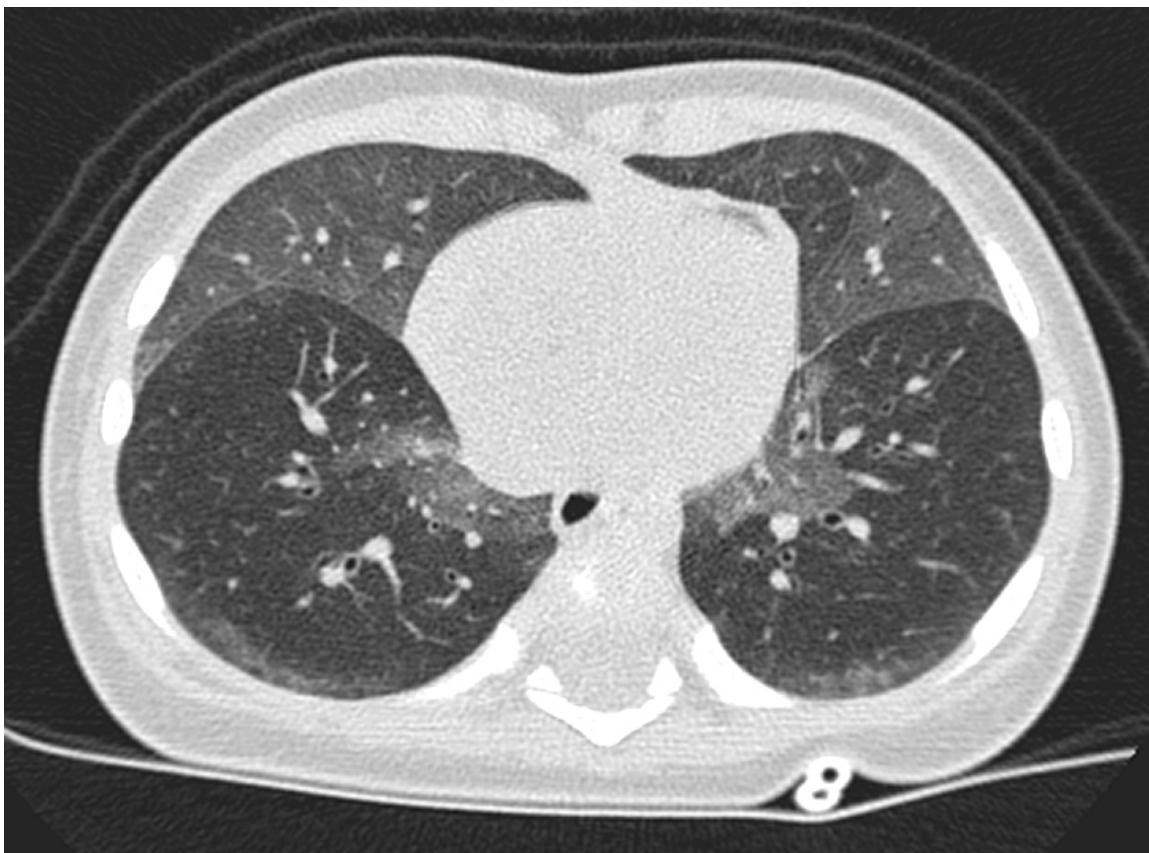


5B.



5C.

FIG 6



References

1. Bokulic RE, Hilman BC. Interstitial lung disease in children. *Pediatric Clinics of North America* 1994;41:543-567.
2. Fan LL, Langston C. Chronic interstitial lung disease in children. *Pediatr Pulmonol* 1993;16:184-196.
3. Nicholson AG, Kim H, Corrin B, Bush A, du Bois RM, Rosenthal M, Sheppard MN. The value of classifying interstitial pneumonitis in childhood according to defined histological patterns. *Histopathology* 1998;33:203-211.
4. Deutsch GH, Albright E, Chou PM, Cool CD, Coventry S, Davis MM, Dishop MK, Galambos C, Patterson K, Wert SE, White FV, Cutz E, Langston C. Defining the spectrum of diffuse lung disease in infancy: A working classification of the pediatric interstitial lung disease cooperative (abstract). *Modern Pathology* 2005;18:304.
5. Langston C, Dishop M. Infant lung biopsy: Clarifying the pathologic spectrum. *Pathol International* 2004;54, Suppl 1:S419-421.
6. Deutsch GH, Young LR, Deterding RR, Fan LL, Dell SD, Bean JA, Brody AS, Nogee LM, Trapnell BC, Langston C, Pathology Cooperative G, Albright EA, Askin FB, Baker P, Chou PM, Cool CM, Coventry SC, Cutz E, Davis MM, Dishop MK, Galambos C, Patterson K, Travis WD, Wert SE, White FV, Ch ILDRG-o. Diffuse lung disease in young children: Application of a novel classification scheme. *Am J Respir Crit Care Med* 2007;176:1120-1128.
7. Canakis A-M, Cutz E, Manson D, O'Brodovich H. Pulmonary interstitial glycogenosis: A new variant of neonatal interstitial lung disease.[see comment]. *Am J Respir Crit Care Med* 2002;165:1557-1565.
8. Nogee LM, Garnier G, Dietz HC, Singer L, Murphy AM, deMello DE, Colten HR. A mutation in the Surfactant Protein B gene responsible for fatal neonatal respiratory disease in multiple kindreds. *J Clin Invest* 1994;93:1860-1863.

9. Nogee LM. Alterations in sp-b and sp-c expression in neonatal lung disease. *Annual Review of Physiology* 2004;66:601-623.
10. Shulenin S, Nogee LM, Annilo T, Wert SE, Whitsett JA, Dean M. ABCA3 gene mutations in newborns with fatal surfactant deficiency.[see comment]. *N Engl J Med* 2004;350:1296-1303.
11. Clement A, Force ERST. Task force on chronic interstitial lung disease in immunocompetent children. *Eur Respir J* 2004;24:686-697.
12. Fan LL, Mullen AL, Brugman SM, Inscore SC, Parks DP, White CW. Clinical spectrum of chronic interstitial lung disease in children. *J Pediatr* 1992;121:867-872.
13. Fan LL, Kozinetz CA, Deterding RR, Brugman SM. Evaluation of a diagnostic approach to pediatric interstitial lung disease. *Pediatrics* 1998;101:82-85.
14. Van Hook KN, Brody AS, Deterding RR, Fan LL, Young LR. Evaluation of a definition of children's interstitial lung disease (child) syndrome. *Proceedings of the American Thoracic Society* 2006;3:A244.
15. Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: A national survey in the united kingdom and ireland. *Pediatr Pulmonol* 2002;34:23-29.
16. Fan LL, Kozinetz CA, Wojtczak HA, Chatfield BA, Cohen AH, Rothenberg SS. Diagnostic value of transbronchial, thoracoscopic, and open lung biopsy in immunocompetent children with chronic interstitial lung disease. *J Pediatr* 1997;131:565-569.
17. Lynch DA, Hay T, Newell JD, Jr., Divgi VD, Fan LL. Pediatric diffuse lung disease: Diagnosis and classification using high-resolution ct. *AJR American Journal of Roentgenology* 1999;173:713-718.
18. Copley SJ, Padley SP. High-resolution ct of paediatric lung disease. *Eur Radiol* 2001;11:2564-2575.
19. Vrielynck S, Mamou-Mani T, Emond S, Scheinmann P, Brunelle F, de Blic J. Diagnostic value of high-resolution ct in the evaluation of chronic infiltrative lung disease in children. *AJR Am J Roentgenol* 2008;American Journal of Roentgenology. 191:914-920.
20. Brody AS, Guillerman RP, Hay TC, Wagner BD, Young LR, Deutsch GH, Fan LL, Deterding RR. Neuroendocrine cell hyperplasia of infancy: Diagnosis with high-resolution ct. *AJR Am J Roentgenol* 2010;American Journal of Roentgenology. 194:238-244.

21. Popler J, Gower WA, Mogayzel PJ, Jr., Nogee LM, Langston C, Wilson AC, Hay TC, Deterding RR. Familial neuroendocrine cell hyperplasia of infancy. *Pediatr Pulmonol* 2010;45:749-755.
22. Vassal HB, Malone M, Petros AJ, Winter RM. Familial persistent pulmonary hypertension of the newborn resulting from misalignment of the pulmonary vessels (congenital alveolar capillary dysplasia). *J Med Genet* 1998;35:58-60.
23. Boggs S, Harris MC, Hoffman DJ, Goel R, McDonald-McGinn D, Langston C, Zackai E, Ruchelli E. Misalignment of pulmonary veins with alveolar capillary dysplasia: Affected siblings and variable phenotypic expression. *J Pediatr* 1994;124:125-128.
24. Gutierrez C, Rodriguez A, Palenzuela S, Forteza C, Rossello JL. Congenital misalignment of pulmonary veins with alveolar capillary dysplasia causing persistent neonatal pulmonary hypertension: Report of two affected siblings. *Pediatr Dev Pathol* 2000;3:271-276.
25. Fan LL, Kozinetz CA. Factors influencing survival in children with chronic interstitial lung disease. *Am J Respir Crit Care Med* 1997;156:939-942.
26. Sondheimer HM, Lung MC, Brugman SM, Ikle DN, Fan LL, White CW. Pulmonary vascular disorders masquerading as interstitial lung disease. *Pediatr Pulmonol* 1995;20:284-288.
27. Modrykamien AM, Gudavalli R, McCarthy K, Parambil J. Echocardiography, 6-minute walk distance, and distance-saturation product as predictors of pulmonary arterial hypertension in idiopathic pulmonary fibrosis. *Respir Care* 2010;55:584-588.
28. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003;167:735-740.
29. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, Girgis RE. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: Impact of interstitial lung disease. *Arthritis Rheum* 2009;60:569-577.
30. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008;31:1357-1367.
31. Shlobin OA, Nathan SD. Pulmonary hypertension secondary to interstitial lung disease. *Expert Rev Respir Med* 2011;5:179-189.
32. Polomis D, Runo JR, Meyer KC. Pulmonary hypertension in interstitial lung disease. *Curr Opin Pulm Med* 2008;14:462-469.

33. Kowal-Bielecka O, Avouac J, Pittrow D, Huscher D, Behrens F, Denton CP, Foeldvari I, Humbert M, Matucci-Cerinic M, Nash P, Opitz CF, Rubin LJ, Seibold JR, Strand V, Furst DE, Distler O. Echocardiography as an outcome measure in scleroderma-related pulmonary arterial hypertension: A systematic literature analysis by the eposs group. *J Rheumatol* 2010;37:105-115.
34. Owens C. Radiology of diffuse interstitial pulmonary disease in children. *Eur Radiol* 2004;14 Suppl 4:L2-12.
35. Copley SJ, Coren M, Nicholson AG, Rubens MB, Bush A, Hansell DM. Diagnostic accuracy of thin-section ct and chest radiography of pediatric interstitial lung disease. *AJR American Journal of Roentgenology* 2000;174:549-554.
36. Donnelly LF. Use of three-dimensional reconstructed helical ct images in recognition and communication of chest wall anomalies in children. *AJR American Journal of Roentgenology* 2001;177:441-445.
37. Frush DP. Pediatric ct: Practical approach to diminish the radiation dose. *Pediatr Radiol* 2002;32:714-717; discussion 751-714.
38. Long FR, Castile RG, Brody AS, Hogan MJ, Flucke RL, Filbrun DA, McCoy KS. Lungs in infants and young children: Improved thin-section ct with a noninvasive controlled-ventilation technique--initial experience. *Radiology* 1999;212:588-593.
39. Brody AS. Imaging considerations: Interstitial lung disease in children. *Radiologic Clinics of North America* 2005;43:391-403.
40. Lucaya J, Garcia-Pena P, Herrera L, Enriquez G, Piqueras J. Expiratory chest ct in children. *AJR American Journal of Roentgenology* 2000;174:235-241.
41. Garcia-Pena P, Lucaya J. Hrct in children: Technique and indications. *Eur Radiol* 2004;14 Suppl 4:L13-30.
42. Mechri M, Epaud R, Emond S, Coulomb A, Jaubert F, Tarrant A, Feldmann D, Flamein F, Clement A, de Blic J, Abou Tamm R, Brunelle F, Ducou le Pointe H. Surfactant Protein C gene (*SFTPC*) mutation-associated lung disease: High-resolution computed tomography (hrct) findings and its relation to histological analysis. *Pediatr Pulmonol* 2010;45:1021-1029.
43. Failo R, Wielopolski PA, Tiddens HAWM, Hop WCJ, Mucelli RP, Lequin MH. Lung morphology assessment using mri: A robust ultra-short tr/te 2d steady state free precession sequence used in cystic fibrosis patients. *Magn Reson Med* 2009;61:299-306.
44. Puderbach M, Eichinger M, Gahr J, Ley S, Tuengerthal S, Schmahl A, Fink C, Plathow C, Wiebel M, Muller F-M, Kauczor H-U.

Proton mri appearance of cystic fibrosis: Comparison to ct. *Eur Radiol* 2007;17:716-724.

45. Long FR. High-resolution ct of the lungs in infants and young children. *Journal of Thoracic Imaging* 2001;16:251-258.

46. Lell MM, May M, Deak P, Alibek S, Kuefner M, Kuettner A, Kohler H, Achenbach S, Uder M, Radkowi T. High-pitch spiral computed tomography: Effect on image quality and radiation dose in pediatric chest computed tomography. *Invest Radiol* 2011;46:116-123.

47. Mason KP, Prescilla R, Fontaine PJ, Zurakowski D. Pediatric ct sedation: Comparison of dexmedetomidine and pentobarbital. *AJR Am J Roentgenol* 2011;American Journal of Roentgenology. 196:W194-198.

48. Chun TH, Amanullah S, Karishma-Bahl D, Machan JT, Andrada ER, Lewander WJ. Comparison of methohexital and pentobarbital as sedative agents for pediatric emergency department patients for computed tomography. *Pediatr Emerg Care* 2009;25:648-650.

49. Sargent MA, McEachern AM, Jamieson DH, Kahwaji R. Atelectasis on pediatric chest ct: Comparison of sedation techniques. *Pediatr Radiol* 1999;29:509-513.

50. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, de Gonzalez AB. Radiation exposure from ct scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. *Lancet* 2012;380:499-505.

51. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric ct. *AJR Am J Roentgenol* 2001;American Journal of Roentgenology. 176:289-296.

52. Castile R, Filbrun D, Flucke R, Franklin W, McCoy K. Adult-type pulmonary function tests in infants without respiratory disease. *Pediatr Pulmonol* 2000;30:215-227.

53. Feher A, Castile R, Kisling J, Angelicchio C, Filbrun D, Flucke R, Tepper R. Flow limitation in normal infants: A new method for forced expiratory maneuvers from raised lung volumes. *Journal of Applied Physiology* 1996;80:2019-2025.

54. Lum S, Stocks J, Castile R, Davis S, Henschen M, Jones M, Morris MG, Ranganathan S, Sly PD, Tepper R. Raised volume forced expirations in infants: Guidelines for current practice. Ats/ers statement. *Am J Respir Crit Care Med* 2005;172:1463-1471.

55. Jones M, Castile R, Davis S, Kisling J, Filbrun D, Flucke R, Goldstein A, Emsley C, Ambrosius W, Tepper RS. Forced expiratory flows and volumes in infants. Normative data and lung growth. *Am J Respir Crit Care Med* 2000;161:353-359.
56. Goldstein AB, Castile RG, Davis SD, Filbrun DA, Flucke RL, McCoy KS, Tepper RS. Bronchodilator responsiveness in normal infants and young children. *Am J Respir Crit Care Med* 2001;164:447-454.
57. Kerem E, Bentur L, England S, Reisman J, O'Brodivich H, Bryan AC, Levison H. Sequential pulmonary function measurements during treatment of infantile chronic interstitial pneumonitis. *J Pediatr* 1990;116:61-67.
58. Young LR, Brody AS, Inge TH, Acton JD, Bokulic RE, Langston C, Deutsch GH. Neuroendocrine cell distribution and frequency distinguish neuroendocrine cell hyperplasia of infancy from other pulmonary disorders. *Chest* 2011;139:1060-1071.
59. Kerby GS, Kopecky C, Wilcox SL, Wagner B, Hay T, Popler J, Accurso FJ, Deterding RR. Infant pulmonary function testing in children with neuroendocrine cell hyperplasia with and without lung biopsy. *Am J Respir Crit Care Med* 2009;179:A5965.
60. Kerby GS, Wilcox SL, Heltshe SL, Accurso FJ, Deterding RR. Infant pulmonary function in pediatric interstitial lung disease. (abstract). *Proceedings of the American Thoracic Society* 2005;2:A474.
61. Kerby GS, Wagner BD, Wilcox SL, Kopecky C, Deterding RR. Infant pulmonary function in patients with neuroendocrine cell hyperplasia of infancy correlates with future spirometry and room air oxygen saturations. *Am J Respir Crit Care Med* 2012;185 ABSTRACTS:A2487.
62. Kerby GS, Wagner BD, Popler J, Hay T, Kopecky C, Wilcox SL, Quinones RR, Giller RH, Accurso FJ, Deterding RR. Abnormal infant pulmonary function in young children with neuroendocrine cell hyperplasia of infancy *Pediatr Pulmonol* 2012.
63. Wood RE. Pediatric bronchoscopy. *Chest Surgery Clinics of North America* 1996;6:237-251.
64. Riedler J, Grigg J, Robertson CF. Role of bronchoalveolar lavage in children with lung disease. *Eur Respir J* 1995;8:1725-1730.
65. Barbato A, Panizzolo C, Cracco A, de Blic J, Dinwiddie R, Zach M. Interstitial lung disease in children: A multicentre survey on diagnostic approach. *Eur Respir J* 2000;16:509-513.

66. de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, Green C, Grigg J, Kotecha S, Kurland G, Pohunek P, Ratjen F, Rossi G. Bronchoalveolar lavage in children. European task force on bronchoalveolar lavage in children. European respiratory society. *Eur Respir J* 2000;15:217-231.
67. Reynolds HY. Use of bronchoalveolar lavage in humans--past necessity and future imperative. *Lung* 2000;178:271-293.
68. King TE, Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005;172:268-279.
69. Deterding RR, Laguna T, Emmett R, Sontag M, Accurso F. Cytokine profiles in bronchoalveolar lavage fluid from children with interstitial lung diseases. *Proceedings of the American Thoracic Society* 2006;3:A164.
70. Thouvenin G, Abou Taam R, Flamein F, Guillot L, Le Bourgeois M, Reix P, Fayon M, Counil F, Depontbriand U, Feldmann D, Pointe HD-L, de Blic J, Clement A, Epaud R. Characteristics of disorders associated with genetic mutations of Surfactant Protein C. *Arch Dis Child* 2010;95:449-454.
71. Popler J, Wagner BD, Accurso FJ, Deterding RR. Airway cytokine profiles in children's interstitial lung diseases. *Am J Respir Crit Care Med* 2010;181:A3316.
72. Deterding RR, Wolfson A, Harris JK, Walker J, Wagner BD, Accurso FJ. Bronchoalveolar lavage protein biomarkers in children with surfactant dysfunction mutations; an aptamer proteomics approach. *Proceedings of the American Thoracic Society* 2011;8:210.
73. Rock MJ. The diagnostic utility of bronchoalveolar lavage in immunocompetent children with unexplained infiltrates on chest radiograph. *Pediatrics* 1995;95:373-377.
74. Baker AM, Bowton DL, Haponik EF. Decision making in nosocomial pneumonia. An analytic approach to the interpretation of quantitative bronchoscopic cultures. *Chest* 1995;107:85-95.
75. Molina-Teran A, Hilliard TN, Saglani S, Haxby E, Scallan M, Bush A, Davies JC. Safety of endobronchial biopsy in children with cystic fibrosis. *Pediatr Pulmonol* 2006;41:1021-1024.
76. Hilliard TN, Regamey N, Shute JK, Nicholson AG, Alton EFW, Bush A, Davies JC. Airway remodelling in children with cystic fibrosis. *Thorax* 2007;62:1074-1080.

77. Turner JS, Willcox PA, Hayhurst MD, Potgieter PD. Fiberoptic bronchoscopy in the intensive care unit--a prospective study of 147 procedures in 107 patients. *Critical Care Medicine* 1994;22:259-264.
78. Godfrey S. Pulmonary hemorrhage/hemoptysis in children. *Pediatr Pulmonol* 2004;37:476-484.
79. Burkhalter A, Silverman JF, Hopkins MB, 3rd, Geisinger KR. Bronchoalveolar lavage cytology in pulmonary alveolar proteinosis. *American Journal of Clinical Pathology* 1996;106:504-510.
80. de Blic J. Pulmonary alveolar proteinosis in children. *Paediatr Respir Rev* 2004;5:316-322.
81. Takemura T, Fukuda Y, Harrison M, Ferrans VJ. Ultrastructural, histochemical, and freeze-fracture evaluation of multilamellated structures in human pulmonary alveolar proteinosis. *American Journal of Anatomy* 1987;179:258-268.
82. Refabert L, Rambaud C, Mamou-Mani T, Scheinmann P, de Blic J. Cd1a-positive cells in bronchoalveolar lavage samples from children with langerhans cell histiocytosis. *J Pediatr* 1996;129:913-915.
83. Basset F, Soler P, Jaurand MC, Bignon J. Ultrastructural examination of broncho-alveolar lavage for diagnosis of pulmonary histiocytosis x: Preliminary report on 4 cases. *Thorax* 1977;32:303-306.
84. Chollet S, Soler P, Dournovo P, Richard MS, Ferrans VJ, Basset F. Diagnosis of pulmonary histiocytosis x by immunodetection of langerhans cells in bronchoalveolar lavage fluid. *American Journal of Pathology* 1984;115:225-232.
85. Tessier V, Chadelat K, Baculard A, Housset B, Clement A. Bal in children: A controlled study of differential cytology and cytokine expression profiles by alveolar cells in pediatric sarcoidosis. *Chest* 1996;109:1430-1438.
86. Uyan ZS, Karadag B, Ersu R, Kiyan G, Kotiloglu E, Sirvanci S, Ercan F, Dagli T, Karakoc F, Dagli E. Early pulmonary involvement in niemann-pick type b disease: Lung lavage is not useful. *Pediatr Pulmonol* 2005;40:169-172.
87. Fan LL, Lung MC, Wagener JS. The diagnostic value of bronchoalveolar lavage in immunocompetent children with chronic diffuse pulmonary infiltrates.[see comment]. *Pediatr Pulmonol* 1997;23:8-13.
88. Tredano M, De Blic J, Griesse M, Fournet JC, Elion J, Bahuau M. Clinical biological and genetic heterogeneity of the inborn errors of

pulmonary surfactant metabolism. *Clinical Chemistry & Laboratory Medicine* 2001;39:90-108.

89. Latzin P, Tredano M, Wust Y, de Blic J, Nicolai T, Bewig B, Stanzel F, Kohler D, Bahuau M, Griesse M. Anti-gm-csf antibodies in paediatric pulmonary alveolar proteinosis. *Thorax* 2005;60:39-44.

90. Price A, Manson D, Cutz E, Dell S. Pulmonary alveolar proteinosis associated with anti-gm-csf antibodies in a child: Successful treatment with inhaled gm-csf. *Pediatr Pulmonol* 2006;41:367-370.

91. Martinez-Moczygemba M, Doan ML, Elidemir O, Fan LL, Cheung SW, Lei JT, Moore JP, Tavana G, Lewis LR, Zhu Y, Muzny DM, Gibbs RA, Huston DP. Pulmonary alveolar proteinosis caused by deletion of the gm-csfralpha gene in the x chromosome pseudoautosomal region 1. *J Exp Med* 2008;205:2711-2716.

92. Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, Smolarek T, Dishop MK, Wert SE, Whitsett JA, Grabowski G, Carey BC, Stevens C, van der Loo JCM, Trapnell BC. Familial pulmonary alveolar proteinosis caused by mutations in csf2ra. *J Exp Med* 2008;205:2703-2710.

93. Parto K, Kallajoki M, Aho H, Simell O. Pulmonary alveolar proteinosis and glomerulonephritis in lysinuric protein intolerance: Case reports and autopsy findings of four pediatric patients. *Human Pathology* 1994;25:400-407.

94. Parto K, Svedstrom E, Majurin ML, Harkonen R, Simell O. Pulmonary manifestations in lysinuric protein intolerance. *Chest* 1993;104:1176-1182.

95. Sakagami T, Beck D, Uchida K, Suzuki T, Carey BC, Nakata K, Keller G, Wood RE, Wert SE, Ikegami M, Whitsett JA, Luisetti M, Davies S, Krischer JP, Brody A, Ryckman F, Trapnell BC. Patient-derived granulocyte/macrophage colony-stimulating factor autoantibodies reproduce pulmonary alveolar proteinosis in nonhuman primates. *Am J Respir Crit Care Med* 2010;182:49-61.

96. Ahrens P, Noll C, Kitz R, Willigens P, Zielen S, Hofmann D. Lipid-laden alveolar macrophages (Ilam): A useful marker of silent aspiration in children. *Pediatr Pulmonol* 1999;28:83-88.

97. Furuya MEY, Moreno-Cordova V, Ramirez-Figueroa JL, Vargas MH, Ramon-Garcia G, Ramirez-San Juan DH. Cutoff value of lipid-laden alveolar macrophages for diagnosing aspiration in infants and children. *Pediatr Pulmonol* 2007;42:452-457.

98. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. *Pediatr Pulmonol* 1999;27:419-422.
99. Starosta V, Kitz R, Hartl D, Marcos V, Reinhardt D, Griesse M. Bronchoalveolar pepsin, bile acids, oxidation, and inflammation in children with gastroesophageal reflux disease. *Chest* 2007;132:1557-1564.
100. Miller J, Colasurdo GN, Khan AM, Jajoo C, Patel TJ, Fan LL, Elidemir O. Immunocytochemical detection of milk proteins in tracheal aspirates of ventilated infants: A pilot study. *Pediatr Pulmonol* 2002;34:369-374.
101. Elidemir O, Fan LL, Colasurdo GN. A novel diagnostic method for pulmonary aspiration in a murine model. Immunocytochemical staining of milk proteins in alveolar macrophages. *Am J Respir Crit Care Med* 2000;161:622-626.
102. Meyer KC, Raghu G, Baughman BP, Brown KK, Costabel U, Du Bois RM, Drent M, Haslam PL, Kim DS, Nagai S, Rottoli P, Saltini C, Selman M, Strange C, Wood B. An official american thoracic society clinical practice guideline: The clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012;185:1004-1014.
103. Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. *Curr Opin Pediatr* 2007;19:314-320.
104. Nogee LM. Genetic mechanisms of surfactant deficiency. *Biology of the Neonate* 2004;85:314-318.
105. Whitsett JA, Wert SE, Xu Y. Genetic disorders of surfactant homeostasis. *Biology of the Neonate* 2005;87:283-287.
106. Wert SE, Whitsett JA, Nogee LM. Genetic disorders of surfactant dysfunction. *Pediatr Dev Pathol* 2009;12:253-274.
107. Stankiewicz P, Sen P, Bhatt SS, Storer M, Xia Z, Bejjani BA, Ou Z, Wiszniewska J, Driscoll DJ, Maisenbacher MK, Bolivar J, Bauer M, Zackai EH, McDonald-McGinn D, Nowaczyk MMJ, Murray M, Hustead V, Mascotti K, Schultz R, Hallam L, McRae D, Nicholson AG, Newbury R, Durham-O'Donnell J, Knight G, Kini U, Shaikh TH, Martin V, Tyreman M, Simoncic I, Willatt L, Paterson J, Mehta S, Rajan D, Fitzgerald T, Gribble S, Prigmore E, Patel A, Shaffer LG, Carter NP, Cheung SW, Langston C, Shaw-Smith C. Genomic and genic deletions of the fox gene cluster on 16q24.1 and inactivating mutations of foxf1 cause alveolar capillary dysplasia and other malformations.[erratum appears in am j hum genet. 2009

oct;85(4):537 note: Multiple author names added]. *Am J Hum Genet* 2009;84:780-791.

108. Breedveld GJ, van Dongen JWF, Danesino C, Guala A, Percy AK, Dure LS, Harper P, Lazarou LP, van der Linde H, Joosse M, Gruters A, MacDonald ME, de Vries BBA, Arts WFM, Oostra BA, Krude H, Heutink P. Mutations in *tcf-1* are associated with benign hereditary chorea. *Hum Mol Genet* 2002;11:971-979.

109. Breedveld GJ, Percy AK, MacDonald ME, de Vries BBA, Yapijakis C, Dure LS, Ippel EF, Sandkuijl LA, Heutink P, Arts WFM. Clinical and genetic heterogeneity in benign hereditary chorea. *Neurology* 2002;59:579-584.

110. Carre A, Szinnai G, Castanet M, Sura-Trueba S, Tron E, Broutin-L'Hermite I, Barat P, Goizet C, Lacombe D, Moutard M-L, Raybaud C, Raynaud-Ravni C, Romana S, Ythier H, Leger J, Polak M. Five new *tcf1/nkx2.1* mutations in brain-lung-thyroid syndrome: Rescue by *pax8* synergism in one case. *Hum Mol Genet* 2009;18:2266-2276.

111. Devriendt K, Vanhole C, Matthijs G, de Zegher F. Deletion of thyroid transcription factor-1 gene in an infant with neonatal thyroid dysfunction and respiratory failure. *N Engl J Med* 1998;338:1317-1318.

112. Iwatani N, Mabe H, Devriendt K, Kodama M, Miike T. Deletion of *nkx2.1* gene encoding thyroid transcription factor-1 in two siblings with hypothyroidism and respiratory failure. *J Pediatr* 2000;137:272-276.

113. Krude H, Schutz B, Biebermann H, von Moers A, Schnabel D, Neitzel H, Tonnies H, Weise D, Lafferty A, Schwarz S, DeFelice M, von Deimling A, van Landeghem F, DiLauro R, Gruters A. Choreoathetosis, hypothyroidism, and pulmonary alterations due to human *nkx2-1* haploinsufficiency. *J Clin Invest* 2002;109:475-480.

114. Pohlenz J, Dumitrescu A, Zundel D, Martine U, Schonberger W, Koo E, Weiss RE, Cohen RN, Kimura S, Refetoff S. Partial deficiency of thyroid transcription factor 1 produces predominantly neurological defects in humans and mice. *J Clin Invest* 2002;109:469-473.

115. Willemsen MAAP, Breedveld GJ, Wouda S, Otten BJ, Yntema JL, Lammens M, de Vries BBA. Brain-thyroid-lung syndrome: A patient with a severe multi-system disorder due to a de novo mutation in the thyroid transcription factor 1 gene. *Eur J Pediatr* 2005;164:28-30.

116. Kramer MR, Berkman N, Mintz B, Godfrey S, Saute M, Amir G. The role of open lung biopsy in the management and outcome of patients with diffuse lung disease. *Annals of Thoracic Surgery* 1998;65:198-202.
117. Jaklitsch MT, Linden BC, Braunlin EA, Bolman RM, 3rd, Foker JE. Open-lung biopsy guides therapy in children.[see comment]. *Annals of Thoracic Surgery* 2001;71:1779-1785.
118. Early GL, Williams TE, Kilman JW. Open lung biopsy. Its effects on therapy in the pediatric patient. *Chest* 1985;87:467-469.
119. Gauthier F, Montupet P, Renouard C, Valayer J. [surgical pulmonary biopsy in children]. *Chirurgie Pediatrique* 1985;26:92-94.
120. Coren ME, Nicholson AG, Goldstraw P, Rosenthal M, Bush A. Open lung biopsy for diffuse interstitial lung disease in children. *Eur Respir J* 1999;14:817-821.
121. Stefanutti D, Morais L, Fournet JC, Jan D, Casanova JL, Scheinmann P, de Blic J. Value of open lung biopsy in immunocompromised children.[see comment]. *J Pediatr* 2000;137:165-171.
122. Steinberg R, Freud E, Ben-Ari J, Schonfeld T, Golinsky D, Mor C, Zer M. Open lung biopsy--successful diagnostic tool with therapeutic implication in the critically ill paediatric population. *Acta Paediatr* 1998;87:945-948.
123. Gururangan S, Lawson RA, Jones PH, Stevens RF, Campbell RH. Evaluation of the usefulness of open lung biopsies. *Pediatric Hematology & Oncology* 1992;9:107-113.
124. Sebire NJ, Ramsay AD, Malone M. Histopathological features of open lung biopsies in children treated with extracorporeal membrane oxygenation (ecmo). *Early Human Development* 2005;81:455-460.
125. Inwald D, Brown K, Gensini F, Malone M, Goldman A. Open lung biopsy in neonatal and paediatric patients referred for extracorporeal membrane oxygenation (ecmo). *Thorax* 2004;59:328-333.
126. Bond SJ, Lee DJ, Stewart DL, Buchino JJ. Open lung biopsy in pediatric patients on extracorporeal membrane oxygenation.[see comment]. *J Pediatr Surg* 1996;31:1376-1378.
127. Stillwell PC, Cooney DR, Telander RL, Weiland LH, O'Connell EJ. Limited thoracotomy in the pediatric patient. *Mayo Clinic Proceedings* 1981;56:673-677.

128. Rothenberg SS. Thoracoscopy in infants and children. *Seminars in Pediatric Surgery* 1998;7:194-201.
129. Visner GA, Faro A, Zander DS. Role of transbronchial biopsies in pediatric lung diseases. *Chest* 2004;126:273-280.
130. Fontalvo LF, Amaral JG, Temple M, Chait PG, John P, Krishnamuthy G, Smith C, Connolly B. Percutaneous us-guided biopsies of peripheral pulmonary lesions in children. *Pediatr Radiol* 2006;36:491-497.
131. Cahill AM, Baskin KM, Kaye RD, Fitz CR, Towbin RB. Ct-guided percutaneous lung biopsy in children. *Journal of Vascular & Interventional Radiology* 2004;15:955-960.
132. Davies L, Dolgin S, Kattan M. Morbidity and mortality of open lung biopsy in children. *Pediatrics* 1997;99:660-664.
133. Kornecki A, Shemie SD. Open lung biopsy in children with respiratory failure. *Critical Care Medicine* 2001;29:1247-1250.
134. Langston C, Patterson K, Dishop MK, ch ILDPC-oG, Askin F, Baker P, Chou P, Cool C, Coventry S, Cutz E, Davis M, Deutsch G, Galambos C, Pugh J, Wert S, White F. A protocol for the handling of tissue obtained by operative lung biopsy: Recommendations of the child pathology co-operative group. *Pediatr Dev Pathol* 2006;9:173-180.
135. Rothenberg SS, Wagner JS, Chang JH, Fan LL. The safety and efficacy of thoracoscopic lung biopsy for diagnosis and treatment in infants and children. *J Pediatr Surg* 1996;31:100-103; discussion 103-104.
136. Takamori S, Hayashi A, Matsuo T, Mitsuoka M, Tanigawa H, Fukunaga M, Miwa K, Sueyasu Y, Hotta M, Shirouzu K. Thoracoscopic lung biopsy for diffuse infiltrative lung disease. *Kurume Medical Journal* 2000;47:263-265.
137. Nogee LM. Genetic basis of children's interstitial lung disease. *Pediatric Allergy, Immunology, and Pulmonology* 2010;23:15-24.
138. Langston C. Pediatric lung biopsy. In: Cagle P, editor. Diagnostic pulmonary pathology. New York: Marcel Dekker; 2000. p. 19-47.
139. Eulmesekian P, Cutz E, Parvez B, Bohn D, Adatia I. Alveolar capillary dysplasia: A six-year single center experience. *J Perinat Med* 2005;33:347-352.
140. Fullmer JJ, Langston C, Dishop MK, Fan LL. Pulmonary capillaritis in children: A review of eight cases with comparison to other alveolar hemorrhage syndromes. *J Pediatr* 2005;146:376-381.

141. Michalsky MP, Arca MJ, Groenman F, Hammond S, Tibboel D, Caniano DA. Alveolar capillary dysplasia: A logical approach to a fatal disease. *J Pediatr Surg* 2005;40:1100-1105.
142. Bensard DD, McIntyre RC, Jr., Waring BJ, Simon JS. Comparison of video thoracoscopic lung biopsy to open lung biopsy in the diagnosis of interstitial lung disease. *Chest* 1993;103:765-770.
143. Ponsky TA, Rothenberg SS, Tsao K, Ostlie DJ, St Peter SD, Holcomb GW, 3rd. Thoracoscopy in children: Is a chest tube necessary? *Journal of Laparoendoscopic & Advanced Surgical Techniques Part A* 2009;19 Suppl 1:S23-25.
144. Faro A, Hamvas A. Lung transplantation for inherited disorders of surfactant metabolism. *NeoReviews* 2008;9:e468-e476.
145. Hamvas A, Nogee LM, Mallory GB, Jr., Spray TL, Huddleston CB, August A, Dehner LP, deMello DE, Moxley M, Nelson R, Cole FS, Colten HR. Lung transplantation for treatment of infants with Surfactant Protein B deficiency. *J Pediatr* 1997;130:231-239.
146. Palomar LM, Nogee LM, Sweet SC, Huddleston CB, Cole FS, Hamvas A. Long-term outcomes after infant lung transplantation for Surfactant Protein B deficiency related to other causes of respiratory failure. *J Pediatr* 2006;149:548-553.
147. Nogee LM, Dunbar AE, 3rd, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the Surfactant Protein C gene associated with familial interstitial lung disease. *N Engl J Med* 2001;344:573-579.
148. Wegner DJ, Hertzberg T, Heins HB, Elmberger G, MacCoss MJ, Carlson CS, Nogee LM, Cole FS, Hamvas A. A major deletion in the Surfactant Protein-b gene causing lethal respiratory distress. *Acta Paediatr* 2007;96:516-520.
149. Agrawal A, Hamvas A, Cole FS, Wambach JA, Wegner DJ, Coghil C, Harrison K, Nogee LM. An intronic ABCA3 mutation that is responsible for respiratory disease. *Pediatr Res* 2012;71:633-637.
150. Brasch F, Schimanski S, Muhlfeld C, Barlage S, Langmann T, Aslanidis C, Boettcher A, Dada A, Schroten H, Mildemberger E, Prueter E, Ballmann M, Ochs M, Johnen G, Griesse M, Schmitz G. Alteration of the pulmonary Surfactant system in full-term infants with hereditary ABCA3 deficiency. *Am J Respir Crit Care Med* 2006;174:571-580.
151. Deterding RR, Sontag M, Kerby GS, Brody AS, Krawiec M, Nogee LM, Hamvas A. Clinical characteristics of Surfactant Protein (sp-c) mutations in children. (abstract). *Proceedings of the American Thoracic Society* 2005;2:A474.

152. Flamein F, Riffault L, Muselet-Charlier C, Pernelle J, Feldmann D, Jonard L, Durand-Schneider A-M, Coulomb A, Maurice M, Nogee LM, Inagaki N, Amselem S, Dubus JC, Rigourd V, Bremont F, Marguet C, Brouard J, de Blic J, Clement A, Epauld R, Guillot L. Molecular and cellular characteristics of ABCA3 mutations associated with diffuse parenchymal lung diseases in children. *Hum Mol Genet* 2012;21:765-775.
153. Garmany TH, Moxley MA, White FV, Dean M, Hull WM, Whitsett JA, Nogee LM, Hamvas A. Surfactant composition and function in patients with ABCA3 mutations. *Pediatr Res* 2006;59:801-805.
154. Hamvas A, Nogee LM, Wegner DJ, Depass K, Christodoulou J, Bennetts B, McQuade LR, Gray PH, Deterding RR, Carroll TR, Kammesheidt A, Kasch LM, Kulkarni S, Cole FS. Inherited surfactant deficiency caused by uniparental disomy of rare mutations in the Surfactant Protein-b and atp binding cassette, subfamily a, member 3 genes. *J Pediatr* 2009;155:854-859.e851.
155. Nogee LM, Dunbar AE, 3rd, Wert S, Askin F, Hamvas A, Whitsett JA. Mutations in the Surfactant Protein C gene associated with interstitial lung disease. *Chest* 2002;121:20S-21S.
156. Nogee LM, Wert SE, Proffitt SA, Hull WM, Whitsett JA. Allelic heterogeneity in hereditary Surfactant Protein B (sp-b) deficiency. *Am J Respir Crit Care Med* 2000;161:973-981.
157. Wert SE, Deutsch GH, Hamvas A, Whitsett JA, Nogee LM. Mutations in the Surfactant Protein C gene (*SFTPC*) are associated with acute and chronic lung disease in full term infants. . *Am J Respir Crit Care Med* 2005;Abstracts 2:A23.
158. Garmany TH, Wambach JA, Heins HB, Watkins-Torrey JM, Wegner DJ, Bennet K, An P, Land G, Saugstad OD, Henderson H, Nogee LM, Cole FS, Hamvas A. Population and disease-based prevalence of the common mutations associated with surfactant deficiency. *Pediatr Res* 2008;63:645-649.
159. Hamvas A, Trusgnich M, Brice H, Baumgartner J, Hong Y, Nogee LM, Cole FS. Population-based screening for rare mutations: High-throughput DNA extraction and molecular amplification from Guthrie cards. *Pediatr Res* 2001;50:666-668.
160. Tredano M, Cooper DN, Stuhmann M, Christodoulou J, Chuzhanova NA, Roudot-Thoraval F, Boelle P-Y, Elion J, Jeanpierre M, Feingold J, Couderc R, Bahuau M. Origin of the prevalent *SFTPB*

- indel g.1549c > gaa (121ins2) mutation causing Surfactant Protein B (sp-b) deficiency. *Am J Med Genet A* 2006;Part A. 140:62-69.
161. Galambos C, Levy H, Cannon CL, Vargas SO, Reid LM, Cleveland R, Lindeman R, deMello DE, Wert SE, Whitsett JA, Perez-Atayde AR, Kozakewich H. Pulmonary pathology in thyroid transcription factor-1 deficiency syndrome. *Am J Respir Crit Care Med* 2010;182:549-554.
162. Kleinlein B, Griesse M, Liebisch G, Krude H, Lohse P, Aslanidis C, Schmitz G, Peters J, Holzinger A. Fatal neonatal respiratory failure in an infant with congenital hypothyroidism due to haploinsufficiency of the nkx2-1 gene: Alteration of pulmonary surfactant homeostasis. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F453-456.
163. Maquet E, Costagliola S, Parma J, Christophe-Hobertus C, Oligny LL, Fournet J-C, Robitaille Y, Vuissoz J-M, Payot A, Laberge S, Vassart G, Van Vliet G, Deladoey J. Lethal respiratory failure and mild primary hypothyroidism in a term girl with a de novo heterozygous mutation in the titf1/nkx2.1 gene. *J Clin Endocrinol Metab* 2009;94:197-203.
164. Guillot L, Carre A, Szinnai G, Castanet M, Tron E, Jaubert F, Broutin I, Counil F, Feldmann D, Clement A, Polak M, Epauld R. Nkx2-1 mutations leading to surfactant Protein promoter dysregulation cause interstitial lung disease in "brain-lung-thyroid syndrome". *Hum Mutat* 2010;31:E1146-1162.
165. Yu S, Shao L, Kilbride H, Zwick DL. Haploinsufficiencies of foxf1 and foxc2 genes associated with lethal alveolar capillary dysplasia and congenital heart disease. *Am J Med Genet A* 2010;Part A. 152A:1257-1262.
166. Zufferey F, Martinet D, Osterheld M-C, Niel-Butschi F, Giannoni E, Schmutz NB, Xia Z, Beckmann JS, Shaw-Smith C, Stankiewicz P, Langston C, Fellmann F. 16q24.1 microdeletion in a premature newborn: Usefulness of array-based comparative genomic hybridization in persistent pulmonary hypertension of the newborn. *Pediatr Crit Care Med* 2011;12:e427-432.
167. Bullard JE, Nogee LM. Heterozygosity for ABCA3 mutations modifies the severity of lung disease associated with a Surfactant Protein C gene (*SFTPC*) mutation. *Pediatr Res* 2007;62:176-179.
168. Bullard JE, Wert SE, Whitsett JA, Dean M, Nogee LM. ABCA3 mutations associated with pediatric interstitial lung disease.[see comment]. *Am J Respir Crit Care Med* 2005;172:1026-1031.

169. Brasch F, Griesse M, Tredano M, Johnen G, Ochs M, Rieger C, Mulugeta S, Muller KM, Bahuau M, Beers MF. Interstitial lung disease in a baby with a de novo mutation in the *SFTPC* gene.[see comment]. *Eur Respir J* 2004;24:30-39.
170. Hamvas A, Nogee LM, White FV, Schuler P, Hackett BP, Huddleston CB, Mendeloff EN, Hsu F-F, Wert SE, Gonzales LW, Beers MF, Ballard PL. Progressive lung disease and surfactant dysfunction with a deletion in Surfactant Protein C gene. *Am J Respir Cell Mol Biol* 2004;30:771-776.
171. Nogee LM. Abnormal expression of Surfactant Protein C and lung disease. *Am J Respir Cell Mol Biol* 2002;26:641-644.
172. Stevens PA, Pettenazzo A, Brasch F, Mulugeta S, Baritussio A, Ochs M, Morrison L, Russo SJ, Beers MF. Nonspecific interstitial pneumonia, alveolar proteinosis, and abnormal proprotein trafficking resulting from a spontaneous mutation in the Surfactant Protein C gene. *Pediatr Res* 2005;57:89-98.
173. Cameron HS, Somaschini M, Carrera P, Hamvas A, Whitsett JA, Wert SE, Deutsch G, Nogee LM. A common mutation in the Surfactant Protein C gene associated with lung disease. *J Pediatr* 2005;146:370-375.
174. Doan ML, Guillerman RP, Dishop MK, Nogee LM, Langston C, Mallory GB, Sockrider MM, Fan LL. Clinical, radiological and pathological features of ABCA3 mutations in children. *Thorax* 2008;63:366-373.
175. Guillot L, Epaud R, Thouvenin G, Jonard L, Mohsni A, Couderc R, Counil F, de Blic J, Taam RA, Le Bourgeois M, Reix P, Flamein F, Clement A, Feldmann D. New Surfactant Protein C gene mutations associated with diffuse lung disease.[erratum appears in j med genet. 2010 jul;47(7):485]. *J Med Genet* 2009;46:490-494.
176. McBee AD, Wegner DJ, Carlson CS, Wambach JA, Yang P, Heins HB, Saugstad OD, Trusgnich MA, Watkins-Torry J, Nogee LM, Henderson H, Cole FS, Hamvas A. Recombination as a mechanism for sporadic mutation in the Surfactant Protein-c gene. *Pediatr Pulmonol* 2008;43:443-450.
177. Thomas AQ, Lane K, Phillips J, 3rd, Prince M, Markin C, Speer M, Schwartz DA, Gaddipati R, Marney A, Johnson J, Roberts R, Haines J, Stahlman M, Loyd JE. Heterozygosity for a Surfactant Protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred.[see comment]. *Am J Respir Crit Care Med* 2002;165:1322-1328.

178. Griesse M, Ripper J, Sibbersen A, Lohse P, Lohse P, Brasch F, Schams A, Pamir A, Schaub B, Muensterer OJ, Schon C, Glockner-Pagel J, Nicolai T, Reiter K, Hector A. Long-term follow-up and treatment of congenital alveolar proteinosis. *BMC Pediatr* 2011;11:72.
179. Suzuki T, Maranda B, Sakagami T, Catellier P, Couture CY, Carey BC, Chalk C, Trapnell BC. Hereditary pulmonary alveolar proteinosis caused by recessive csf2rb mutations. *Eur Respir J* 2011;37:201-204.
180. Suzuki T, Sakagami T, Young LR, Carey BC, Wood RE, Luisetti M, Wert SE, Rubin BK, Kevill K, Chalk C, Whitsett JA, Stevens C, Nogee LM, Campo I, Trapnell BC. Hereditary pulmonary alveolar proteinosis: Pathogenesis, presentation, diagnosis, and therapy. *Am J Respir Crit Care Med* 2010;182:1292-1304.
181. Tanaka T, Motoi N, Tsuchihashi Y, Tazawa R, Kaneko C, Nei T, Yamamoto T, Hayashi T, Tagawa T, Nagayasu T, Kuribayashi F, Ariyoshi K, Nakata K, Morimoto K. Adult-onset hereditary pulmonary alveolar proteinosis caused by a single-base deletion in csf2rb. *J Med Genet* 2011;48:205-209.
182. Doyle DA, Gonzalez I, Thomas B, Scavina M. Autosomal dominant transmission of congenital hypothyroidism, neonatal respiratory distress, and ataxia caused by a mutation of nkx2-1. *J Pediatr* 2004;145:190-193.
183. Popa V, Colby TV, Reich SB. Pulmonary interstitial disease in ig deficiency. *Chest* 2002;122:1594-1603.
184. Prober CG, Whyte H, Smith CR. Open lung biopsy in immunocompromised children with pulmonary infiltrates. *American Journal of Diseases of Children* 1984;138:60-63.
185. Deterding RR, Wagener JS. Lung biopsy in immunocompromised children: When, how, and who?[see comment][comment]. *J Pediatr* 2000;137:147-149.
186. de Blic J, Blanche S, Danel C, Le Bourgeois M, Caniglia M, Scheinmann P. Bronchoalveolar lavage in hiv infected patients with interstitial pneumonitis. *Arch Dis Child* 1989;64:1246-1250.
187. Buckley RH. Pulmonary complications of primary immunodeficiencies. *Paediatr Respir Rev* 2004;5:S225-S233.
188. Tangsinmankong N, Bahna SL, Good RA. The immunologic workup of the child suspected of immunodeficiency. *Annals of Allergy, Asthma, & Immunology* 2001;87:362-369; quiz 370.
189. Gennery AR, Cant AJ. Diagnosis of severe combined immunodeficiency. *Journal of Clinical Pathology* 2001;54:191-195.

190. de Vries E. Immunological investigations in children with recurrent respiratory infections. *Paediatr Respir Rev* 2001;2:32-36.
191. Graham SM. Hiv and respiratory infections in children. *Current Opinion in Pulmonary Medicine* 2003;9:215-220.
192. Thomas H, Risma KA, Graham TB, Brody AS, Deutsch GH, Young LR, Joseph PM. A kindred of children with interstitial lung disease. *Chest* 2007;132:221-230.
193. Cha SI, Fessler MB, Cool CD, Schwarz MI, Brown KK. Lymphoid interstitial pneumonia: Clinical features, associations and prognosis. *Eur Respir J* 2006;28:364-369.
194. Langston C, Dishop MK. Diffuse lung disease in infancy: A proposed classification applied to 259 diagnostic biopsies. *Pediatr Dev Pathol* 2009;12:421-437.
195. Deterding RR, Young LR, Dishop M, Fan LL, Dell SD, Sweet SC, Hagood J, Redding G, Castile R, Kurland G, Prestidge A, Morton R, Galambos C, White F, Askin F, Trapnell BC, Langston C. Diffuse lung disease in older children--report of the child network review. *Am J Respir Crit Care Med* 2007;175:A148.
196. Travis WD, King TE, Jr., Bateman ED, Lynch DA. ATS/ERSInternational multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277-304.
197. Deterding RR, Pye C, Fan LL, Langston C. Persistent tachypnea of infancy is associated with neuroendocrine cell hyperplasia. *Pediatr Pulmonol* 2005;40:157-165.
198. Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med* 2006;173:475-482.
199. Leonard MB. Glucocorticoid-induced osteoporosis in children: Impact of the underlying disease. *Pediatrics* 2007;119 Suppl 2:S166-174.
200. Ward LM. Osteoporosis due to glucocorticoid use in children with chronic illness. *Horm Res* 2005;64:209-221.
201. Easterbrook M. Detection and prevention of maculopathy associated with antimalarial agents. *Int Ophthalmol Clin* 1999;39:49-57.
202. Chang WH, Katz BJ, Warner JEA, Vitale AT, Creel D, Digre KB. A novel method for screening the multifocal electroretinogram in patients using hydroxychloroquine. *Retina* 2008;28:1478-1486.

203. Radley-Smith R, Aurora P. Transplantation as a treatment for end-stage pulmonary hypertension in childhood. *Paediatr Respir Rev* 2006;7:117-122.
204. Webber SA, McCurry K, Zeevi A. Heart and lung transplantation in children. *Lancet* 2006;368:53-69.
205. Mallory GB, Spray TL. Paediatric lung transplantation. *Eur Respir J* 2004;24:839-845.
206. Woo MS. An overview of paediatric lung transplantation. *Paediatr Respir Rev* 2004;5:249-254.
207. Khan MS, Heinle JS, Samayoa AX, Adachi I, Schechter MG, Mallory GB, Jr., Morales DLS. Is lung transplantation survival better in infants? Analysis of over 80 infants. *J Heart Lung Transplant* 2012.
208. Moreno A, Maestre J, Balcells J, Marhuenda C, Cobos N, Roman A, Soler J, Montferrer N, Linan S, Gartner S, Roqueta J, Majo J. Lung transplantation in young infants with interstitial pneumonia. *Transplantation Proceedings* 2003;35:1951-1953.
209. Benden C, Aurora P, Edwards LB, Kucheryavaya AY, Christie JD, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI. The registry of the international society for heart and lung transplantation: Fourteenth pediatric lung and heart-lung transplantation report--2011. *J Heart Lung Transplant* 2011;30:1123-1132.
210. Bott L, Beghin L, Devos P, Pierrat V, Matran R, Gottrand F. Nutritional status at 2 years in former infants with bronchopulmonary dysplasia influences nutrition and pulmonary outcomes during childhood. *Pediatr Res* 2006;60:340-344.
211. Konstan MW, Butler SM, Wohl ME, Stoddard M, Matousek R, Wagener JS, Johnson CA, Morgan WJ, Investigators, Coordinators of the Epidemiologic Study of Cystic F. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr* 2003;142:624-630.
212. Zemel BS, Jawad AF, FitzSimmons S, Stallings VA. Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: Analysis of the cystic fibrosis foundation national cf patient registry. *J Pediatr* 2000;137:374-380.
213. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB, Advisory Committee on Immunization Practices CfDC, Prevention. Prevention and control of influenza. Recommendations of the advisory committee on immunization practices (acip).[erratum appears in mmwr morb mortal wkly rep. 2005 aug 5;54(30):750.][update of

- mmwr recomm rep. 2004 may 28;53(rr-6):1-40; pmid: 15163927].
MMWR Recomm Rep 2005;54:1-40,.
214. Fenton C, Scott LJ, Plosker GL. Palivizumab: A review of its use as prophylaxis for serious respiratory syncytial virus infection. *Paediatr Drugs* 2004;6:177-197.
215. Kristensen K, Hjuler T, Ravn H, Simoes EAF, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: A population-based cohort study. *Clin Infect Dis* 2012;54:810-817.
216. Bluebond-Langer M. In the shadow of illness : Parents and siblings of the chronically ill child. Princeton, N.J.: Princeton University Press; 1996.