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Infants and Young Children with Children's Interstitial Lung Disease

Robin R. Deterding, M.D.[1,2]

Though interstitial lung disease (ILD) can occur at any age in children, disorders more common in infancy and young children have received increased attention as an important group that is disproportionally affected, linked to lung development and lung injury, and represents disorders not seen in adult ILD. Identifying those children with potential children's ILD (chILD) and establishing a specific chILD diagnosis has evolved and is critical for pediatric pulmonologists, neonatologists, radiologists, and pathologists to recognize. Specific disorders more common in infancy include diffuse developmental disorders, growth abnormalities, pulmonary interstitial glycogenosis, neuroendocrine cell hyperplasia of infancy, and surfactant mutation dysfunction mutations. The presentation, evaluation, treatment, and clinical course are discussed for each of these specific disorders and other categories less common in infants and young children are briefly mentioned. Resources for physicians and families are also reviewed.

Introduction

Children's interstitial lung disease (chILD) is a term used to describe a heterogeneous group of rare and diffuse lung diseases that produce considerable morbidity and mortality.[1] These disease processes may affect different compartments of the lung to include not only the interstitium but also the airways, alveolar space, vascular bed, lymphatic channels, and pleural space. Because of disease involvement beyond the interstitium, some currently prefer the term rare diffuse lung disease.[2]

The true incidence and prevalence of these collective disorders have not been determined; though a national survey conducted in the United Kingdom and Ireland from 1995 to 1998 reported an estimated prevalence of 3.6 cases per million of chronic ILD in immunocompetent children.[3] This reported prevalence is likely a significant underestimate for the following reasons: 1) the survey occurred prior to the recognition of specific disorders (*e.g.*, ABCA3 mutations and neuroendocrine cell hyperplasia of infancy [NEHI]) and the development of the new classification systems for children with diffuse lung disease; 2) it required a child to have a lung biopsy for inclusion; and 3) it included pediatricians in practice, which may or may not have included neonatologists to gain an appreciation for neonatal disorders. In fact, as the diagnostic criteria for each chILD disorder has evolved and been broadly disseminated, increased identification of children with chILD has occurred worldwide. No prevalence data are available on specific disorders, with the exception of limited data on surfactant protein mutations.[4–6] In summary, though individually rare, chILD disorders as a collective group may represent a sizeable population of children.

Infants and Young Children with ChILD

Three landmark pediatric ILD studies demonstrate that infants and young children are disproportionately affected. Clement and colleagues conducted a questionnaire in European centers to identify pediatric patients who met the definition of ILD.[7] In this population of 185 children with ILD, 31% were <2 years of age. Deutsch and colleagues in the North America Children's Interstitial Lung Disease Research Network (CHILDRN) applied a new pediatric classification system to 186 lung biopsies obtained over 5 years from children under 2 years of age at 11 centers in North America.[2] Table 1 lists the proposed classification system and categories for children with diffuse lung disease disorders. Over half the biopsies could be categorized as "Disorders more Prevalent in Infancy." Recently, Langston and Dishop reviewed over 250 lung biopsies from infants under 1 year of age and applied the same pediatric classification system

[1]Breathing Institute at the Children's Hospital Denver and Section of Pediatric Pulmonary Medicine, University of Colorado Denver, Aurora, Colorado.
[2]Children's Interstitial Lung Disease Research Network (CHILDRN).

Table 1. Proposed Pediatric Diffuse Lung Disease Classification

Disorders more prevalent in infancy	*Specific disorders in disorders prevalent in infancy*	*Other categories*	*Specific disorders in other category*
Diffuse developmental disorders	ACDMPV, congenital alveolar dysplasia	Disorders of the normal host	Infection, hypersensitivity, aspiration
Growth abnormalities	Pulmonary hypoplasia, chronic neonatal lung disease of prematurity, trisomy 12, congenital heart disease	Disorders of systemic disease	Metabolic disease, collagen vascular and autoimmune
Pulmonary interstitial glycogenosis (PIG)	Patchy PIG with growth abnormalitiesDiffuse PIG without growth abnormalities	Disorders of the immune compromised	Infection, lymphocytic disorders, transplant-related
Neuroendocrine cell hyperplasia of infancy (NEHI)		Disorders masquerading as ILD	Lymphatic abnormalities, pulmonary arterial or vein abnormalities
Surfactant dysfunction disorders	Surfactant proteins B and C; ABCA3, TTF1, lysinuric protein intolerance, undefined	Unclassified	Poor quality biopsy

as Deutsch et al.[8] Sixty-eight percent of the biopsies were also placed in the category "Disorders more Prevalent in Infancy," reinforcing the importance of this group of disorders and highlighting the need for pediatric pulmonologists, pathologists, radiologists, and neonatologists to recognize and understand these disorders.

Not surprisingly, the category "Disorders more Prevalent in Infancy" highlights the need to consider interactions between lung development and disease in young children. Most disorders in this category arise at different stages of fetal lung development, unlike categories more commonly seen in older children that are associated with lung injury and repair. Understanding lung development and the developing lung's response to disease is integral to determining mechanisms of disease and developing therapeutic interventions specific for infants and young children with chILD.

The new classification schema for children with ILD has also been critically important. The adult ILD classification systems have many short comings for children. Adult ILD classification systems do not include nomenclature for or recognition of disorders more prevalent in infants such as NEHI or pulmonary interstitial glycogenosis (PIG) and may include disorders not seen in infants and young children such as usual interstitial pneumonitis (UIP), which has created significant confusion.[9,10] The new pediatric classification system has been essential to avoid confusion, improve diagnosis, create specific treatments, and pursue research for chILD in young children.[2]

It is also clear that young children with chILD have significant disease burden. Hypoxemia and tachypnea are the most common symptoms.[7,11] A significant number of children also have poor growth requiring nutritional supplementation, gastroesophageal reflux, and pulmonary hypertension. A mortality rate of 30% has been quoted in the literature for all chILD with the presence of pulmonary hypertension recognized as a considerable risk factor for mortality.[2,12] Mortality is often higher in children with specific disorders: developmental disorders, growth disorders, and certain surfactant dysfunction mutations, emphasizing the need to make a more specific chILD diagnosis.[2]

Evaluation

A major diagnostic step is to recognize children who require further investigation for chILD. To improve recognition, the CHILDRN developed a working clinical definition to identify children who may benefit from a chILD evaluation. This clinical definition has been labeled chILD syndrome. ChILD syndrome requires the presence of at least 3 of the 4 following criteria in the absence of other known disorders: (1) respiratory symptoms (cough, rapid breathing, or exercise intolerance), (2) signs (resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse abnormalities on chest X-ray or computed tomography (CT) scan.[1] Retrospectively applying this definition to a cohort of children with chILD under 2 years of age, investigators found 91% of 218 cases met criteria.[1] This suggests that the chILD syndrome criterion may be a sensitive screening tool for young children who could benefit from an ILD evaluation. One caveat for applying chILD syndrome is to determine if children, who could be excluded for other known disorders, could also have a chILD disorder. For example, children with suspected chronic lung disease of prematurity or congenital heart disease may also have PIG.[2] Thus, children with known disease, who have pulmonary symptoms out of proportion to what would be expected, may also benefit from a chILD evaluation. Further study is required to refine the criterion, understand the applications to older children, and evaluate specificity.

Clinical context can provide valuable differential diagnostic clues. Children presenting in the immediate newborn period are more likely to have specific diagnoses such

as developmental lung disorders, PIG, and surfactant protein dysfunction mutations (SPB and ABCA3). Prematurity, congenital heart disease and trisomy 21 may be associated with alveolar simplification seen in growth abnormalities. Congenital anomalies may be associated with alveolar capillary dysplasia associated with misalignment of pulmonary veins (ACDMPV).[13,14] Congenital or transient hypothyroidism with even subtle developmental delays or chorea may point to a thyroid transcription factor 1 deletion or mutation (also known as NKX2-1 or brain–thyroid–lung syndrome) in a child with lung disease, which should not just be attributed to aspiration.[15–17] A family history of ILD, prolonged oxygen requirements, or early infant death may suggest genetic disorders such as ACDMPV, surfactant dysfunction mutations, or NEHI.[13,18,19] Environmental exposure to birds that can give rise to hypersensitivity pneumonitis and serious infections such as adenovirus that can result in bronchiolitis obliterans should also be sought in the history.[20] Though helpful to guide clinical reasoning, suggest a possible diagnose, and direct the diagnostic evaluation, clinical history alone is usually insufficient to diagnose specific chILD disorders.

Diagnostic evaluations that may be required include bronchoscopy with bronchoalveolar lavage (BAL), high-resolution CT (HRCT), infant pulmonary function testing (iPFTs), genetic testing, and ultimately a lung biopsy if less invasive testing is not diagnostic. Bronchoscopy with BAL may rule out specific diagnoses related to infection, airway anomalies, pulmonary hemorrhage, or histiocytosis.[21] BAL that failed to detect CD1a cells would not rule out histiocytosis. A high-quality volumetric-controlled HRCT free of motion artifact can suggest a diagnosis of bronchiolitis obliterans, surfactant dysfunction mutations, or NEHI.[22] Though not widely performed, centers experienced in infant PFTs have reported characteristic patterns of air trapping and obstruction for NEHI.[23] Major improvements in genetic analysis, lung biopsy techniques especially in infants as small as 3 kg,[24,25] and the new clinicopathologic classification system for diffuse lung disease in children[2,8] have improved our diagnostic abilities and changed the diagnostic paradigm in chILD. Any child presenting with unexplained chILD should be considered for surfactant dysfunction mutation (SPB, SPC, ABCA3, or TTF1) genetic testing if possible before obtaining a lung biopsy.[19] Choosing the appropriate surfactant mutation for testing depends upon the age of clinical presentation and associated findings. If the diagnosis is not apparent at the completion of less invasive testing, a lung biopsy should strongly be considered to establish the diagnosis in a child who has persistent symptoms (at least 2 months), progressively worsening disease or life-threatening disease.[1] Examination of pulmonary tissue may be diagnostic by classification, rule out other disease processes, or provide helpful guidance to determine treatment options based upon the histological pattern present.

Disorders More Prevalent in Infancy

A brief overview of specific disorders in this important category of chILD will be provided in this manuscript with detailed descriptions of HRCT and histological features provided in companion manuscripts by Guillerman[26] and Dishop.[27]

Diffuse developmental disorders

Disorders in this category arise early in lung development and are diagnosed from lung biopsy or postmortem tissue based upon histological criteria.[27] Disorders include acinar/alveolar dysgenesis, congenital alveolar dysplasia, and ACDMPV. ACDMPV is the more common disorder with over 200 cases reported in the literature, including 10% with a familial history suggestive of an autosomal recessive inheritance pattern.[13]

Term infants usually present in the immediate neonatal period with rapidly progressive respiratory failure and severe pulmonary hypertension that progress to death in the first 2 months of life despite therapeutic interventions for pulmonary hypertension, advanced ventilation strategies, and extracorporeal membrane oxygenation (ECMO).[28] Rare reports document the potential for a later presentation and survival for months with therapy.[29] In a small series of 23 infants only half were suspected of having ACDMPV clinically before lung biopsy or postmortem analysis, suggesting that some cases may go undiagnosed.[28] The majority of patients reported also had at least one associated anomaly affecting the cardiovascular, gastrointestinal (GI), or genitourinary system.

Recently, microdeletions in the *FOX* gene cluster on 16q24.1 and mutations of FOXF1 have been associated with familial cases of ACDMPV and associated congenital anomalies.[13] Mutation and microdeletion analysis of the *FOXF1* gene and genetic counseling should now be considered in suspected cases of ACDMPV. Furthermore, ACDMPV should also be considered in the differential and genetic testing considered in patients with hypoplastic left heart (HLH), GI malrotations or atresias, or renal abnormalities who have significant respiratory failure and pulmonary hypertension.[13,30] A low threshold of suspicion to look for ACDMPV is important for future family planning and genetic counseling. With more advanced understanding of these genetic abnormalities, a broader spectrum of ACDMPV phenotypes will likely be recognized.

As ACDMPV is universally fatal, lung transplantation is the only viable treatment option; at least one child has successfully undergone lung transplant.[31] The option of lung transplantation is frequently limited due the severity and rapidly progressive nature of the lung disease, which limits patient transport to a pediatric lung transplant center and survival on the waiting list. Once a definitive diagnosis is established, many families currently elect to discontinue support.

Growth abnormalities

Growth abnormalities are associated with prenatal and postnatal defective alveolarization resulting in varying degrees of alveolar simplification and were the most common diffuse lung disease category represented in the lung biopsy reviews by Deutsch and the CHILDRN and Langston. This category included (1) pulmonary hypoplasia associated with prenatal conditions (eg, oligohydramnios, neuromuscular disease, etc.), (2) chronic lung disease of prematurity from postnatal insults (many may consider this the "new BPD"), (3) trisomy 21 growth abnormalities, and (4) growth abnormalities associated with congenial heart disease.[8,31]

Though not traditionally included in the differential of chILD, growth abnormalities are important to consider. They distort lung architecture in different compartments of the lung, including the interstitium. A significant number of patients with growth abnormalities may also be further compromised by interstitial patchy areas of PIG. The CHILDRN lung biopsy review provides valuable clinical information about growth abnormalities. Indications for lung biopsies were frequently symptoms out of proportion to gestational age or clinical status. Unless the patient was premature, growth abnormalities were usually unsuspected by the clinician and frequently underreported on the pathology report at the biopsying center, even when significant. Imaging did not appear to be helpful to the clinician in distinguishing these disorders. The clinical context of prematurity and congenital heart disease was highly predictive of a growth abnormality. Mortality rates in this population were significant at 34%; marked alveolar simplification as identified by enlargement of alveolar spaces and pulmonary hypertensive changes were associated with increased mortality.

A full review of lung growth abnormalities and treatment is outside the scope of this manuscript.[32] However, growth abnormalities remain an important differential diagnosis in children with chILD syndrome who have prematurity, trisomy 21, congenital heart disease, and risk factors for pulmonary hypoplasia. Furthermore, the finding that PIG may complicate growth disorders could prompt consideration for a diagnostic lung biopsy and the use of systemic corticosteroids as a therapeutic treatment option in acutely ill infants with striking oxygen requirements after weighing the risks and benefits.

Pulmonary interstitial glycogenosis

Since the original description of 7 atypical neonatal lung cases of undefined etiology in 2002, PIG has increasingly been recognized in pediatric lung biopsies.[33] It is diagnosed histologically by the presence of round, glycogen laden, mesenchymal cells that widen the interstitial walls.[27] These cells are poorly understood but are not believed to be inflammatory or typical fibroblast cells. Electron microscopy is the most reliable diagnostic method to demonstrate the diagnostic deposits of intracellular glycogen and occasionally lipid, which have led some to postulate that these cells may be lipofibroblasts.[8] As the diagnosis of PIG requires examination of lung tissue, the true incidence of this condition may be much more common than currently appreciated.

Infants with PIG usually present immediately or soon after birth in the neonatal period with tachypnea and oxygen requirements out of proportion to the clinical situation. When considering the markedly widened interstitium created by these cells, the pathophysiology of a significant diffuse defect that produces out of proportion hypoxemia is better appreciated. Both diffuse interstitial PIG without growth abnormalities and patchy PIG involvement in preterm infants with growth abnormalities have been recognized histologically. It can also complicate the course of children with congenital heart disease[31] and has been reported in monozygotic 31-week preterm twins.[34] Finally, PIG has only been reported in the literature in lung biopsies from young children <6 months of age, though we have seen it in an explanted lung of one child who was transplanted at 8 months. Based on these findings, some believe PIG may have a role in lung development.

Treatment with glucocorticoids has been used with subjective improvements in oxygenation status. Many chILD centers will recommend such therapy for acutely ill children after weighing the risk and benefits of glucocorticoid therapy. Clinical outcomes can be varied in this heterogeneous disorder. No mortality has been seen in pure diffuse PIG but deaths have occurred in the presence of growth abnormalities and pulmonary hypertension.[2,33]

A recent case report provides intriguing insights into potential mechanisms of disease.[31] An infant with congenital heart disease underwent a lung biopsy that showed PIG at 10 days of age and was rapidly weaned from the ventilator 5 days after glucocorticoid treatment. The same infant was subsequently re-biopsied 39 days later during an intrathoracic operation related to previous congenital heart surgery. Immunostaining analysis of the initial lung biopsy demonstrated increased markers of proliferation in the PIG cells but on the subsequent biopsy limited proliferation markers and increased markers of apoptosis were present. This interesting case report suggests that PIG mesenchymal cells can actively proliferate, expanding the interstitial space, and that apoptosis may be involved in the resolution of this process. The role of glucocorticoid therapy is not clear. There are many fundamental questions to be studied related to PIG that could impact clinical care: associated long-term clinical outcomes in infants with PIG, the role of these cells in lung development and growth abnormalities, mechanisms of cellular regulation and identification (eg, could these mesenchymal cells be a lipofibroblast?), and biomarker identification for less invasive diagnostic strategies.

Neuroendocrine cell hyperplasia of infancy

Children with NEHI usually present in the first year of life after the newborn period with classic findings of tachypnea, retractions, hypoxemia, and crackles on examination.[35] Most patients do not have significant cough or wheezing. The diagnostic goal standard has been the identification of a specific number of bombesin-immunopositive neuroendocrine cells in the bronchioles and neuroendocrine cell bodies in the interstitium, in the absence of other known pathologic features.[27]

Since the original description of NEHI in 2005 by Deterding,[35] patients have been reported from around the world. Recent reports have also increased our understanding of NEHI and added to our diagnostic strategies. After reviewing 23 biopsy proven NEHI CTs and 6 CTs from other patients with chILD conditions, investigators have reported a more "classic" NEHI pattern consisting of ground-glass opacities in the right middle and lingual and air trapping in the lower lobes.[36] The CT sensitivity and specificity to diagnose NEHI in this study was 78% and 100%, respectively. Infant pulmonary function data from a single center experience demonstrate that physiologically NEHI is associated with significant air trapping and airway obstruction when compared with disease controls and that this degree of air trapping is even greater than infants with bronchopulmonary dysplasia.[23] Preliminary data from a small number of older NEHI children nearing their second decade of life also suggest that air trapping may be persistent in some patients.[37] Based upon these data, if a patient has

characteristic symptoms, CT findings, and infant pulmonary functions for NEHI, some centers are now forgoing lung biopsies in these patients and diagnosing these patients clinically with NEHI syndrome.

The etiology for NEHI and the role of neuroendocrine cells remains unclear. Cytokine analysis of BAL from NEHI patients has demonstrated no significant inflammatory cytokines.[38] These findings in conjunction with the lack of inflammatory cells on lung biopsy tissue and subjective clinical reports that corticosteroids do not reverse symptoms strongly support that NEHI does not have a classic inflammatory basis for disease. Familial cases of NEHI have now been reported suggesting a possible genetic basis for NEHI.[39] Novel biomarkers for NEHI are now being identified in BAL,[40] which could provide further insights into disease mechanisms and possible new therapeutic targets.

Treatment at this time is largely supportive and focused on preventing hypoxemia, maintaining good nutrition, and preventing infections. Except for brief glucocorticoid bursts with viral infections, systemic corticosteroid therapy is not recommended by chILD experts in NEHI.

Long-term outcomes in NEHI have been good with no reported deaths.[2,35] However, significant morbidity is reported as most patients require oxygen for many years and many require aggressive nutritional supplementation. Many families subjectively report a significant impact on the young child and family's quality of life, though formal assessment of quality of life has not been completed. Furthermore, adolescent patients with NEHI have had persistent air trapping and nonspecific exercise complaints suggesting that NEHI may have long-term clinical implications beyond childhood.[37]

Surfactant metabolism dysfunction mutations

The identification of genetic mutations in proteins involved in surfactant metabolism has revolutionized our understanding of certain types of chILD, especially for infants and young children. Children with surfactant mutation disorders can present immediately from birth with respiratory failure (SPB and ABCA3) or later in childhood (SPC and ABCA3) with persistent tachypnea and hypoxemia. Clinically these disorders can be suspected in infants and young children with chILD syndrome who have diffuse, hazy, ground-glass infiltrates on chest radiographic imaging or HRCT without other compelling etiologies. Some families may have a history of lung disease, especially with SPC mutations, but many do not. Potential clues may also include BAL fluid that may show signs of positive PAS material and in infants nonspecific elevations in serum LDH. As the speed of genetic mutational analysis has improved significantly over the last few years, many clinicians now assess for these mutations before pursuing a lung biopsy. If disease causing mutations are identified, most children do not need to proceed to lung biopsy. Lung biopsy should still be the definitive test in a symptomatic child without genetic mutations, with only one disease causing ABCA3 mutation or with genetic mutations in surfactant proteins that may not clearly be disease causing. Recently BAL biomarkers have been found in a small group of infants and children with surfactant mutations, which could provide future novel methods for diagnosis and therapeutic targets.[40]

Treatment strategies for infants range from lung transplant for lethal surfactant mutation disease in children who present with respiratory failure for SPB and ABCA3 to aggressive chronic ventilation for children with respiratory failure from a SPC mutation. Children who present in infancy and early in childhood with SPC mutations have been shown to improve over time but it is unclear if this is related to therapeutic intervention or the natural history of the disease.[41] For this reason, consideration for lung transplantation in infants and young children with SPC mutations should be done with caution and favor given toward chronic ventilation. Older patients and adults with SPC mutations still may require a lung transplant for end-stage pulmonary fibrosis. Currently, there is only anecdotal experience from single centers related to pharmacological approaches. Many patients receive trials of pulse corticosteroids (10–30 mg/kg a day for 3 days), hydroxychloroquine (Plaquenil) 5–7 mg/kg per day,[42] and azithromycin[43] to look for a clinical response. If this approach is pursued, there must be close attention to side effects to include prevention of opportunistic infection, fluid retention, hypertension, retinopathy, and bone density. Aggressive nutritional supplementation with gastrostomy and Nissen fundoplication is frequently necessary for growth. Every attempt should be made to prevent infections and treatment with Synagis (palivizumab) should strongly be considered as infections could further activate lung injury. Perhaps most important is to seek consultation with a center of excellence for children with chILD.

Recently it is has become increasingly recognized that mutations in thyroid transcription factor 1, also known as the *NKX2-1* gene, can cause lung disease ranging from ILD to severe respiratory failure in the newborn period or with viral infections.[15,44] Many of these children can have varying degrees of hypothyroidism from congenital onset to transient low levels or developmental delays with or without chorea. Children can present with respiratory failure as a newborn or present outside the neonatal period with recurrent viral infections and persistent hypoxemia. Many older children may have been misdiagnosed with aspiration. Though these children may aspirate the degree of lung injury and symptoms are usually out of proportion to the expected course. Because of the variability in clinical symptoms, many cases may be unrecognized, requiring a high index of suspicion for children with any combination of lung disease, hypothyroidism, or developmental delay. Similar treatment approaches that have been used for the other surfactant mutations have also been used for TTF1 mutations though there is limited experience. Patients may also need to be referred for lung transplantation.

A more complete review of these disorders can be found in the manuscript by Dr. Nogee entitled "Genetic Basis of Children's Interstitial Lung Disease."[19]

Other Categories

Though "Disorders more Prevalent in Infancy" was the most frequent category recognized in lung biopsy reviews, other conditions can also be found in infants and young children that are primarily related to lung injury and repair. The second most common category is disorders of the normal host, which usually result from an environmental insult. This insult is frequently related to postinfection complications that include chronic bronchiolitis and bronchiolitis

obliterans[45] but can also include eosinophilic pneumonia and aspiration.[2] Disorders in the immunocompromised host associated with immune deficiencies should prompt a close evaluation for infection and lymphocytic disorders such as follicular bronchiolitis and lymphocytic interstitial pneumonitis (LIP). A unique group of immunocompromised patients include the easily identified but growing group of infant and young children undergoing bone marrow transplantation. Infection is also a concern in these children but so too is lung injury associated with the clinical syndrome of noninfectious idiopathic pneumonia syndrome (IPS), which causes significant mortality in this population and is poorly understood. Systemic disorders with pulmonary hemorrhages,[46] sarcoidosis, and metabolic diseases are also reported but are rarer. Pulmonary hemorrhage associated with collagen vascular diseases are much more common in children older than 2 years of age. Finally, lymphatic[47][48] and pulmonary vein abnormalities can also masquerade at chILD in this age group and should be ruled out.

Resources for Physicians and Families

The Children's Interstitial Lung Disease (chILD) Foundation (www.childfoundation.us) is a 501(c) 3 nonprofit organization dedicated to the education of families and research to improve the care and find cures for chILD disorders. Excellent resources have been created for physicians and families that can be downloaded from the chILD Foundation Web site. The chILD Foundation can also be an excellent source of support for families through direct parent-to-parent communication. The American Thoracic Society (ATS) has also recently produced an excellent free handout entitled American Thoracic Society Patient Information Series: What is ILD in children[49]? Further information on the development of educational material through the collaboration of the chILD Foundation and chILD physicians can be found in the manuscript by McDougal et al.[50]

The CHILDRN is a multidisciplinary international group of physicians committed to improve the care and create research to provide cures for infants and young children with these disorders. CHILDRN, in partnership with the chILD Foundation and the Children's Hospital in Denver, will soon launch an international registry/database to capture natural history, clinical features, response to therapies, and outcome data on these children. The goal will be to collect information in one electronic location for quality improvement initiative, better patient management, open label clinical trials, and translational research.

Author Disclosure Statement

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Address correspondence to:
Robin R. Deterding, M.D.
13123 E. 16th Ave B395
Aurora, CO 80045

E-mail: deterding.robin@tchden.org

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