Pediatric Interstitial Lung Disease Revisited

Leland L. Fan, MD,1* Robin R. Deterding, MD,2 and Claire Langston, MD3

Summary. The spectrum of pediatric interstitial lung disease (PILD) includes a diverse group of rare disorders characterized by diffuse infiltrates and disordered gas exchange. Children with these conditions typically present with tachypnea, crackles, and hypoxemia. Recent advances have been made in the identification of different types of PILD that are unique to infancy. More exciting has been the discovery of genetic abnormalities of surfactant function, now described in both children and adults. A systematic evaluation of the child presenting with diffuse infiltrates of unknown etiology is essential to the diagnosis. Most often, lung biopsy is required. Current treatment options remain less than satisfactory, and morbidity and mortality remain considerable. Pediatr Pulmonol. 2004; 38:369–378. © 2004 Wiley-Liss, Inc.

Key words: children; infants; interstitial lung disease.

INTRODUCTION

The spectrum of interstitial lung disease (ILD) includes a group of rare, mostly chronic pulmonary disorders characterized by diffuse infiltrates and disordered gas exchange. Pediatric interstitial lung disease (PILD) is difficult to define due to the diverse nature of the diseases encountered. It should perhaps be considered a syndrome characterized by tachypnea, crackles, hypoxemia, and/or diffuse infiltrates, which once identified should trigger a search for a more specific disorder.

It has been 11 years since two of us (L.L.F. and C.L.) wrote our first review of PILD for this Journal.1 Since then, much has been learned. The idiopathic interstitial pneumonias have been reclassified to clarify the distinctive features of these diseases. Newer entities unique to infants and children have been identified and described. The genetic basis for certain types of familial lung disease has been linked to genetic defects in surfactant processing. In this review, we will focus on these and other developments that have improved our understanding of these diverse and rare disorders in children.

EPIDEMIOLOGY

Though limited data exist regarding the epidemiology of PILD, the published prevalence of ILD is much lower in children than in adults. In a population-based registry in Bernalillo County, New Mexico, Coultaas et al. reported an ILD prevalence of 80.9/100,000 for adult males and 67.2/100,000 for adult females.2 In contrast, a national survey of pediatricians with known interest in lung disease in the United Kingdom and Ireland identified 46 cases of biopsy-proven PILD, aged 0–16 years.3 There were 29 males and 17 females, with 9 cases reported from four families. Thirty-five patients presented in the first year of life. The prevalence of PILD was estimated to be 0.36/100,000. This study suggests that ILD in children is truly rare. However, with improved definitions, optimal identification strategies, and awareness of new distinct
entities in PILD, the estimated prevalence may increase in the future.

CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

No classification scheme for PILD is entirely satisfactory, since consensus has not been reached on a precise definition of PILD and which conditions should be included or excluded.

Recently, an expert panel of pulmonologists, radiologists, and pathologists from the American Thoracic Society and the European Respiratory Society formulated an International Consensus Statement to standardize the classification of idiopathic interstitial pneumonias in adults. This classification defines the histologic pattern and relates it to the clinical-radiologic-pathologic diagnosis (Table 1). The scheme is helpful in clarifying the various and somewhat confusing terms that have been used to describe these various conditions. With the exception of usual interstitial pneumonitis (UIP), discussed below, and respiratory bronchiolitis, reported in adults who smoke, the remaining idiopathic interstitial pneumonias listed in Table 1 have been recognized in children.

Other types of PILD can be categorized as a primary lung process or part of a systemic process (Table 2). Since our original review, a number of “new” ILDs have been described, mainly in neonates and infants (Table 3). Unfortunately, it is not possible to discuss every form of PILD in detail, so we will emphasize certain conditions for which new information is available.

Usual Interstitial Pneumonitis: Does It Exist in Children?

The International Consensus Statement validates the concept that UIP is the pathologic pattern for patients with a clinical diagnosis of idiopathic pulmonary fibrosis (IPF) or cryptogenic fibrosing alveolitis (CFA). The key histologic features of UIP are architectural destruction, fibrosis often with honeycombing, scattered fibroblastic foci, patchy distribution, and involvement of the periphery of the acinus or lobule. Some authorities emphasize that the fibroblastic foci are the leading edge of the fibrotic process, and their presence is essential to the diagnosis of UIP.

To our knowledge, despite more than 100 reported cases of UIP (and its clinical equivalents, IPF and CFA) in children (including two reported by L.L.F.), the diagnostic fibroblastic foci were not described in any of these reports. A recent pathologic study of 25 PILD cases at the Royal Brompton Hospital in London uncovered no cases with the

TABLE 1—Classification of Idiopathic Interstitial Pneumonias

<table>
<thead>
<tr>
<th>Histologic patterns</th>
<th>Clinical-radiologic-pathologic diagnosis</th>
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<tbody>
<tr>
<td>Usual interstitial pneumonia</td>
<td>Idiopathic pulmonary fibrosis/cryptogenic fibrosis alveolitis</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia</td>
<td>Nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>Cryptogenic organizing pneumonia</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Acute interstitial pneumonia</td>
</tr>
<tr>
<td>Respiratory bronchiolitis</td>
<td>Respiratory bronchiolitis interstitial lung disease</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia</td>
<td>Lymphoid interstitial pneumonia</td>
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2Actual cases not reported in children.

TABLE 2—Other Forms of Interstitial Lung Disease

<table>
<thead>
<tr>
<th>Primary pulmonary disorders</th>
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<tbody>
<tr>
<td>Alveolar hemorrhage syndromes</td>
</tr>
<tr>
<td>Aspiration syndromes</td>
</tr>
<tr>
<td>Drug- or radiation-induced lung disease</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
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<tr>
<td>Infectious or postinfectious chronic lung disease</td>
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<tr>
<td>Pulmonary alveolar proteinosis</td>
</tr>
<tr>
<td>Pulmonary infiltrates with eosinophilia</td>
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<tr>
<td>Pulmonary lymphatic disorders</td>
</tr>
<tr>
<td>Pulmonary microlithiasis</td>
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<tr>
<td>Pulmonary vascular disorders (proliferative and congenital)</td>
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</table>

Systemic disorders with pulmonary involvement

<table>
<thead>
<tr>
<th>Connective tissue disease</th>
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<tbody>
<tr>
<td>Histiocytosis</td>
</tr>
<tr>
<td>Lipid storage diseases</td>
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<tr>
<td>Neurocutaneous syndromes</td>
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<tr>
<td>Malignancies</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Other inborn errors of metabolism (lysinuric protein intolerance)</td>
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TABLE 3—Unique Forms of Interstitial Lung Disease in Infancy

<table>
<thead>
<tr>
<th>Disorders of lung growth and development</th>
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<tbody>
<tr>
<td>Neuroendocrine cell hyperplasia of infancy/persistent tachypnea of infancy</td>
</tr>
<tr>
<td>Follicular bronchitis/bronchiolitis</td>
</tr>
<tr>
<td>Cellular interstitial pneumonitis/pulmonary interstitial glycogenosis</td>
</tr>
<tr>
<td>Acute idiopathic pulmonary hemorrhage of infancy</td>
</tr>
<tr>
<td>Chronic pneumonitis of infancy/genetic defects of surfactant function</td>
</tr>
</tbody>
</table>
histologic features of UIP. The prognosis of adults with UIP is poor, with the majority of patients succumbing within 5 years of diagnosis. In contrast, children given a diagnosis of IPF or CFA often live much longer and have a nonprogressive course, suggesting that they do not have UIP. These findings have led authorities to question if true UIP actually exists in children.5

Other Idiopathic Interstitial Pneumonias in Children

Desquamative interstitial pneumonitis (DIP) and lymphocytic interstitial pneumonitis (LIP) are seen in children, although they also remain quite rare. In contrast to DIP in adults, DIP in children is not linked to smoking. LIP is seen most often in patients with immune defects (such as HIV infection) and connective tissue disorders. The reader is referred to our original review, as there has been very little new information reported with regard to these entities in children.

In adults, nonspecific interstitial pneumonitis (NSIP) has come to be recognized as a distinctive form of ILD that conveys a better prognosis than UIP. It must be emphasized that NSIP is a histologic diagnosis that may be seen in a number of clinical settings and with various exposure histories, although most cases are of unknown etiology. NSIP histologically is a mixture of inflammation and fibrosis, and has been subdivided into a cellular and a fibrosing pattern based on the relative prominence of these particular components. It lacks the specific diagnostic features of other idiopathic interstitial pneumonias. In adults with NSIP, those with a cellular histologic pattern have a better response to steroid therapy and may resolve completely, while those with fibrosis are likely to progress to end-stage lung disease. In a pathologic study of 25 children with ILD, 4 children had cellular NSIP and 3 had fibrotic NSIP.6

Cryptogenic organizing pneumonia (previously called bronchiolitis obliterans organizing pneumonia) has also been described in children, either as an isolated phenomenon or in children with infection, asthma, drug reactions, malignancies undergoing chemotherapy, bone marrow transplantation, and autoimmune disorders. Interestingly, organizing pneumonia has also been described as a distinctive pulmonary complication of cystic fibrosis. As in adults, the prognosis is usually excellent, with a favorable response to corticosteroids.

Acute interstitial pneumonia (AIP) is a rapidly progressive disorder with a histologic appearance consistent with the organizing form of diffuse alveolar damage. Probably some of the original cases of interstitial fibrosis reported by Hamman and Rich were actually cases of AIP. Although there are no reported pediatric cases, we have encountered AIP in children, generally with a poor prognosis.

Pediatric Interstitial Lung Disease Syndromes Unique to Infancy

Since our previous review, a number of “new” and unique forms of PILD have been described in neonates and infants. It is quite likely that these entities are not new, but actually more precise descriptions of previously misidentified disorders. For many years, pediatric lung specialists would try to fit their ILD cases into adult categories. Since many of these patients were infants, it is quite likely that a number of these cases called UIP, IPF, and CFA were actually cases of these newly defined entities.

Persistent Tachypnea of Infancy/Neuroendocrine Cell Hyperplasia of Infancy (NEHI)

We identified a group of infants who presented with persistent tachypnea, crackles, hypoxemia, and no evidence of an underlying disease to explain their symptoms. Affected infants exhibited hyperinflation on chest radiographs and hyperinflation and ground-glass opacities on high-resolution computed tomography (HRCT). Consistent with radiographic findings, infant pulmonary function testing demonstrated air trapping. Lung biopsies showed no interstitial involvement or inflammation, and no known pathologic disease process. Mild and nonspecific changes were found, including mild airway smooth muscle hyperplasia and increased numbers of alveolar macrophages. Interestingly, hyperplasia of neuroendocrine cells, as demonstrated by bombesin immunohistochemistry, was a consistent and significant finding in the distal airways. Aggregates of neuroendocrine cells, called neuroendocrine bodies, were also increased within the lobular parenchyma. No infectious agents were recovered from patients. Most striking was the discrepancy between the infants’ ill appearance clinically and the lack of demonstrably significant abnormalities in chest films, HRCT, and biopsies.

No study has systematically evaluated the treatment of this condition, but clinical improvement with corticosteroids, bronchodilators, and other agents has been inconsistent. Although patients have been symptomatic and often required oxygen for months to years, their clinical condition gradually improved over time. There have been no known pulmonary-related deaths. Many patients, followed for over 5 years, may still have occasional mild pulmonary symptoms associated with viral infections or exercise, and there is evidence in some of continued hyperinflation. Longitudinal studies will be required to determine the impact of this disorder on adult lung disease.

Originally, we used the term “persistent tachypnea of infancy” to describe the clinical condition, but with the recognition of neuroendocrine cell hyperplasia in the distal airways, we believe “neuroendocrine cell hyper-
interstitial pneumonitis.” Although the patients remained asymptomatic, their clinical presentation with ILD syndrome and the presence of neuroendocrine bodies in the parenchyma still suggest that this disorder best fits under the heading of PILD.

**Follicular Bronchitis/Bronchiolitis**

Kinane et al.\(^{24}\) reported on 5 infants with follicular bronchitis/bronchiolitis presenting with tachypnea, fine crackles, and chronic cough by 6 weeks of age. Lung biopsy revealed follicular lymphocytic infiltration surrounding and locally infiltrating the bronchial walls; no organisms were recovered. All patients improved gradually over several years. Similar features were reported more recently by Hull et al.\(^{25}\) who described chronic bronchiolitis in 8 infants, although 2 had normal biopsies. It is quite possible that NEHI and follicular or chronic bronchiolitis are the same entity, although in our experience, airway inflammation is not a prominent or consistent feature of NEHI.

**Cellular Interstitial Pneumonitis/Pulmonary Interstitial Glycogenosis**

Schroeder et al.\(^{26}\) described 5 infants with tachypnea since birth and diffuse infiltrates of unknown etiology. Lung biopsy revealed interstitial proliferation of bland, nondescript histiocytic-type cells and minimal or no inflammation. The authors called this new entity “cellular interstitial pneumonitis.” Although the patients remained tachypneic for prolonged periods of time (4–18 months after diagnosis), the overall clinical course was marked by general improvement in 4 of 5 infants. The fifth infant died at 3.5 years of age. Since then, three other cases of cellular interstitial pneumonitis have been reported, all with favorable outcomes.\(^{27,28}\)

Recently, Canakis et al.\(^{29}\) described 7 infants whose lung biopsies had the histologic appearance of cellular interstitial pneumonitis. Utilizing electron microscopy, they demonstrated that these characteristic interstitial cells contained monoparticulate glycogen, and postulated an abnormality of lung cytodifferentiation. The authors used the term “pulmonary interstitial glycogenosis” to describe this finding. Six of 7 infants had a favorable outcome, but one died of extreme prematurity and bronchopulmonary dysplasia. Thus pulmonary interstitial glycogenosis is probably a more complete description of cellular interstitial pneumonitis.

**Chronic Pneumonitis of Infancy**

Katzenstein et al.\(^{30}\) described 9 infants with ILD characterized by alveolar septal thickening, striking pneumocyte hyperplasia, and an alveolar exudate containing numerous macrophages, occasional eosinophilic globules, and rare cholesterol clefts. As this pattern was markedly different from the previously described classic patterns of ILD (DIP, UIP, and LIP) and from the cellular interstitial pneumonitis of infancy, they chose the term “chronic pneumonitis of infancy” to reflect the uniqueness of this entity. Of the 6 whose clinical course was known, 2 died and 1 required lung transplantation. Actually, Fisher et al.\(^{31}\) had previously described a similar process in 8 children, although the majority were much older. Typical chest radiograph findings include ground-glass densities, consolidation, volume loss, and hyperinflation.\(^{32}\) An autopsy study of 12 cases of chronic pneumonitis of infancy revealed an age of onset of 1–9 months, with an ultimate fatal outcome despite treatment.\(^{33}\) Thus it appears this condition carries a high mortality rate. Since these original reports, we have come to recognize that many cases with the histologic pattern of chronic pneumonitis of infancy have genetic abnormalities of surfactant function (unpublished data).

**Genetic Abnormalities of Surfactant Function**

Without a doubt, the most important advance in this field has been the discovery of genetic defects of surfactant function. These include mutations in the surfactant protein B (SP-B) gene, expressed recessively;\(^{34,35}\) the surfactant protein C (SP-C) gene, expressed dominantly;\(^{36,37}\) and the newly described ABCA3 gene, expressed recessively.\(^{38}\) SP-B and SP-C are hydrophobic proteins that closely interact with surfactant lipids to facilitate adsorption to the air-liquid interface. ABCA3 is a member of the ATP binding cassette protein family. It is a transmembrane protein that transports substances across biologic membranes and has been localized to the limiting membrane of lamellar bodies. Although defects in SP-B, when homozygous for the most common mutation (121ins2), are highly lethal in newborns, patients with defects in SP-C and ABCA3 genes can have a more variable clinical presentation. Patients with SP-C mutations can present with severe symptoms in the first few months of life, develop symptoms consistent with ILD in adulthood, or remain asymptomatic. Although adults with SP-C deficiency were described with a variety of histologic subtypes, including UIP, DIP, and NSIP,\(^{35,36}\) we believe a more systematic review of the pathology would show some evidence of alveolar lipoproteinosis, which is characteristic of this disorder. The newly described ABCA3 mutations also appear to be lethal in the newborn period, but patients have been recognized to survive longer (personal communication with Dr. Larry Nogee). It is highly likely that some infants previously given a diagnosis of IPF of infancy and familial DIP have genetic abnormalities of surfactant function.\(^{39–42}\)
As surfactant dysfunction mutations have major genetic implications for families, physicians should consider looking for these in any patient with 1) severe unexplained lung disease in the newborn period, 2) diffuse disease involving the entire lung on HRCT, 3) histopathology that demonstrates findings of congenital alveolar proteinosis, DIP, NSIP, or chronic pneumonitis of infancy, and 4) electron microscopy demonstrating abnormal or absent lamellar bodies. The story of surfactant dysfunction mutations is evolving and worthy of ongoing attention. For a complete description of these disorders, including known mutations to date, the reader is referred to the State-of-the-Art later in this series by Larry Nogee.

**DIAGNOSIS**

Studies to diagnose PILD can be divided into those used: 1) to assess extent and severity of disease, 2) to identify disorders that predispose to ILD, and 3) to identify the primary ILD (Table 4). We demonstrated that a systematic approach, utilizing a combination of history, physical examination, and noninvasive and invasive studies, is essential to the diagnosis of PILD. In a prospective study of 51 children, presenting with ILD of unknown etiology, Fan et al. demonstrated that a specific diagnosis was established by history and physical examination alone in one patient, noninvasive studies alone in 8 others, and invasive studies including lung biopsy in another 26. Of the remaining patients, 8 had a suggestive diagnosis, and 8 had no specific diagnosis. These findings were essentially confirmed in a larger multicenter European study, although noninvasive studies alone were slightly less helpful in establishing a diagnosis.

**TABLE 4—Diagnostic Studies**

<table>
<thead>
<tr>
<th>Diagnostic Studies</th>
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<tbody>
<tr>
<td>To assess extent and severity of disease</td>
</tr>
<tr>
<td>Chest films, high-resolution computed tomography, ventilation-perfusion scan</td>
</tr>
<tr>
<td>Pulmonary function studies: spirometry, pulse oximetry and arterial blood gases (resting, sleeping, and with exercise), 6-min walk</td>
</tr>
<tr>
<td>diffusion, pressure-volume curve, infant studies</td>
</tr>
<tr>
<td>Electrocardiogram, echocardiogram</td>
</tr>
<tr>
<td>To identify primary disorders that predispose to ILD</td>
</tr>
<tr>
<td>Immune studies: HIV, immunoglobulins including IgE, skin tests for delayed hypersensitivity, response to immunizations, T and B subsets, complement, others as indicated</td>
</tr>
<tr>
<td>Barium swallow, pH probe</td>
</tr>
<tr>
<td>To identify primary ILD</td>
</tr>
<tr>
<td>Noninvasive: antinuclear antibody, antineutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody,</td>
</tr>
<tr>
<td>hypersensitivity pneumonitis screen, angiotensin converting enzyme, infectious disease evaluation (cultures, titer, skin tests),</td>
</tr>
<tr>
<td>genetic studies for surfactant dysfunction, serum and urine amino acids</td>
</tr>
<tr>
<td>Invasive: cardiac catheterization (in selected cases), bronchoalveolar lavage, transbronchial biopsy, transthoracic lung biopsy</td>
</tr>
</tbody>
</table>

**Pulmonary Function Tests**

Conventional pulmonary function tests in older children typically show a pattern of restrictive lung disease with reduced forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV1), and a normal or elevated FEV1/FVC ratio. However, although total lung capacity (TLC) may be reduced, functional residual capacity (FRC) and residual volume (RV) are often normal or elevated, resulting in an increased FRC/TLC and RV/TLC. The latter finding suggests air trapping, and the composite picture may be one of mixed restrictive/obstructive disease.

Pressure-volume curves are typically shifted downward and to the right, with an increase in elastic recoil pressure at maximum inspiration consistent with restrictive lung disease. Diffusion of carbon monoxide is low in absolute terms, but normal when corrected for alveolar volume.

Infant pulmonary function testing can also be used to follow infants with ILD and their response to treatment. In 3 infants with chronic ILD, respiratory system compliance, measured by multiple occlusion and end-inspiratory techniques, improved following administration of hydroxychloroquine and/or pulse corticosteroids. With recent advances, infant testing is proving useful in evaluating PILD syndromes. Preliminary studies suggest that these techniques can identify functional patterns that distinguish different disorders and correlate with radiologic and histologic findings (personal communication with Dr. Robert Castle).

Most patients with mild disease are normoxic under all conditions, but they may desaturate with exercise or during sleep as the disease progresses and ventilation-perfusion mismatch ensues. Patients with more advanced disease will be hypoxemic at rest. The development of pulmonary hypertension is often indicative of a poor prognosis. In our original review, we presented a severity-of-illness classification based on these progressive changes (Table 5). The validation of this classification is presented in Outcome, below.

**High-Resolution Computed Tomography (HRCT)**

In PILD, HRCT is being utilized with greater frequency to provide precise detail about the extent and distribution.

**TABLE 5—Severity of Illness Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Symptoms</th>
<th>Saturation &lt;90% exercise/sleep</th>
<th>Saturation &lt;90% rest</th>
<th>Pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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of parenchymal disease and to select appropriate biopsy sites. In addition, HRCT may increase the level of diagnostic confidence for the diagnosis of pediatric ILD, improve diagnostic accuracy, and provide a useful classification system. In a recent study of 20 children with biopsy-proven ILD, Lynch et al. found that 56% of the confident first-choice diagnoses on HRCT were correct. Diseases were classified into five distinct groups based on dominant HRCT features: geographic hyperlucency (bronchiolitis obliterans or bronchocentric granulomatosis), septal thickening (lymphangiomatosis, hemangiomatosis, and microlithiasis), ground-glass opacification (DIP, LIP, and HSP), lung cysts and nodules (histiocytosis), and consolidation (aspiration and bronchiolitis obliterans organizing pneumonia). The diagnostic accuracy of HRCT in PILD was confirmed in a subsequent similar study. Our limited experience with HRCT in children with SP-C mutations suggests that they have diffuse involvement of most of the lung parenchyma, with ground-glass opacities or fibrotic changes with cystic lung disease.

In infants, the usefulness of HRCT was previously limited by rapid breathing causing motion artifacts. The problem can be overcome by a method known as controlled ventilation HRCT (CV-HRCT), recently described by Long et al. With this technique, a sedated child is hyperventilated by applying positive pressure through a facemask to produce a brief respiratory pause. As a result, motionless HRCT images can be obtained at either full inflation or resting end-expiration. This technique was successfully used to obtain both infant lung function testing and HRCT in a single sedation period.

Bronchoalveolar Lavage (BAL)

In children, as in adults, BAL is now routinely performed for sampling cellular and biochemical components of alveolar lining fluid. Recent reports established normal pediatric BAL indices with which abnormal values can be compared. In most of these studies, the normal pediatric values for BAL fluid constituents were similar to those found in adults. The technique lacks standardization with respect to lavage fluid amount and temperature, dwell time, and inclusion of the first aliquot. Pediatric pulmonologists either correct for size or body weight (e.g., 10% FRC or 1 ml/kg/aliquot x 3 aliquots), or use a fixed amount of lavage fluid regardless of size (e.g., 10 ml/aliquot x 2 aliquots). A recent report supports the former approach by demonstrating that a BAL protocol adjusted to body weight will yield constant fractions of epithelial lining fluid in children aged 3–15 years, facilitating the comparison of BAL fluid constituents in children of different age groups.

The most common indication for pediatric BAL has been to detect infection in the immunocompromised host. The overall diagnostic yield for a specific infectious agent was 47% (117 of 249 patients) in eight studies of immunocompromised children without AIDS. The yield was 77% (134 of 174 patients) in five studies of children with AIDS. BAL was also used to detect infection in immunocompromised hosts. However, it is often difficult to determine whether recovered organisms represent true infection, colonization, or contamination.

The recovery of lipid-laden macrophages from BAL was suggested as an indicator of aspiration in children. However, the presence of lipid-laden macrophages in BAL may be sensitive but not specific for aspiration, as any lung injury may result in the release of lipid from damaged cell membranes. Although the detection of specific milk proteins in alveolar macrophages in BAL fluid was more sensitive and specific for aspiration in a mouse model, the results were not as promising in a study of tracheal aspirates in neonates.

The recovery of hemosiderin-laden macrophages has been used to detect alveolar hemorrhages. However, similar to lipid, hemosiderin in macrophages may be sensitive for alveolar hemorrhages, but not specific for an alveolar hemorrhage syndrome. In a murine model, Epstein et al. showed that hemosiderin-laden macrophages appear at 3 days, peak at 1 week, and persist in small numbers for 2 months following a single episode of hemorrhage. BAL was also used to diagnose alveolar proteinosis, lysosomal storage disorders, histiocytosis, and surfactant protein deficiency in children.

As a diagnostic tool in immunocompetent children with ILD, Fan et al. found that BAL, studied prospectively, was diagnostic of a primary disorder in only 5 of 29 patients: aspiration was detected in 3, and infection in 2. The presence of lymphocytosis, neutrophilia, or eosinophilia narrowed down the differential diagnosis in 15 patients. A secondary disorder was uncovered in 8 patients. These results suggest that BAL provides useful information in children with ILD, but that its ability to determine the primary cause is limited.

Bronchoalveolar lavage has been used on a limited basis to study disease mechanisms in PILD. In children with ILD, Clement et al. demonstrated that BAL fluid contained an increase in oxygen metabolites release by alveolar macrophages and an increase in insulin-like growth factor binding protein-2. In a similar pediatric group, Rhonchetti et al. reported increased numbers of foamy macrophages and increases in fibronectin, hyaluronic acid, and albumin in the early stages of disease, and increased lymphocytes in long-standing disease. Taken together, these studies suggest that, in PILD, lung injury may be in part due to oxidant damage and certain profibrotic constituents can be identified in BAL.
studies are needed to determine if these findings are predictive of fibrosis.

In children with sarcoidosis, Chadelat et al.\textsuperscript{79} found that BAL fluid contained more lymphocytes, with an elevated CD4/CD8 ratio, and an enhanced ability of alveolar macrophages to release hydrogen peroxide, an effect that diminished after corticosteroid treatment. In a subsequent study, the same group found varying degrees of IL-1β, TNF-α, IL-6, and TGF-β expression not found in the control group.\textsuperscript{80}

Finally, Ratjen et al.\textsuperscript{81} found an increase in lymphocytes in children with hypersensitivity pneumonitis. Unlike adults, no differences were found in CD4/CD8 ratios between children with hypersensitivity pneumonitis and those without lung disease, but there was increased expression of human leukocyte antigen-DR and elevation of natural killer cells in most subjects. These studies in pediatric sarcoidosis and hypersensitivity pneumonitis confirm the presence of a lymphocytic alveolitis, and suggest that cellular and cytokine expression patterns in BAL fluid may help evaluate disease activity and severity. However, the prognostic significance of these BAL constituents needs further validation before they can be used to predict outcome in individual patients.

**Lung Biopsy**

A tissue diagnosis is required for most types of PILD. Although transbronchial or percutaneous needle biopsy was successfully used in some cases, a transthoracic approach, either by open lung biopsy (OLB) or video-assisted thoracoscopic surgery (VATS), remains the gold standard for obtaining tissue adequate for diagnosis.

Lung biopsy material must be processed in a consistent manner to ensure optimal interpretation. This includes the preparation of imprints from biopsy tissue and the preservation of tissue using several modalities for optimum diagnostic yield. Tissue for light microscopy should be fixed in expansion by methods that we previously reported.\textsuperscript{1} Tissue should also be frozen for immunofluorescence and other studies, as well as preserved in gluteraldehyde for electron microscopy. It is critical that all biopsies be interpreted by a pathologist with considerable expertise in pediatric lung disease, since the normal lung of an infant differs markedly from that of an older child or adolescent, and any pathologic findings should be interpreted in the light of the normal age-dependent variations of lung architecture.

As in adults, the use of VATS is rapidly becoming the method of choice for lung biopsy in children, and technical modifications permit it even in infants.\textsuperscript{82} In a prospective study in a small group of immunocompetent children with ILD, Fan et al.\textsuperscript{83} found that the diagnostic yield was comparable for OLB (57%) and VATS (54%), but the morbidity from VATS was clearly lower with respect to duration of surgery, chest tube, and hospitalization. Overall, the diagnostic yield from transthoracic lung biopsy (OLB and VAT) was disappointing, due in large part to an extremely low diagnostic yield in children less than 2 years of age. As this study was done before many of the recently defined ILD syndromes of infants were described, the diagnostic yield in infants is likely to be much higher at present.

**TREATMENT**

Since our original review, very little progress has been made in terms of treatment, which remains based solely on anecdotal evidence. This is not surprising, since PILD encompasses a heterogeneous group of rare disorders, making it difficult to find enough patients in each group to perform proper randomized, prospective therapeutic trials, even with multicenter collaboration.

It is said that the less one understands about a given condition, the more likely one is to try corticosteroids for it. This is certainly true for PILD. Based only on “experience,” the most treatable condition appears to be hypersensitivity pneumonitis. In a review of 86 reported pediatric cases of hypersensitivity pneumonitis, approximately 60% were treated with corticosteroids, with an excellent response in all but one.\textsuperscript{84} Other conditions thought to be steroid-responsive include NSIP, DIP, LIP, cryptogenic organizing pneumonia, eosinophilic pneumonia, sarcoidosis, pulmonary hemosiderosis, and PILD associated with connective tissue disease. However, we found highly variable responses to corticosteroids for each of these disorders.

Given the suggested but unproven benefit of corticosteroids, treatment decisions should be based on disease risk vs. treatment risk. Since many of these disorders are associated with considerable morbidity and mortality, treatment with corticosteroids or steroid-sparing agents may be justified in many cases.\textsuperscript{85} However, a recent study, demonstrating potential long-term adverse effects on neuromotor and cognitive function as a result of early administration of corticosteroids to infants to prevent bronchopulmonary dysplasia, should make one more cautious about the long-term use of corticosteroids, especially in the developing infant.\textsuperscript{86}

Pulse steroid therapy was used with anecdotal success in PILD.\textsuperscript{47,87,88} We currently prefer this method to oral daily or every-other-day therapy because it is associated with fewer side effects. The recommended dose of methylprednisolone is 30 mg/kg with a maximum of 1 g, given intravenously over 1 hr, daily, for 3 consecutive days and repeated monthly.

Alternative or steroid-sparing agents include hydroxychloroquine, azathioprine, cyclophosphamide, methotrexate, cyclosporin, and intravenous gammaglobulin. Of these, hydroxychloroquine has probably been used...
most frequently, again with anecdotal success in ILD and alveolar hemorrhage syndromes. Newer therapies directed against certain cytokines, oxidants, and growth factors that may be involved in the fibrotic process hold promise for the future.

More children are receiving lung transplantation for end-stage PILD. The survival rates are at least as good for PILD as they are for cystic fibrosis and pulmonary hypertension. For some highly lethal diseases such as surfactant protein B and ABCA3 mutations, and alveolar capillary dysplasia, lung transplantation remains the only effective treatment, but proper diagnosis must be made as soon as possible after birth to give these patients a chance to undergo transplant.

OUTCOME

The prognosis for children with ILD is variable. Infants with NEHI or pulmonary interstitial glycogenosis generally do well, although they may remain symptomatic and require oxygen for years. At the other end of the spectrum, neonates and infants with SP-B and ABCA3 mutations, as well as older children with PILD and growth failure, pulmonary hypertension, and severe fibrosis, do poorly.

Fan and Kozinetz reviewed the outcomes of 99 children with a variety of PILDs seen in Denver, Colorado over a 15-year period (1980–1994). There were 15 recorded deaths with a probability that a patient would survive to 24, 48, and 60 months after onset of symptoms of 83%, 72%, and 64%, respectively. Of the clinical features present at time of initial evaluation, weight less than the fifth percentile, crackles, clubbing, family history of ILD, and symptom duration were not associated with decreased survival. In contrast, the severity of illness classification, proposed in our original review (Table 5), appeared to be a useful measure of outcome, with an increasing score associated with a higher probability of decreased survival. The severity of illness classification also appeared to be a useful measure of outcome in another study of children with bronchiolitis obliterans.

CONCLUSIONS

PILD comprises a large, heterogeneous group of mostly rare disorders that are associated with considerable morbidity and mortality and are difficult to diagnose and treat. Although many of these diseases overlap their adult counterparts, many have features unique to children. A systematic approach to diagnosis is valuable to clinicians confronted with so large a differential diagnosis. As in adult ILD, response to treatment of pediatric ILD is inconsistent. Due to the rarity of each entity in children, multicenter collaboration should be encouraged, because no single center can see a sufficient number of patients to adequately study these diseases.

REFERENCES


