Diffuse Lung Disease in Young Children

Application of a Novel Classification Scheme

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***Rationale*: Considerable confusion exists regarding nomenclature, classification, and management of pediatric diffuse lung diseases due to the relative rarity and differences in the spectrum of disease between adults and young children.**

***Objectives*: A multidisciplinary working group was formed to: (*1*) apply consensus terminology and diagnostic criteria for disorders presenting with diffuse lung disease in infancy; and (*2*) describe the distribution of disease entities, clinical features, and outcome in young children who currently undergo lung biopsy in North America.**

***Methods*: Eleven centers provided pathologic material, clinical data, and imaging from all children less than 2 years of age who underwent lung biopsy for diffuse lung disease from 1999 to 2004.**

***Measurements and Main Results*: Multidisciplinary review categorized 88% of 187 cases. Disorders more prevalent in infancy, including primary developmental and lung growth abnormalities, neuroendocrine cell hyperplasia of infancy, and surfactant-dysfunction disorders, constituted the majority of cases (60%). Lung growth disorders were often unsuspected clinically and under-recognized histologically. Cases with known surfactant mutations had characteristic pathologic features. Age at biopsy and clinical presentation varied among categories. Pulmonary hypertension, presence of a primary developmental abnormality, or *ABCA3* mutation was associated with high mortality, while no deaths occurred in cases of pulmonary interstitial glycogenosis, or neuroendocrine cell hyperplasia of infancy.**

***Conclusions*: This retrospective cohort study identifies a diverse spectrum of lung disorders, largely unique to young children. Application of a classification scheme grouped clinically distinct patients with variable age of biopsy and mortality. Standardized terminology and classification will enhance accurate description and diagnosis of these disorders.**

Keywords: infant; pulmonary; interstitial lung disease; surfactant; neuroendocrine hyperplasia

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There are only limited studies of diffuse lung disease in infants. Progress has been hindered by the rarity of these disorders and the use of adult terminology and classification systems that do not adequately address pediatric or genetic entities.

What This Study Adds to the Field

This multicenter study of diffuse lung disease in infants employs a new classification system emphasizing infant disorders. Its use in a large cohort of infants with lung biopsy provides new information on disease frequency, clinical settings, and outcome.

Diffuse lung disease in children, which includes interstitial lung disease (ILD), comprises a heterogeneous group of uncommon disorders characterized by impaired gas exchange and diffuse infiltrates by imaging (1). To date, description and management of pediatric ILD has largely been based on case reports and small series, complicating accurate diagnosis, assessment of prevalence, and definitive therapy for these disorders. In contrast, significant progress has been made in generating a standardized classification of adult idiopathic interstitial pneumonias by integrating international clinical, radiographic, and pathologic expertise (2).

While there is some overlap in the histologic patterns of ILD between adults and children, direct application of the adult classification scheme to pediatric ILD is limited by differing frequency and spectrum of disease, clinical manifestations, and outcome. Specifically, usual interstitial pneumonia (UIP), the pathologic correlate of idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis (IPF/CFA), is the most common ILD in adults; nonetheless, the defining histologic feature of UIP, fibroblastic foci, has yet to be described in any pediatric case (3, 4). Furthermore, children given the diagnosis of IPF/CFA have a clinical course that differs from that of adults, as pediatric cases are characterized by nonprogressive symptoms and relative

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longevity (5, 6). Likewise, despite sharing similar histology, desquamative interstitial pneumonia (DIP) has different etiologic and prognostic implications in adults and children. In adults, DIP is linked to smoking and is often responsive to steroids, while DIP in children has a more aggressive course and familial forms have been identified (5, 7, 8). Recently, DIP has been described in patients with mutations in the ATP-binding cassette transporter A3 (*ABCA3*) gene, and less commonly in the surfactant protein C (*SFTPC*) gene, both necessary for surfactant metabolism (9–11).

Although there are known causes of pediatric ILD including infection, environmental exposures, and collagen vascular and metabolic disease, the literature is becoming progressively populated by reports of idiopathic lung disorders that appear distinct to infants and young children. These include chronic pneumonitis of infancy (CPI) (12–14), pulmonary interstitial glycogenosis (also termed infantile cellular interstitial pneumonitis) (15, 16), and persistent tachypnea of infancy associated with neuroendocrine cell hyperplasia (17). Recognition of these unique disorders has been hindered by lack of uniform terminology and the use of somewhat overlapping names to describe entities with different prognostic implications. For example, infantile cellular interstitial pneumonitis/pulmonary interstitial glycogenosis, which carries a favorable prognosis, has been confused with chronic pneumonitis of infancy, a potentially lethal ILD that has been associated with *SFTPC* mutations (18).

It has been suggested that histologic patterns of pediatric diffuse lung disease differ from those of adults, particularly for those presenting in neonates and young children (19); Langston and Dishop have proposed a classification scheme to reflect the morphologic and etiologic spectrum of infant lung disease (20). This study has applied this classification to a large cohort of young children who underwent lung biopsy with radiographic evidence of diffuse lung disease. It was initiated by the ChILD Research Co-operative to provide a coherent basis for further investigations of diffuse lung disease in the pediatric population, including defining histologic criteria and estimating the relative frequency of specific entities found at lung biopsy in this population. Our hypothesis was that entities unique to young children would be largely represented in this patient population, and that categorization would correlate with clinical features and outcomes.

Some of the results of this study have been previously reported in the form of abstracts (21–25).

METHODS

Based on the combined experience of clinicians and pathologists from 11 institutions, a previously proposed classification scheme was modified to facilitate analysis of a diverse group of disorders (20). Consensus was reached on histologic terminology and criteria for inclusion in the different categories, and it was agreed to use this classification as a framework for this study.

Eleven children's hospitals in North America (Appendix 1) provided pathologic material from all diagnostic lung biopsies performed from July 1999 to July 2004 in children less than 2 years of age with diffuse radiographic lung disease (Figure 1). Cases received in consultation, needle and transbronchial biopsies, lobectomies, segmental resections, and biopsies performed for focal pulmonary lesions (e.g., granuloma, abscess, metastatic nodule) were excluded. A standardized data collection form detailing clinical, pathologic, and radiographic information was completed for each case by chart review. Prematurity was defined as less than 37 weeks gestational age. In a series of multidisciplinary workshops, members of the pathology and clinical working groups (Appendix 2) retrospectively reviewed and discussed each case in a group format. Specific diagnoses and/or categorizations were assigned by the group based on the clinical setting and pathologic features. The imaging working group (Appendix 2) reviewed a subset of cases. Approval for the study was obtained through the institutional review board of each participating institution. Before the initiation of this study, some cases previously had DNA sequence analysis for the *SFTPC* and *ABCA3* gene mutations by a separate IRB approval (Johns Hopkins University School of Medicine).

The classification comprises known clinical-pathologic entities that have been associated with diffuse lung disease in children (5, 26) and gives emphasis to disorders that are more prevalent in infancy (27–29), including primary aberrations in lung development (Diffuse developmental disorders), presumed secondary alterations in lung growth characterized by deficient alveolarization (Growth abnormalities), pulmonary interstitial glycogenosis and neuroendocrine cell hyperplasia of infancy (Specific conditions of undefined etiology), and disorders suggestive of a metabolic abnormality in surfactant metabolism (Surfactant dysfunction disorders).

To determine the best clinical predictors of mortality in this population, a logistic regression model was constructed containing four possible predictors: sex, preterm birth, congenital heart disease, and pulmonary hypertension (SAS version 9.1, Cary, NC). This model was also applied within the histologic category of "Growth abnormalities." Within other histologic categories, and to examine the relationship of death to category, testing was done by Chi square analysis, and odds ratio (OR) was estimated from the 2×2 contingency table. Mean age across categories was compared using ANOVA (Prism 4; Graph Pad Software, Inc., San Diego, CA).

RESULTS

Clinical Characteristics of Study Population

Eleven centers provided pathologic material, clinical data, and imaging studies from children less than 2 years of age who had a lung biopsy for diagnosis of radiographically diffuse lung disease, yielding 187 cases for review. There was marked variation in the number of biopsies performed among the participating centers (range, 4–37; mean, 17). Age at biopsy favored younger infants (mean 8.3 ± 0.6 mo) (Figure 2). Clinical features of the study population are shown in Table 1. A substantial proportion (57%) required oxygen at birth, although prematurity was a feature of only 51% of the cases that required early intubation. A variable constellation of signs and symptoms was observed (Figure 3). Over half of patients received systemic steroids before lung biopsy. Imaging studies of sufficient quality were not available in enough cases to provide meaningful radiologic description and correlation.

Outcome data was available for 86.6% of cases (Table 2). The mean age at follow-up for patients alive at the time of study data collection was 31.3 months, with a significantly longer mean follow-up duration after biopsy compared with the patients who died (21.8 versus 3.6 mo after lung biopsy, respectively, $P < 0.001$). Forty-nine (30.2%) patients had died, with a mean age of death of 7.7 months. A disease severity scale (7, 27) was used to classify the 79 cases that were symptomatic at the time of follow-up. In a logistic regression model of clinical predictors, mortality was not significantly different based on female sex (OR, 1.75; 95% confidence interval [CI], 0.73–4.20) or congenital heart disease (OR, 0.49; 95% CI, 0.17–1.36). Prematurity and a clinical diagnosis of pulmonary hypertension at the time of lung biopsy were associated with increased mortality (OR, 3.60; 95% CI, 1.18–10.96 and OR, 6.84; 95% CI, 2.57–18.20, respectively).

Figure 1 lists the number of cases and specific entities within each category. Significantly, within the proposed classification scheme, disorders more prevalent in infancy constituted the majority (60%) of diagnostic cases. The following text details the pathologic and clinical features by category, and Table 2 displays the mean age at biopsy and mortality by category.

Diffuse Developmental Disorders

The diffuse developmental disorders are a group of rare and poorly understood primary disorders of lung development of

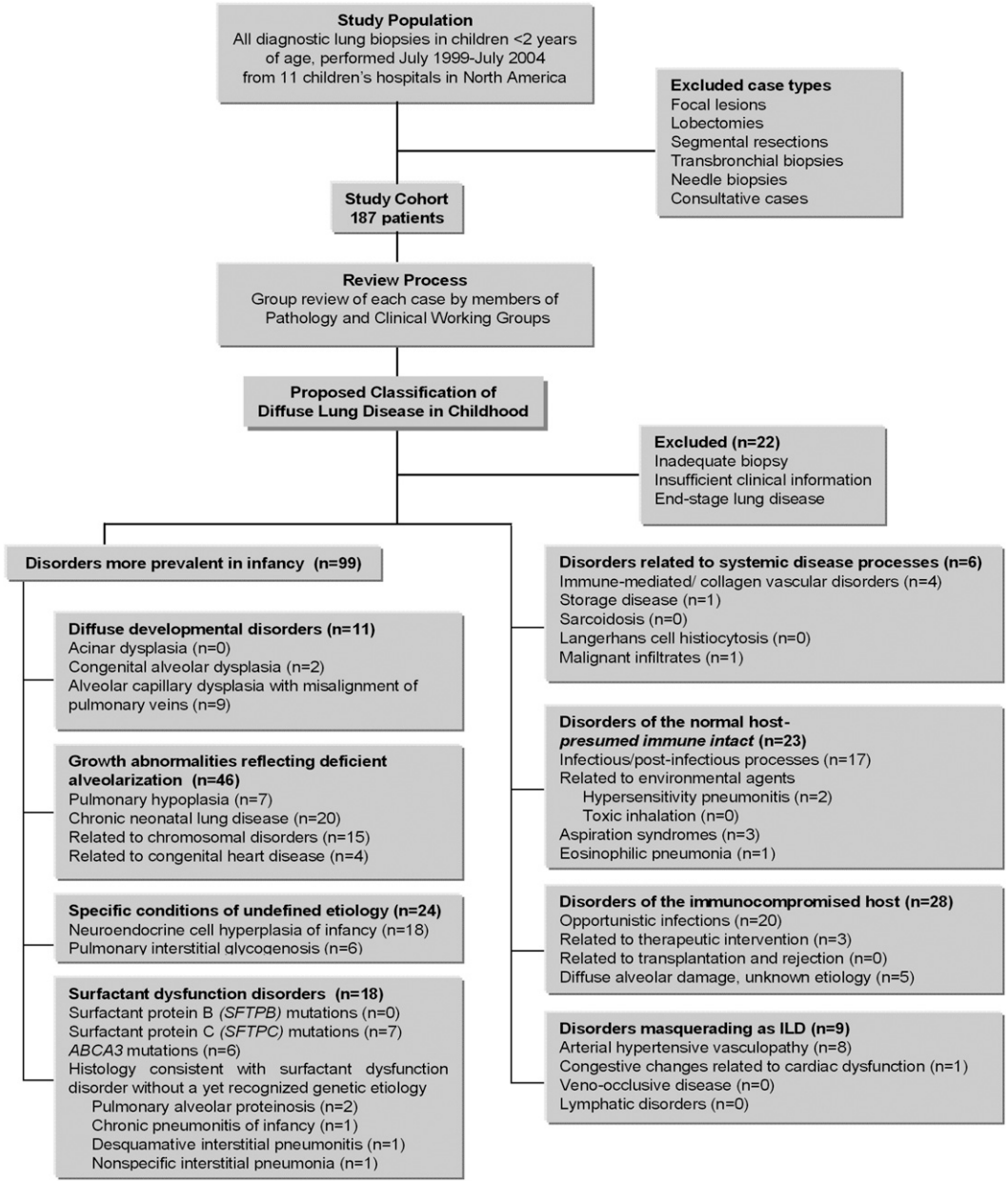

Figure 1. Study cohort and proposed classification of diffuse lung disease in children. The study cohort was composed of patients under the age of 2 who had a diagnostic lung biopsy during the designated 5-year interval; exclusion criteria are listed. The clinical–pathologic classification scheme is detailed with numbers of cases and specific entities identified within each category. Some unusual entities not seen are also listed, but there are clearly other entities associated with diffuse lung disease not seen in this cohort that have not been listed.

unknown etiology, but largely believed to be due to aberrations in one of the primary molecular mechanisms of lung and/or pulmonary vascular development; they include acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV). Acinar dysplasia is characterized by lung growth arrest in the pseudoglandular or early canalicular phase. Congenital alveolar dysplasia is characterized by growth arrest in the late canalicular/early saccular phase of lung development. The constellation of malposition of pulmonary veins adjacent to small pulmonary arteries, medial hypertrophy of pulmonary arteries and arterioles, and reduced capillary density with lobular maldevelopment was considered diagnostic for ACDMPV. Eleven (6%) cases were classified as diffuse developmental disorders. No case of acinar dysplasia was identified in this cohort; identified cases included congenital alveolar dysplasia (n = 2) and ACDMPV (n = 9). All biopsies were characterized by a striking arrest in lobular development and reduced alveolar capillary density. Cases occurred in term infants, and all presented at birth with hypoxia and persistent pulmonary hypertension unresponsive to ventilatory support. With the exception of one child with ACDMPV who underwent lung transplantation at 5 months of age, mortality was 100% within the first month of life.

Growth Abnormalities

A lung growth abnormality reflective of impaired pre- or postnatal alveolarization was the principal diagnosis in this review (24.6% of total) and the leading category for 5 of 11 centers. These abnormalities of alveolarization are largely secondary and may be seen in a wide variety of circumstances. The best known of these is pulmonary hypoplasia, in which prenatal conditions (restriction of fetal thoracic space, abnormalities in amniotic fluid volume, skeletal anomalies, neuromuscular problems resulting in decreased or absent fetal breathing movements, cardiac abnormalities limiting pulmonary blood supply, abdominal wall defects, and a variety of chromosomal abnormalities) result in deficient lung growth (30). Postnatal growth abnormalities are largely limited to the population of premature

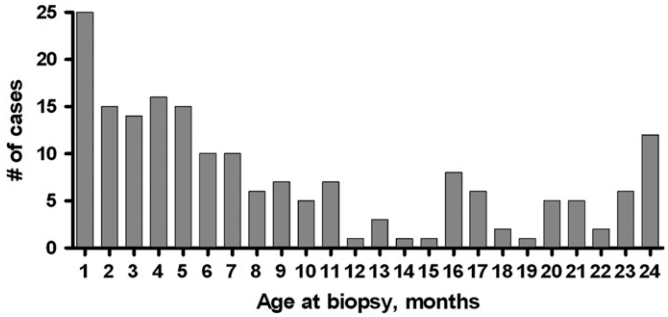

Figure 2. Age at biopsy of study population. Of the 187 cases reviewed, 30% underwent lung biopsy by 3 months of age, over half (52%) by 6 months, and 72% in the first year of life.

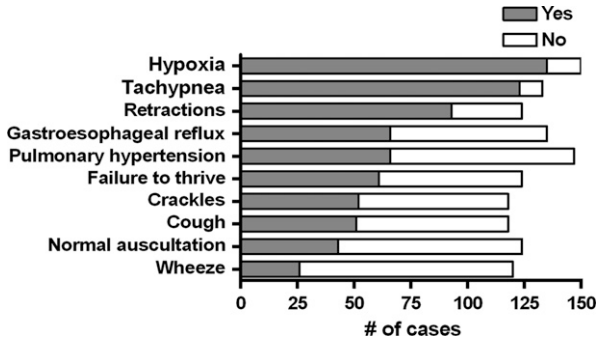

Figure 3. Clinical signs and symptoms. Clinical information was collected by retrospective chart review. Diagnoses of gastroesophageal reflux and pulmonary hypertension were reported based on chart record only, without requirement for specific diagnostic testing.

infants with chronic lung disease of prematurity (also known as chronic neonatal lung disease, and formerly bronchopulmonary dysplasia); however, a few term infants with early postnatal lung injury may also show these changes. Lung biopsy is not generally done for diagnosis of these disorders, and the population of infants with lung growth abnormalities who come to biopsy in this setting typically have pulmonary symptoms and morbidity thought to be disproportionate to their clinical circumstances. Unexplained pulmonary symptoms and morbidity were the indication for lung biopsy, even in cases performed at the time of cardiac repair. Histologically, this abnormality is characterized by variable lobular simplification with alveolar enlargement, often most prominent subpleurally. Figure 4 illustrates the spectrum of histopathology in this category. While there were seven cases of pulmonary hypoplasia, most cases occurred in the setting of prematurity (59.1%), congenital heart disease (65%), a chromosomal abnormality (32.6%), or a combination of the above. Chromosomal abnormalities, with Trisomy 21 the most frequent (n = 13), were strongly associated with congenital heart disease (91.7%); however, characteristic alveolar abnormalities (31) (Figure 4C) were also identified in one case without a cardiac defect. A history of prematurity or congenital heart disease was highly predictive of lung growth abnormality as the primary histologic finding (OR, 8.4; 95% CI, 3.7–18.9 and OR, 7.3; 95% CI, 3.5–15.6, respectively). No case with chromosomal abnormality was identified in any other category.

Outside the setting of preterm birth or known pulmonary hypoplasia, a lung growth abnormality was infrequently suspected by the clinician or reported by the pathologist (22.5% each), although pathology interpretation often noted the presence of "emphysematous changes" in these cases. Furthermore, in 19 of the 46 cases, patchy changes consistent with pulmonary interstitial glycogenosis (PIG) (*see below*) were present (Figure 4D), yet described by the submitting institution in only four instances (one confirmed by electron microscopy). In contrast, hypertensive changes of the pulmonary vasculature (Figure 4C), which were common in this category (74% of cases), were reported in the majority.

Within this group, age at biopsy was not significantly different based on history of congenital heart disease or prematurity. Overall mortality in this category was 34%; however, prematurity was an independent clinical predictor of mortality (OR, 4.29; 95% CI, 1.12–16.44), while congenital heart disease and pulmonary hypertension were associated with trends toward increased mortality (OR, 1.53; 95% CI, 0.38–6.08 and OR, 4.32; 95% CI, 0.79–23.69, respectively). Severity of the growth abnormality, as judged by dramatically increased alveolar size (Figure 4B), was associated with increased mortality (80%), as was moderate to severe hypertensive change. In the subset of cases with focal PIG, the age at biopsy was significantly younger (3.0 ± 0.6 mo versus 7.0 ± 1.3 mo, $P = 0.007$), although there was no significant difference in frequency of prematurity, congenital heart disease, or mortality (OR, 3.33; 95% CI, 0.91–12.2).

TABLE 1. CLINICAL FEATURES OF STUDY POPULATION

Characteristics	No. (%)	No. reported (maximum *187*)
Male sex	104 (58.1)	179
Family history of lung disease	33 (34.0)	97
Preterm birth	41 (28.1)	146
Intubation at birth	52 (38.8)	134
Oxygen required at birth	76 (56.7)	134
Congenital heart disease	54 (32.9)	164
Immunocompromised	28 (17.8)	157
Pre-biopsy therapies		
Surfactant	25 (21.2)	118
Systemic steroids	67 (51.9)	129
Outcome		162 (86.6%)
Asymptomatic	32 (19.8)	
Symptomatic, normal room air saturation	35 (21.6)	
Symptomatic, abnormal saturation with sleep or exercise	8 (4.9)	
Symptomatic, abnormal saturation at rest	28 (17.3)	
Symptomatic, pulmonary hypertension	8 (4.9)	
Transplant	3 (1.9)	
Death	49* (30.2)	

* Includes one patient who died after lung transplantation.

PIG

The hallmark histologic feature of PIG is the diffuse accumulation of mesenchymal cells in the alveolar interstitium, classically described as an isolated finding in a neonate with respiratory distress at or near birth (15, 16). In this review, PIG was the only significant histologic finding in six cases (3.2%) (Figure 5A). In two of these cases, accumulation of monoparticulate glycogen in the interstitial cell cytoplasm was confirmed by ultrastructural examination; histology was characteristic in the other cases. Five biopsies were from term infants, and one from an infant born at 34 weeks of gestation. All but one presented with hypoxia at birth; the latter presented with tachypnea, retractions, and hypoxia at 7 days of age. The mean age at biopsy was 1.3 ± 0.4 mo. No case was suspected clinically; pathologic examination at the submitting institution led to the diagnosis in four cases. There were no deaths (OR, < 0.001), although most remained symptomatic.

TABLE 2. AGE AT BIOPSY AND OUTCOME BY CATEGORY

Category	Age at Biopsy, mo Mean ± SEM (*range*)	% Mortality	Age at Death, mo Mean ± SEM (*range*)	Age at Follow-up of Survivors, mo Mean ± SEM (*range*)
Diffuse developmental disorders	0.7 ± 0.2 (0.3–1.2)	100%	0.7 ± 0.1 (0.3–1.2)	n/a
Lung growth abnormalities	5.35 ± 0.8 (0.3–22)	34%	9.5 ± 2.7 (0.3–31)	25.3 ± 3.1 (3–64)
Pulmonary interstitial glycogenosis	1.3 ± 0.4 (0.3–3.0)	0%	n/a	20.3 ± 6.1 (2–43)
Neuroendocrine cell hyperplasia of infancy	13.9 ± 1.7 (2.7-24)*	0%	n/a	37.9 ± 5.3 (15–71)
Surfactant dysfunction (all)	5.8 ± 1.6 (0.2–22)	41.2%	1.9 ± 0.6 (0.4–4.5)	36.9 ± 7.9 (10–73)
SP-C mutations	8.9 ± 3.0 (2.0 –22)	0%	n/a	36.8 ± 8.4 (10–61)
ABCA-3 mutations	1.3 ± 0.5 (0.2 –3.0)†	100%	1.9 ± 0.7 (0.4–4.5)	n/a
Disorders of the normal host	13.1 ± 1.7 (1.2–24)	5%	15.0	39.7 ± 4.8 (11–72)
Disorders resulting from systemic disease processes	10.5 ± 3.6 (1–22)	20%	1.4	23.5 ± 3.8 (16–33)
Disorders of the immunocompromised host	11.6 ± 1.3 (1.5–24)	30.8%	12.4 ± 2.9 (2.5–28)	36.1 ± 3.3 (10–61)
Disorders masquerading as ILD	7.3 ± 2.3 (0.2–24)	28.6%	11.0 ± 5.0 (6–16)	17.8 ± 5.5 (7–33)

Definition of abbreviations: ILD = interstitial lung disease; NEHI = neuroendocrine cell hyperplasia of infancy; SP-C = surfactant protein C.
* $P < 0.05$ for NEHI versus other disorders of infancy.
† $P < 0.01$ for ABCA-3 versus SP-C.

Neuroendocrine Cell Hyperplasia of Infancy

As recently reported (17), neuroendocrine cell hyperplasia of infancy (NEHI) is a disorder of undefined etiology distinct to infants and young children. It is characterized by prominent pulmonary symptomatology out of proportion to the minor and nonspecific lung biopsy findings. Affected children have a characteristic clinical presentation and course; despite significant tachypnea, hypoxia, and failure to thrive, they do not have respiratory failure and typically are hospitalized only for investigation or biopsy. The only consistent histologic abnormality is hyperplasia of neuroendocrine cells within bronchioles, best demonstrated by bombesin immunohistochemistry (Figure 5B); however, this change must be seen in the appropriate histologic background (near normal lung histology) and clinical setting, as alterations in bombesin immunopositivity may be seen in a wide variety of disorders (32). In this series, 18 cases were categorized as NEHI with 11 confirmed by bombesin staining; clinical features were similar and pathologic findings were typical and minimal in the 7 suspected cases for which bombesin staining had not been performed. Clinical history differed from other categories in that no patient was intubated at birth, no case occurred in a premature infant and none had congenital heart disease. Crackles were commonly reported and there was a male predominance (72.2%). The mean age at biopsy was significantly older (13.9 ± 1.7 mo) than for other disorders more prevalent in infancy ($P < 0.05$) (Table 2). Although no deaths were reported ($P < 0.001$), 69% remained symptomatic at follow-up.

Surfactant Dysfunction Disorders

Genetic abnormalities of surfactant function, specifically mutations in the surfactant protein B (*SFTPB*) (OMIM 178640), surfactant protein C (*SFTPC*) (OMIM 178620), and *ABCA3* (OMIM 601615) genes (9, 11, 18, 33–35) account for an increasing number of formerly idiopathic pediatric and adult ILD. Lung biopsy findings in young patients with these genetic abnormalities consistently show the histopathology of congenital pulmonary alveolar proteinosis (PAP), CPI, DIP, and nonspecific interstitial pneumonia (NSIP) (Figure 6). In our series there were seven cases with *SFTPC* mutations and six with *ABCA3* mutations. An additional five cases were suspected based on the pathology of PAP, CPI, DIP, and fibrotic NSIP. CPI (Figure 6A) was the predominant histologic pattern seen in the *SFTPC* cases (5 CPI, 1 PAP, 1 fibrotic NSIP), whereas PAP (Figure 6C) was more typical of the *ABCA3* cases (4 PAP, 2 DIP). Lung biopsies from a sibling pair with DIP and *ABCA3* mutation also demonstrated markedly abnormal lung growth characteristic of a diffuse developmental disorder. All cases occurred in term infants, with two-thirds presenting at birth with tachypnea and hypoxia. Of those with confirmed mutations, 9 of 13 were clinically suspected before biopsy. Family history was positive in one-third of cases (4 *SFTPC* cases had a family history of IPF or unknown fatal lung disease as well as above sib-pair with *ABCA-3* mutations). Wheezing and congenital heart disease were not reported and crackles were rare, but cough, gastroesophageal reflux, and failure to thrive were common. The mean age at biopsy was significantly younger for *ABCA3* cases compared with *SFTPC* (1.3 mo versus 8.9 mo). *ABCA3* mutations were associated with 100% mortality; all patients with *SFTPC* mutations were alive at follow-up but had significant ongoing pulmonary morbidity.

While disorders more prevalent in infancy constituted the majority of cases, the remaining 40% of biopsies included a variety of entities also seen in older children and adults (Figure 1). In general, clinical setting was used to group these diverse disorders.

Disorders of the Normal Host

By definition, patients in this category had no known immunodeficiency or systemic disorder. A history of persistent pulmonary symptoms postviral infection was often reported and the majority of these biopsies revealed predominantly airway changes consistent with an infectious or postinfectious etiology. Other cases showed features of aspiration (3) and hypersensitivity pneumonitis (2). In the two cases associated with prematurity, a minor growth abnormality was present but considered a secondary finding. One death occurred in a child with acute eosinophilic pneumonia and proliferative diffuse alveolar damage. Most patients remained symptomatic, with seven requiring supplemental oxygen.

Disorders Resulting from Systemic Disease Processes

Of the six cases, four were diagnostic of capillaritis, all in children with clinically suspected pulmonary hemorrhage syndrome, one with a history of maternal lupus. One patient had sialidosis and subsequently died. Another had previously undiagnosed myelomonocytic proliferative disorder.

Disorders of the Immunocompromised Host

Patients were deemed immunocompromised based on known immunodeficiency, organ or bone marrow transplantation, or

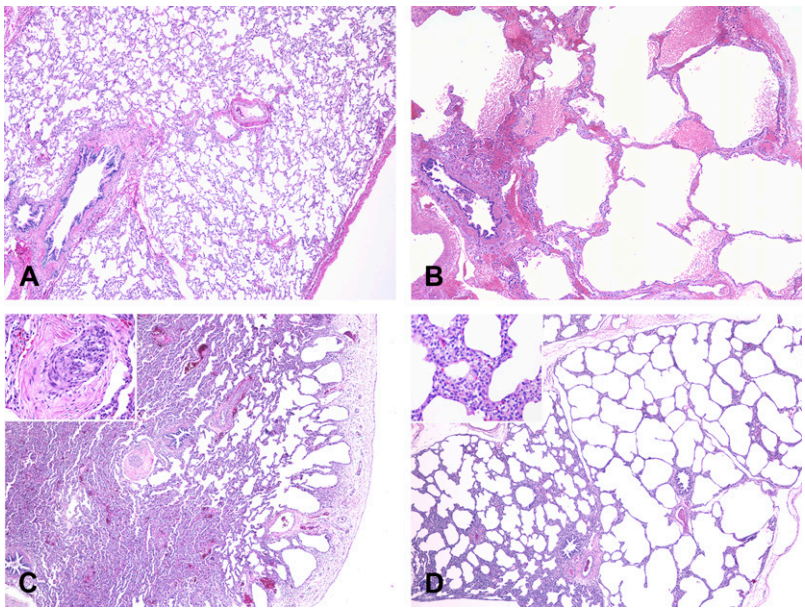

Figure 4. Lung growth abnormalities. Compared with lung from a normal term infant (*A*, hematoxylin and eosin [H&E], ×40), there is reduced alveolarization (deficient lung growth) in an infant with pulmonic stenosis with markedly enlarged alveoli (*see* size relative to bronchioles) (*B*, H&E, ×40). Deficient alveolarization in a patient with Trisomy 21 is characterized by cystic dilatation of subpleural alveoli (*C*, H&E, ×40); pulmonary arterioles demonstrate occlusive intimal hyperplasia (*insert*, H&E, ×200). Lobular simplification in an infant born at 27 weeks gestation is accompanied by patchy pulmonary interstitial glycogenosis (*D*, H&E, ×40). *Inset* (H&E, ×200) displays the characteristic cells with round to oval nuclei, vacuolated cytoplasm, and indistinct cell borders.

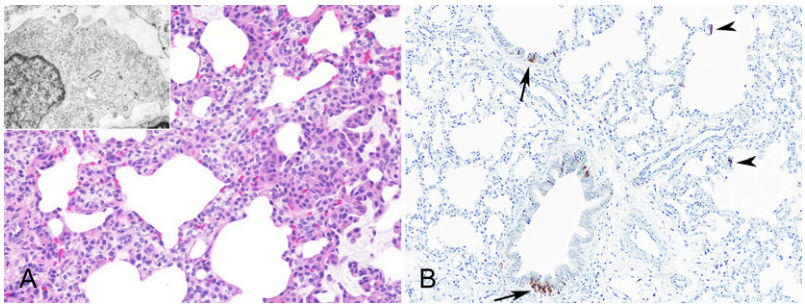

Figure 5. Pulmonary interstitial glycogenosis and neuroendocrine cell hyperplasia of infancy. There is diffuse interstitial widening by mesenchymal cells in a 22-day-old term neonate with tachypnea at birth (*A*, H&E, ×200). The presence of monoparticulate glycogen within the cells, diagnostic of pulmonary interstitial glycogenosis, is demonstrated by ultrastructural examination (*inset*, *A*, ×15,200). Clusters of bombesin-immunopositive cells within bronchioles (*arrows*) and within the lobular parenchyma (*arrowheads*) are shown from a patient with neuroendocrine cell hyperplasia of infancy (*B*, bombesin immunostain [polyclonal; ImmunoStar] ×100).

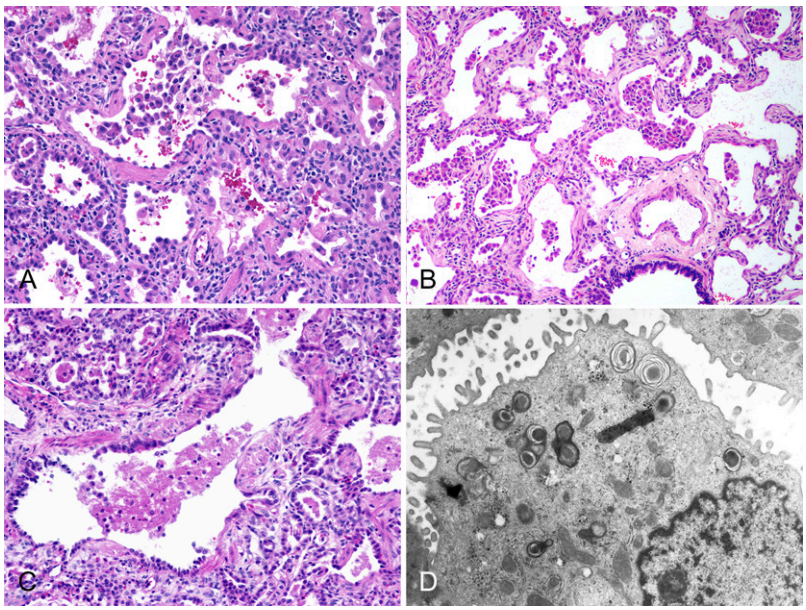

Figure 6. Histology consistent with surfactant dysfunction disorder. The lung biopsies of an infant with an *SFTPC* mutation (*A*, H&E, ×200) and an infant with *ABCA3* mutations (*C*, H&E, ×200) are both characterized by diffuse alveolar septal thickening with uniform prominent type II cells. Accumulation of intra-alveolar macrophages and interstitial infiltrate is more typical in the patient with the *SFTPC* mutation (chronic pneumonitis of infancy pattern), while granular proteinosis is more prominent in the biopsy of the patient with *ABCA3* mutations (pulmonary alveolar proteinosis pattern). Electron micrograph demonstrates the abnormal lamellar bodies with dense inclusions in a 3-month-old with *ABCA3* mutations (*D*, ×16,000). Patchy interstitial fibrosis, characteristic of NSIP, is present in a 22-month-old child who was found to have an SP-C mutation (*B*, H&E, ×200); a small degree of proteinosis with foamy macrophages is still visible (*arrow*).

receiving chemotherapy for malignancy. Those receiving immunomodulating therapies for their systemic disorders were classified according to their underlying disease process. In the immunocompromised group, 9 biopsies were from infants who had undergone bone marrow transplantation, 1 after heart transplantation, 11 with congenital immune deficiency, 2 with HIV infection, and 5 being treated for malignancy. Clinical presentation was variable, and infectious and postinfectious diagnoses

predominated. Epithelial and vascular injury consistent with cytotoxic drug reaction was seen in three cases. At follow-up, 38.5% of these immunocompromised patients were reported asymptomatic from a pulmonary standpoint; lung biopsies from these patients had frequently demonstrated *Pneumocystis jiroveci* pneumonia. The majority of patients who died had a diagnosis of organizing diffuse alveolar damage, and death occurred within one month after biopsy in all but one.

Disorders Masquerading as ILD

Arterial, venous, or lymphatic abnormalities masquerading as ILD by clinical and imaging criteria are known to account for a proportion of cases that come to lung biopsy (36). Of the nine cases in this category, six had a clinical diagnosis of pulmonary hypertension; however, five biopsies were performed for unexplained diffuse lung disease, while vascular abnormalities were suspected in four biopsies obtained at the time of cardiac repair. All patients had congenital heart disease, with a predominance of left-sided lesions including: total anomalous pulmonary venous return (n = 2), atrioventricular canal (n = 2), pulmonary stenosis, large patent ductus arteriosus, mitral stenosis, ventricular septal defect, and double-outlet right ventricle with pulmonary stenosis (1 each). As well as arterial medial hypertrophy and muscularization of arterioles, most cases showed changes of congestive vasculopathy with eccentric intimal fibrosis, arterialization of pulmonary veins, and lymphatic dilatation. Two patients who underwent lung biopsy at relatively younger ages (5 d and 4 mo, versus 8.7 mo for the rest of the cohort) also had histologic evidence of patchy PIG.

Unclassifiable

Twenty-two biopsies were not classifiable, largely due to inadequate tissue sampling, but also the result of insufficient clinical information or end-stage lung disease, which precluded analysis of defining histologic features (Figure 1). The mean age at biopsy was 7.9 $\pm$ 1.7 months. Follow-up data indicated that six infants had died, and one had undergone lung transplantation.

DISCUSSION

Pediatric diffuse lung diseases comprise a spectrum of disorders, which includes differing entities and histologic patterns than that described in the adult literature, particularly for children under the age of 2 years. This multi-center review is the first systematic analysis of the pathologic spectrum of pediatric diffuse lung disease and provides the largest study describing the clinical features of young children who undergo lung biopsy. The clinical-pathologic classification applied to this case series provides consensus terminology and diagnostic criteria for the myriad entities associated with diffuse lung disease in childhood, allowing 88% of cases to be categorized after multidisciplinary review. While this classification highlights entities seen in neonates and infants, some of these same conditions are also seen in older children and adults. Significantly, for disorders more prevalent in the young infants, this classification correlated with clinical features and outcomes including age at biopsy and mortality. Application of this classification scheme to a cohort of older children (age 2–18 yr) is currently being undertaken, and preliminary analyses indicate more overlap of histologic and clinical features with adult pulmonary disorders (37).

The term "interstitial lung disease" has been used synonymously with diffuse pediatric lung disease due to similar clinical presentation, including chronic tachypnea, hypoxia, cough, and/or crackles. Clinical features of children with diffuse lung disease have been examined in several reports (5, 38), and the term "chILD Syndrome" has been invoked to encompass the common clinical presentation of such patients (39). Nonetheless, subsequent lung biopsy often reveals that the pathogenesis of many of these disorders is outside the interstitial compartment, often with airway and airspace involvement. The scope of our study extends beyond conventional definitions of ILD by focusing exclusively on young children who underwent diagnostic lung biopsy for radiographic evidence of diffuse lung disease. As such, the proposed classification is one of diffuse infant lung disease, not specifically focused to ILD. In comparison, a wide-scale physician survey of chronic ILD done by a European consortium focused specifically on immunocompetent children in many of whom a lung biopsy had been performed for diagnosis, although there was no formal systematic review of these biopsies for diagnostic classification (38).

Fan and coworkers have previously evaluated the diagnostic utility of less invasive studies performed before lung biopsy (26). As lung biopsy was the capture point for enrollment in this study, the diagnostic yield or utility of less invasive investigations was not evaluated. Furthermore, a standardized assessment of clinical status before the lung biopsy was not ascertained retrospectively due to variable available clinical data. The impact of therapeutic interventions, particularly corticosteroids given before biopsy, on the histologic findings is uncertain and likely variable depending on the entity and the length and intensity of the intervention. Although all the hospitals contributing cases to this review are pediatric academic centers, the volume of lung biopsies varied greatly. The reason(s) for this variation were not elucidated by this retrospective review, but might reflect practice patterns of pulmonologists, neonatologists, and pediatric surgeons. Nonetheless, cases from each of the major categories were identified from most of the participating centers. Similar to experience with ILD in adults (2), a proportion of the biopsies were deemed nondiagnostic (12%), largely due to inadequate tissue sampling. To address this problem, a consensus protocol for handling tissue obtained at surgical lung biopsy has recently been published (40).

The pathologic entities captured in this analysis draw attention to disorders more prevalent in infancy, including those not typically thought to account for an ILD syndrome. It does not include conditions that are typically lethal early in the neonatal period and, thus, less likely to come to diagnostic lung biopsy. Such conditions, surfactant protein B deficiency and acinar dysplasia, are also far less common than the others captured in this retrospective analysis. Surprisingly, lung growth abnormality was the leading diagnosis at case review, which translated across many centers. Although the literature recognizes that postnatal lung growth is compromised in Down syndrome and congenital heart disease (30, 31), and that lobular simplification is the hallmark of chronic neonatal lung disease/"new" bronchopulmonary dysplasia (41), the majority of our cases were not clinically suspected or reported by the pathologist at the originating institution, underscoring the importance of multicenter review and consensus diagnostic criteria. Moreover, distinguishing a lung growth abnormality from other causes of ILD syndrome has important clinical implications, as steroids may not be indicated in this setting. The presence of patchy PIG in conjunction with a lung growth abnormality or with vascular disease has not been previously reported. Its presence may impact the clinical presentation of these patients and provide insight into the pathogenesis of this idiopathic disorder. Furthermore, it remains unclear whether there is a relationship between NEHI and a variety of pulmonary neuroendocrine cell hyperplasias, dysplasias, and malignancies presenting in adults, including diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (42).

Case reports and small series of patients with surfactant mutations (9–11, 18, 34, 35) have shown four histologic patterns, PAP, CPI, DIP, and NSIP, previously thought to represent distinct disorders. Systematic review of lung biopsies in this category demonstrates that these distinctive histologic patterns are functionally linked by related genetic mechanisms involving defects in a common pathway. The recognition that these previously separate diagnostic categories have related genetic mechanisms provides a rationale for classifying the lung pathology observed in these infants under the inclusive term of surfactant dysfunction. While the number of cases available for analysis was small, this review also provides the first indication that a specific histologic pattern may distinguish an *SFTPC* from *ABCA3* mutations. With the recent availability of testing in clinical genetic laboratories, lung disease due to abnormalities in surfactant metabolism may be diagnosed noninvasively, thereby obviating the need for biopsy in selected cases. If etiologies for specific disorders such as PIG and NEHI can be identified, these will also allow for a more mechanistic classification of diffuse lung disease and ILD in children.

Pediatric ILD has been associated with high morbidity and mortality, and previous studies have suggested that outcomes may be particularly poor for infants and young children (7). In this study, 30% of children had died, and 50% had ongoing pulmonary symptoms at follow-up. Clinical presentation and outcome were consistent with that of previous case series (5, 9, 16, 17), and pulmonary hypertension was the single greatest clinical predictor of mortality (7). Immunocompromised status and the presence of congenital heart disease were not independent predictors of outcome. The defining histopathology in this study frequently suggested important prognostic information, particularly in disorders more prevalent in young children. For example, disorders within the categories of Diffuse developmental, Growth abnormality, and PIG often had similar clinical presentations, but outcome was related to histologic diagnosis.

This multidisciplinary working group reviewed a large number of lung biopsies from young children to formalize diagnostic criteria and terminology for classification of pediatric diffuse lung disease. As diagnostic criteria for the infant lung disorders were formulated during the review process, interobserver agreement and concordance were not assessed. While an imaging group actively participated in this study, the limited availability of high-quality scans precluded inclusion of radiographic description in the current study. We anticipate that the evolving implementation of standard techniques for high-quality CT imaging in young children at a greater number of centers will provide a foundation for clinical-radiographic–pathologic correlation in these disorders. Until specific radiographic–histologic correlations are established, it is unknown whether imaging patterns may decrease the need for lung biopsy in certain infant lung disorders, as has occurred for adults with IPF.

This cross-sectional study highlights the utility of the proposed classification by grouping clinically distinct patients and disease entities. Prospective studies that include clinical, radiographic, and pathologic correlation are required to evaluate the prognostic value of this classification scheme. Protocol-driven evaluation and therapeutic intervention for these unique entities will only be possible once standardized terminology and diagnostic techniques are utilized. Multi-center and multidisciplinary involvement is vital to this effort.

Conflict of Interest Statement: R.R.D. received $6,294 in 2005, $5,132 in 2006, and $606 in 2007 in clinical research grant dollars from Inspire Pharmaceuticals for a multi-center clinical trial. R.R.D. has received speaking fees totaling $2,000 from Inspire Pharmaceuticals for 2006. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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APPENDIX 1

Institutions contributing case material were: Children's Hospital, Columbus, Ohio; Children's Hospital, Denver, Colorado; Children's Hospital and Regional Medical Center, Seattle, Washington; Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; Children's Memorial Hospital, Chicago, Illinois; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Hospital for Sick Children, Toronto, Ontario; James Whitcomb Riley Hospital for Children, Indianapolis, Indiana; Kosair Children's Hospital, Louisville, Kentucky; Washington University, St. Louis, Missouri; Texas Children's Hospital, Houston, Texas.

APPENDIX 2

Members of the ChILD Research Co-operative who participated in the current study.

Pathology Working Group

Chair: Claire Langston, M.D.; *Members*: Eric Albright, M.D., Fred Askin, M.D., Peter Baker, M.D., Pauline Chou, M.D., Carlyne Cool, M.D., Susan Coventry, M.D., Ernest Cutz, M.D., Mary Davis, M.D., Gail Deutsch, M.D., Megan Dishop, M.D., William Funkhouser, M.D., Csaba Galambos, M.D., Kathleen Patterson, M.D., William Travis, M.D., Susan Wert, Ph.D., Frances White, M.D.

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Imaging Working Group

Chair: Alan Brody, M.D.; *Members*: Eric Crotty, M.D., Eric Effman, M.D., Paul Guillerman, M.D., Fred Long, M.D., David Lynch, M.D.