Interstitial lung disease in children

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Purpose of review

In this review, we discuss the recent advances in our understanding of the cause, pathogenesis, presentation, diagnosis, treatment, and prognosis of interstitial lung disease (ILD) in children.

Recent findings

The classification of ILD syndromes in children greater than 2 years of age is based largely on adult classification schemes. In children less than 2 years of age, classification has been developed and evaluated pathologically. Entities can be categorized into developmental disorders, growth abnormalities, and surfactant dysfunction disorders based on pathologic findings. Two distinctive entities, neuroendocrine cell hyperplasia of infancy and pulmonary interstitial glycogenosis, present early in life with characteristic findings. These two disorders appear to have a favorable prognosis. Diagnosis of ILD syndromes is based on the summation of history and physical findings and both noninvasive and invasive studies. Newer approaches are being evaluated to decrease the need for lung biopsy.

Summary

Children's interstitial lung diseases are rare diffuse lung diseases resulting from a variety of pathogenic processes that include genetic factors, association with systemic disease processes, and inflammatory or fibrotic responses to stimuli. There are unique causes and presentations seen in infancy. Diagnosis in these disorders is made by the summation of clinical, radiologic, and pathologic findings.

Keywords

children, interstitial lung disease, neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis

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Introduction

Children's interstitial lung disease (ChILD) is a term that encompasses a heterogeneous group of rare and diffuse lung diseases with varying morbidity [1]. This spectrum of diseases is characterized by inflammatory and fibrotic changes that cause remodeling of the alveolar walls and distal airways and result in disordered gas exchange. Affected infants and children present with signs and symptoms of abnormal breathing, including tachypnea, crackles on examination, and diffuse infiltrates on chest radiograph. The prevalence of pediatric ILD has been estimated to be 3.6 per 1 000 000 in a study in the United Kingdom and Ireland [2], and the incidence to be 1.32 per 1 000 000 in a recent study from Germany [3]. In this review, we will concentrate on the most recent advances in pediatric ILD. A detailed review of each disease process is beyond the scope of this article, but specific attention will be given to those unique to children.

Classification

Table 1 lists the conditions encompassed in ChILD. Children less than 2 years of age often have unique disease processes. Deutsch *et al.* [4] applied a new classification system to 186 biopsies in children under the age of 2 years from 11 centers as part of the North America Children's Interstitial Lung Disease Research Network, as seen in the table.

Idiopathic interstitial pneumonias

The idiopathic interstitial pneumonias are uncommon in children. The usual interstitial pneumonia (UIP)/fibroblastic foci pattern, common in adults, has been described only in one adolescent with late presentation ABCA3 mutations [5]. Nonspecific interstitial pneumonia (NSIP), characterized by a mixture of inflammation and fibrosis and subdivided into cellular and fibrosing patterns, can be seen in a variety of pediatric settings, including inborn errors of surfactant metabolism and

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autoimmune disorders. Desquamative interstitial pneumonia (DIP) is seen as a histologic manifestation of inborn errors of surfactant metabolism [6].

Diffuse developmental disorders

Disorders in this category occur early in lung development, and diagnosis is via lung biopsy or postmortem. Alveolar capillary dysplasia associated with misalignment of pulmonary veins (ACDMPV) is a universally fatal disease, with term neonates presenting early in life with rapidly progressive respiratory failure and severe pulmonary hypertension, refractory to intensive therapies [7]. In this disorder, there is inadequate development of the pulmonary capillary bed and malposition of pulmonary veins in the bronchiolovascular bundles adjacent to pulmonary arteries. There are often associated anomalies of the cardiovascular, gastrointestinal, or genitourinary systems. Recently, microdeletions in the FOX gene cluster on 16q24.1 and mutations of FOXF1 have been identified with cases of ACDMPV with different phenotypic associated congenital anomalies [8]. Genetic evaluation and counseling should be sought in patients with suspected ACDMPV and in neonates with significant respiratory failure and pulmonary hypertension, especially when gastrointestinal, cardiovascular, or genitourinary abnormalities are present.

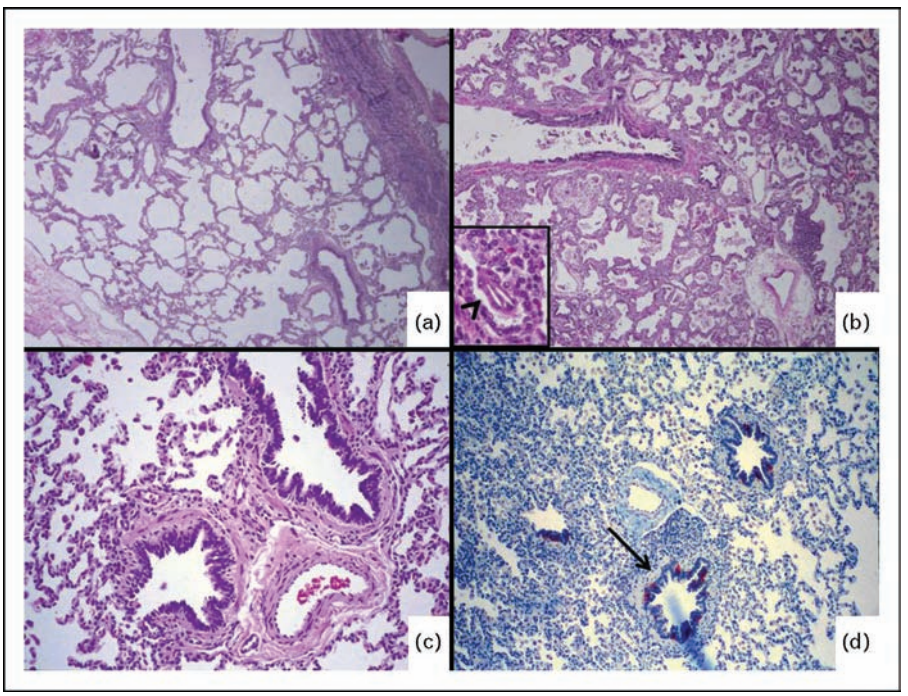
Key points

- Children's interstitial lung diseases are rare diffuse lung diseases resulting from a variety of pathogenic processes that include genetic factors, association with systemic disease processes, and inflammatory or fibrotic responses to stimuli.
- There are causes of interstitial lung disease (ILD) distinctively seen in children, particularly those seen in infancy.
- Diagnosis of children's interstitial lung disease is made by a combination of history/physical exam, imaging studies, functional studies, bronchoalveolar lavage, and, if needed, lung biopsy.
- Treatment for ILD in children involves supportive care and use of anti-inflammatory agents, although currently no randomized controlled trials exist to evaluate the use of these therapies.

Pulmonary growth abnormalities

Growth abnormalities (Fig. 1a) are the most common cause of diffuse lung disease in infants. They are usually

Figure 1 Histopathology in various forms of ILD



(a) Growth abnormality: the lobular architecture is simplified with markedly enlarged alveoli and decreased septation; alveoli are often enlarged to the size of nearby membranous bronchioles. (b) Surfactant protein C mutation: there is simplification of the lobular parenchyma and widening of alveolar walls. There is focally prominent intra-alveolar material. In the inset, there is alveolar epithelial hyperplasia as well as a cholesterol cleft (arrowhead) associated with intra-alveolar macrophages on higher magnification. (c) Neuroendocrine cell hyperplasia of infancy: the lung histology is near normal, with well alveolated parenchyma and normal appearing bronchioles and small pulmonary artery. (d) Bombesin immunostain shows two membranous and one terminal bronchiole; each contains clusters of brightly immunopositive neuroendocrine cells (arrow).

Table 1 Causes of children's interstitial lung disease disorders

Disorders unique to infancy	
Diffuse developmental disorders	Acinar dysplasia
	Congenital alveolar dysplasia
	Alveolar capillary dysplasia with misalignment of pulmonary veins
Growth abnormalities	Chronic neonatal lung disease (in premature and term infants)
	Secondary pulmonary hypoplasia
	Chromosomal abnormalities (i.e., Trisomy 21)
	Associated with congenital heart disease
Surfactant dysfunction disorders	Surfactant protein B mutations
	Surfactant protein C mutations
	ABCA3 mutations
	Thyroid transcription factor-1 mutations
	Histology consistent with surfactant dysfunction disorder without recognized genetic disorder
Neuroendocrine cell hyperplasia of infancy	
Pulmonary interstitial glycogenosis	
Primary lung disease	
Idiopathic interstitial pneumonias	Nonspecific interstitial pneumonia
	Cryptogenic organizing pneumonia
	Acute interstitial pneumonia
	Desquamative interstitial pneumonia
	Lymphocytic interstitial pneumonia
Alveolar hemorrhage syndromes	Includes syndromes with and without pulmonary capillaritis
Pulmonary alveolar proteinosis	Includes congenital, primary, and secondary causes
Pulmonary microlithiasis	
Pulmonary vascular disorders	
Pulmonary lymphatic disorders	Lymphangiomatosis
	Lymphangiectasis
Pulmonary infiltrates with eosinophilia	Includes primary and secondary causes (drugs, parasites, infections, toxins)
Systemic disorders with pulmonary involvement	
Connective tissue disease	Includes SLE, systemic sclerosis, Sjogren's syndrome
Malignancies	
Histiocytosis	
Sarcoidosis	
ILD of specific (known) cause	
Storage disorders	
Aspiration syndromes	
Postinfectious bronchiolitis obliterans	
Drug-induced lung disease	
Hypersensitivity pneumonitis	

ILD, interstitial lung disease; SLE, systemic lupus erythematosus. Adapted from [4].

related to prematurity or pulmonary hypoplasia, but can also be associated with congenital heart disease or chromosomal abnormalities, and, in term infants, with early postnatal lung injury.

Prematurity-associated lung disease is a well known entity, with the 'new' bronchopulmonary dysplasia consisting of alveolar simplification. Pulmonary hypoplasia, resulting from restricted lung growth *in utero*, can be acquired because of oligohydramnios, congenital diaphragmatic hernia, hypoxemia, or nutritional deficiencies, among other causes.

In a review of 259 biopsies by Langston and Dishop [9], 11 biopsies fit into the category of congenital heart disease affecting lung growth, including ventricular septal defects (5/11), large patent ductus arteriosus (3/11), hypoplastic left heart (2/11), and double outlet right ventricle (1/11). Infants with Trisomy 21 (with and without cardiac disease) are known to have simplified alveolar architecture and can be noted to have more severe and earlier pulmonary arterial hypertensive changes. Growth abnormalities in term infants can result from a combination of in-utero and postnatal factors, such as infant of a diabetic mother and infectious insults. Pulmonary vascular disease is a frequent association in this group as well.

Surfactant dysfunction disorders

Mutations in the genes encoding the surfactant proteins B and C (SP-B and SP-C), ATP-binding cassette transporter protein ABCA3, and thyroid transcription factor-1 (TTF-1) have been recognized to cause significant morbidity in infants and children. SP-B deficiency is an autosomal recessive disorder, presents early in life with progressive respiratory distress and failure, and is usually fatal by 3–6 months of age. The typical histopathology is alveolar proteinosis with foamy, eosinophilic, lipoproteinaceous material filling alveoli, thickened alveolar septa with alveolar epithelial hyperplasia, and abnormal lamellar bodies on electron microscopy [10]. Other histologic patterns, including infantile DIP, may be seen occasionally. Lung transplant is currently the only therapeutic option for SP-B deficiency.

The presentation of SP-C deficiency (Fig. 1b) is variable, with a large proportion of patients presenting in late

infancy/early childhood, although some present in early infancy, and still others are discovered in adulthood. In a recent Dutch study, SP-C mutations accounted for approximately 25% of adult familial pulmonary fibrosis cases [11]. It is an autosomal dominant disorder, but about half of the cases are sporadic with de-novo mutations. Late presentation is associated with symptoms of ILD. The histopathologic picture (Fig. 1b) is of uniform alveolar epithelial hyperplasia with mild alveolar wall thickening with mild lymphocytic inflammation and often muscularization of the alveolar septa, foamy alveolar macrophages, and variable amounts of granular to globular alveolar proteinosis with a few cholesterol clefts [10]. Pharmacologic approaches for SP-C deficiency are based on anecdotal evidence, and include pulse corticosteroids, hydroxychloroquine, and azithromycin. Outcome is variable, as some children with SP-C mutations improve over time [12], although others progress to end-stage lung disease.

Mutations in genes encoding ABCA3 are the most common genetic cause of respiratory failure in full-term infants [13]. Most affected infants present in respiratory failure in the newborn period. A subset present with mild disease in the newborn period or later in childhood with chronic ILD. Histologically, infantile DIP and alveolar proteinosis are seen early in life, whereas NSIP is the typical pattern for older children; a UIP pattern with fibroblastic foci has been reported in a single adolescent [5]. Tiny lamellar bodies with densely packed phospholipid membranes and eccentrically placed electron-dense inclusions are characteristic electron microscopy findings [10]. Inheritance is autosomal recessive. For those patients presenting with respiratory failure in early infancy, lung transplant is sometimes offered as a therapeutic option.

Mutations in the TTF-1 (also known as NKX2-1) gene are associated with a syndrome of neurologic (cerebral dysgenesis, chorea, developmental delay), thyroid (hypothyroidism), and pulmonary dysfunction [14]. TTF-1 has been shown to play an important role in pulmonary branching morphogenesis and surfactant homeostasis. Some children with TTF-1 mutations present with respiratory failure in the newborn period or with recurrent viral infections and hypoxemia. Others may present later with chronic ILD. There are limited reports of pulmonary disorder in affected patients; however, a recent report describes alveolar simplification, abundant normal appearing lamellar bodies (in contrast with other surfactant dysfunction disorders), and altered immunoreactivity for surfactant proteins and ABCA3 [15•]. Treatment approaches are similar to those for the other surfactant abnormalities.

Pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare disorder of the lung caused by impaired surfactant homeostasis and characterized by the accumulation of lipoproteinaceous material within the alveolar spaces, resulting in respiratory insufficiency or failure. There are three forms: congenital, primary, and secondary. Primary PAP is an autoimmune disorder and accounts for the majority of cases in adults. Primary PAP is due to high levels of granulocyte/macrophage-colony stimulating factor (GM-CSF) autoantibodies, resulting in altered surfactant homeostasis and impaired surfactant clearance. GM-CSF is required for pulmonary alveolar macrophage catabolism of surfactant, and also is a critical regulator of innate immunity and lung host defense [16]. Patients present with insidious, progressive tachypnea and exercise intolerance, and, in some cases, the classic 'crazy paving' pattern is identified on computed tomography (CT) scan, consisting of smooth interlobular septal thickening and intralobular lines superimposed on ground-glass opacities. Congenital PAP results from genetic mutations in GM-CSF and its receptors. Serum biomarkers have been suggested to assist in diagnosis and differentiation from autoimmune PAP. Suzuki *et al.* [17•] identified a 6-year-old girl with PAP, impaired GM-CSF receptor function, and increased GM-CSF. She was later found to have a CSF2Rα genetic mutation, and, upon further review, eight patients were identified with PAP caused by recessive CSF2Rα mutations. The authors noted that serum GM-CSF autoantibody levels, which are increased in patients with autoimmune PAP, were low in all patients with congenital PAP on this basis. In contrast, GM-CSF levels were elevated in all symptomatic patients with congenital PAP and low in patients with autoimmune PAP. The classic treatment for PAP is whole-lung lavage, which is effective for both forms mentioned. Inhaled GM-CSF may benefit patients with autoimmune disorder, but not congenital PAP.

Neuroendocrine cell hyperplasia of infancy

Originally described as persistent tachypnea of infancy, neuroendocrine cell hyperplasia of infancy (NEHI) typically presents in children less than 1 year of age with tachypnea, retractions, hypoxemia, and crackles on examination [18]. The diagnosis is based on the identification of an increased proportion of bombesin-immunopositive neuroendocrine cells in bronchioles, suggested to be at least 10% in any individual airway and to be found in more than 70% of bronchioles in the sample (Fig. 1c and d) [9]. Lung biopsy otherwise usually has a near-normal appearance. Neuroendocrine cell (NEC) prominence has been shown to be significantly increased in NEHI, as compared with other pulmonary disorders [19]. In their findings, the authors note that the increase in neuroendocrine cells did not correlate with signs of airway injury, suggesting that NEC prominence is not a reparative phenomenon, but is the primary disorder. Characteristic CT findings in NEHI (discussed later) and the presence of normal KL-6, a serum biomarker of type II epithelial

cell activation, can help differentiate NEHI from other infant lung disorder entities, such as errors of surfactant metabolism [20•,21]. The term 'NEHI syndrome' is used when diagnosis is based on characteristic clinical and CT findings, rather than lung biopsy.

Although the underlying cause is unknown, Popler *et al.* [22••] described four families having multiple siblings with clinical, radiographic, and/or histologic findings consistent with NEHI, suggesting a possible genetic or environmental cause. Treatment is supportive with the goal of preventing hypoxia with supplemental oxygen. Long-term corticosteroid use has not been shown to be of benefit, an expected finding given the lack of significant inflammation histologically. Long-term prognosis remains uncertain at this time, although most children improve with time and no deaths have been reported. Recent evidence suggests that children with NEHI have evidence of air trapping that can persist beyond the age of 7 years [23].

Pulmonary interstitial glycogenosis

Although previously described with other names, the entity now known as pulmonary interstitial glycogenosis (PIG) was best detailed in 2002 by Canakis *et al.* [24]. They identified lung biopsies from infants presenting with tachypnea, hypoxemia, and diffuse interstitial infiltrates with a characteristic histology of alveolar septal widening by noninflammatory bland interstitial cells without alveolar epithelial hyperplasia. Periodic acid-Schiff-positive material consistent with glycogen was seen irregularly and in minimal amounts in these cells; however, on electron microscopy the interstitial cells contained abundant monoparticulate glycogen. Infants present with respiratory distress in the first weeks of life. Recent case reports by Lanfranchi *et al.* [25] and Castillo *et al.* [26] illustrate the notion that, in many cases, PIG is not an isolated finding ('diffuse PIG'), but is seen with alveolar simplification related to deficient lung growth ('patchy PIG'). In the review by Langston and Dishop [9], 58% of infants less than 6 months of age with growth abnormalities had associated patchy PIG. Treatment for PIG is largely supportive, and the use of corticosteroid therapy for this condition has been contentious. In the original series by Canakis *et al.*, five of the seven patients received corticosteroids, one of whom (born at 25 weeks' gestation) died. The two infants not treated with corticosteroids survived, although one remained on oxygen for a prolonged period (to at least 10.5 months of age at last contact). Recently, histologic resolution has been reported in a patient with congenital heart disease and PIG, who was treated with 5 days of glucocorticoids in a time frame between the first and second biopsies [27]. A word of caution is noted in the diagnosis of PIG, as imaging can be variable, with findings of septal thickening and ground-glass opacities overlapping in other disorders; and in the prognosis of PIG, as this may be likely related to the underlying growth abnormality/accompanying condition in patchy PIG [28]. The negative consequences of corticosteroids on postnatal alveolarization and neurodevelopmental outcomes are well recognized, and thus the routine use of high-dose corticosteroids for cases in which patchy PIG occurs in the setting of a significant lung growth abnormality is not recommended. Prognosis appears favorable in diffuse (isolated) PIG.

Diagnosis of ChILD syndromes

A systematic approach, combining history and physical exam, pulmonary function studies, imaging studies, bronchoalveolar lavage (BAL), and lung biopsy, is crucial in establishing the diagnosis.

Pulmonary function studies

Pulmonary function tests (PFTs) done in older children typically demonstrate a restrictive pattern with reduced total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV1), with a normal or elevated FEV1/FVC ratio. However, air trapping is suggested by a normal or elevated residual volume, and an elevated residual volume/TLC ratio, resulting in a mixed obstructive/restrictive picture. Infant PFTs can be useful in evaluating pediatric ILD syndromes. The finding that the extent of neuroendocrine cell prominence and severity of small airway obstruction on PFTs are correlated suggests that infant PFTs may aid in the assessment of NEHI [19].

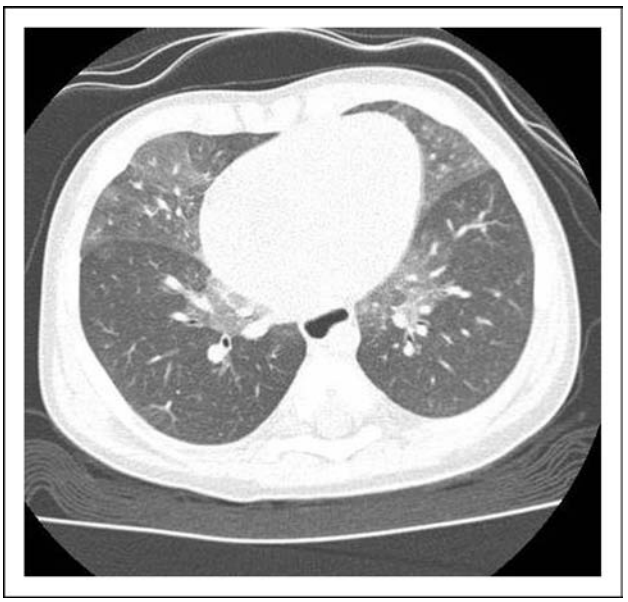
Imaging

High-resolution computed tomography (HRCT) has been employed to provide precise detail about the extent and distribution of disease, and can also improve diagnostic accuracy, sometimes limiting the need for lung biopsy. A characteristic pattern can be seen, for example, in NEHI, with ground-glass opacities involving the right middle lobe and lingula (the so-called 'bat wing deformity') and air trapping represented by mosaic attenuation (Fig. 2). In a recent study, Brody *et al.* [20•] assessed the diagnostic accuracy of CT in 23 cases of biopsy-proven NEHI and six cases from patients with other ILD conditions. The CT sensitivity and specificity for this classic pattern were at least 78 and 100%, respectively. HRCT may also provide prognostic information. Patients with NEHI have a favorable prognosis, whereas children with growth abnormalities and surfactant mutations have considerable mortality. In a recent study of patients with postinfectious bronchiolitis obliterans, severity of CT scan correlated with poorer lung function status several years later [29].

Bronchoscopy/bronchoalveolar lavage and lung biopsy

BAL can aid in the diagnosis of specific disease types. In the appropriate clinical setting, the presence of

Figure 2 High-resolution computed tomography image demonstrating ground-glass attenuation in the bilateral perihilar regions, right middle lobe, and lingula, consistent with neuroendocrine cell hyperplasia of infancy



hemosiderin-laden macrophages (diffuse alveolar hemorrhage), lipid-laden macrophages (aspiration syndromes), lymphocytes (hypersensitivity pneumonitis, sarcoidosis), or eosinophils (eosinophilic pneumonia) can help distinguish among disorders, although controversy remains regarding the specificity of some of these alterations. Recent data suggest BAL fluid cytokine levels differ between ChILD syndromes and disease controls [cystic fibrosis (CF), aspiration syndrome, non-CF bronchiectasis], with interleukin (IL)-8 and macrophage inflammatory protein (MIP)-1β found to be significantly lower [30].

Although lung biopsy remains the gold standard for diagnosis of most of the individual entities that result in ChILD syndrome, this is no longer uniformly the case, as less invasive studies may ascertain diagnosis in some conditions in typical clinical settings.

Treatment

Treatment is directed to the specific disorder. In general, supportive care, including oxygen and ventilatory therapy when needed, nutritional intervention, prevention of infection, and conditioning and rehab are of utmost importance.

Corticosteroids remain the first-line therapy for a number of these disorders, including the surfactant dysfunction disorders, idiopathic interstitial pneumonias, hypersensitivity pneumonia, eosinophilic pneumonia, alveolar hemorrhage, and connective tissue diseases. We recommend the use of intravenous pulse steroids, given as 10–30 mg/kg with a maximum of 1 g once weekly or on three consecutive days monthly instead of daily steroids, as this appears to be associated with fewer side-effects, though no controlled trials exist. Steroid-sparing agents with anti-inflammatory properties, such as hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, and intravenous immunoglobulin, have also been used with some success [31]. This is based on anecdotal evidence, as there have been no randomized controlled trials in children with ILD.

Lung transplantation is an option for children with end-stage diffuse lung disease, with long-term outcomes that appear to be comparable to those with CF and pulmonary hypertension [32].

Conclusion

Children's interstitial lung diseases are rare diffuse lung diseases resulting from a variety of pathogenic processes that include genetic factors, association with systemic disease processes, and inflammatory or fibrotic responses to stimuli. Although some disease types overlap with those seen in adults, there are many causes unique to children, particularly those that occur in infancy. Diagnosis is made by the summation of clinical, radiologic, and pathologic findings, with some disorders having characteristic clinical, pulmonary function, or imaging findings, lessening the need for biopsy. Treatment and prognosis are disease-specific, and can involve a combination of supportive and pharmacologic care.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 362).

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