



INTERSTITIAL LUNG DISEASE IN CHILDREN

by Leland L. Fan, M.D.

Introduction

Interstitial lung disease (ILD) comprises more than 100 disorders characterized by diffuse inflammation and scarring of the lung interstitium, derangement of the alveolar walls and loss of functional alveolar capillary units.

Estimates of ILD incidence and prevalence in adults are imprecise, but some studies suggest ILD may account for as many as 100,000 hospital admissions annually. The diseases are more rare in children, but actual incidence remains unknown and current knowledge is based largely on case reports and information obtained from small series of patients.

ILD poses a clinical challenge to physicians because the disease spectrum can range from mild disease that is responsive to medications to progressive loss of pulmonary function and death.

Corticosteroids and cyclophosphamide result in clinical improvement in a subset of patients, but in other patient groups pharmacologic therapy remains largely empiric and unproven.

Clearly, progress is needed to improve understanding of ILD etiology, pathogenesis, diagnosis and treatment.

Etiology and Pathogenesis

In a minority of cases, ILD evolves from a known insult to the interstitium. A number of collagen vascular diseases have been associated with ILD. Drug-induced lung

injury also contributes a fair number of cases. Among other known causes of ILD, hypersensitivity pneumonitis, an immunologic response to organic dusts such as molds and bird antigens, is relatively common. Aspiration syndromes represent another common source of chronic lung disease in children. Infectious pneumonia may lead to chronic lung disease in either the immunocompetent or immunocompromised host, and previous, clinically unrecognized infection likely contributes to some ILD cases (SEE TABLES 1 & 2).

Other frequently suspected sources of ILD in children include exposure to environmental contaminants, infectious agents and autoimmune reactions and disorders.

However, in an appreciable number of cases, epidemiologic data are insufficient to clearly implicate these factors. Idiopathic

pulmonary fibrosis, which is more common in adults than in children, is characterized by a constellation of clinical, radiographic and pathologic abnormalities in the absence

of an identifiable cause.

Despite the diversity of diseases that constitute ILD of known cause, the majority of patients have idiopathic disease. Among the most common forms of ILD in adults is idiopathic pulmonary fibrosis (IPF, also known as cryptogenic fibrosing alveolitis). A variety of etiologies have been proposed for the lung injury that leads to IPF, but to date none have been proved.

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UPDATE

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IN CHILDREN

MEDICAL SCIENTIFIC

Vol. 13 No. 1, Winter 1995

The conditions that make up ILD, whether of known or unknown origin, have in common an inflammatory process thought to be initiated by an injury to the alveolar wall. This inflammation, combined with the lungs' attempts to repair the injury, leads to distortion of the lung architecture and deposition of connective tissue. A number of inflammatory cells are thought to participate in the evolution of

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ILD, especially neutrophils and alveolar macrophages. T- and B-lymphocytes, monocytes, eosinophils, basophils and mast cells also have been implicated.

Several histologic descriptions are used to designate individual patterns on lung biopsy. This pathologic information is used along with clinical data to lead to a diagnostic categorization of the disease process.

Usual Interstitial Pneumonitis (UIP)

UIP is a histologic pattern characterized by the occurrence of lesions in various stages of development in a patchy distribution in the lung. The heterogeneity of lesions probably reflects progressive involvement of previously unaffected lung tissue. As a result of this heterogeneity, parts of the lung may appear normal while other sections have a honeycomb appearance with dense fibrous tissue, creating cystic spaces. UIP is clinically and histologically distinct from acute interstitial pneumonia, which progresses more rapidly.

Desquamative Interstitial Pneumonitis (DIP)

In contrast to UIP, DIP is characterized by uniform histologic involvement with lesion uniformity, filling of air spaces by macrophages and mononuclear inflammatory cells, interstitial infiltrate of histiocytes, lymphocytes, plasma cells and eosinophils. Usually, only mild thickening of the alveolar septa occurs. Some investigators believe DIP represents an early pattern that evolves into UIP.

Table 1
Pediatric ILD of Known Etiology

- Aspiration Syndromes
- Chronic infection in immunocompetent or immunocompromised host
 - Viral (EBV, CMV, adenovirus, others)
 - Bacterial (Chlamydia, mycoplasma, mycobacterial, others)
 - Fungal (Aspergillosis, histoplasmosis, others)
 - Parasitic (pneumocystis)
- Bronchopulmonary dysplasia
- Occupational, environmental, or physical agents
 - Hypersensitivity pneumonitis
 - Drug-induced lung disease
 - Radiation-induced lung disease
 - Oxygen toxicity-induced lung disease
 - Chemical fume-induced lung disease
 - Mineral dust-induced lung disease
- Lipid storage diseases

Table 2
Pediatric ILD of Unknown Etiology

- Usual interstitial pneumonitis
- Desquamative interstitial pneumonitis
- Lymphocytic interstitial pneumonitis and related disorders
- ILD associated with autoimmune disorders
- ILD associated with malignancies
- Pulmonary hemosiderosis
- Pulmonary histiocytosis
- Pulmonary infiltrates with eosinophilia
- Pulmonary vascular disorders (hemangiomatosis, veno-occlusive disease, telangiectasia)
- Pulmonary lymphatic disorders (lymphangiomatosis, lymphangiectasis)
- Sarcoidosis
- Bronchiolitis obliterans
- Bronchiolitis obliterans with organizing pneumonia
- Alveolar proteinosis^a
- Neurocutaneous syndromes
- Cellular interstitial pneumonitis
- Nonspecific interstitial lung disease

^aDue to deficiency of surfactant protein B in some patients with the congenital variant

Lymphocytic Interstitial Pneumonitis (LIP)

LIP is characterized by a diffuse interstitial infiltrate with a predominance of lymphocytes, accompanied by plasma cells and histiocytes within the interstitial component of the alveolar wall and along lymphatic pathways. Resultant architectural changes typically consist of thickening of the bronchovascular bundles and interlobular septa. Small, non-cleaved lymphocytes may accumulate to produce micronodules.

The classic histologic patterns of idiopathic ILD are seen less often in children. UIP has been described in a fair number of children, but the frequent omission of lung biopsy results in most cases leaves the histologic diagnosis open to question. In the experience at National Jewish, true UIP has been unusual. DIP accounts for fewer pediatric cases of ILD, as the medical literature reflects about a 1:3 ratio of DIP to ILD in children. This ratio is higher than for adults, who have a 1:10 ratio. LIP in children is most commonly associated with underlying autoimmune diseases and immunodeficiency states, especially AIDS. LIP occurs in almost a third of all children with perinatally acquired HIV infection, and the prevalence is likely to increase with the rising prevalence of pediatric AIDS.

Many children have diffuse interstitial inflammation that does not fit any specific histologic category. This observation is similar to that reported by other investigators.

Diagnostic Evaluation

Clinical Presentation

Patients with ILD commonly present with dyspnea on exercise, frequently accompanied by cough and fatigue. Dry rales (also called "Velcro" crackles) may be present on chest auscultation. Pleurisy may occur in association with collagen vascular diseases and with drug-induced ILD. Wheezing is uncommon.

Signs of advanced disease include increased dyspnea and tachypnea, cyanosis and digital clubbing. Advanced disease in children may result in weight loss or failure to thrive.

Symptoms not confined to the chest can point

toward ILD originating from a specific cause. For example, systemic lupus erythematosus may produce a characteristic malar rash; pitting of the fingertips may be a sign of scleroderma; joint tenderness and swelling may indicate rheumatoid arthritis.

While the clinical presentation may help guide the physician to a diagnosis of ILD, it must be combined with other aspects of the evaluation to generate a diagnosis.

Exposure History

The history should focus on attempting to identify a specific etiology. Toward that end, a comprehensive review of potential environmental exposures should be done, including both the workplace and home. Exposure to any type of chemical or organic substance should be covered in detail. Among adults, occupational history should encompass total employment history, not just the current, most recent or longest-lasting job.

A detailed drug history should focus on pharmaceutical agents that have a known association with ILD. The medical history should cover history of pulmonary diseases and infections, immune system disorders and immunodeficiency and conditions associated with ILD, such as collagen vascular diseases.

The link between HIV infection and ILD should not be underestimated. HIV infection predisposes a patient to LIP and to opportunistic infections associated with chronic lung disease. HIV should be high on the list of etiologic suspects in any patient who has diffuse interstitial infiltrates of unidentified origin. Given the typically long latency between exposure and emergence of the infection, the review of HIV risk factors should extend back as many years as necessary to rule out the possibility.

Smoking has a mixed association with ILD. Eosinophilic granuloma has a strong association with smoking, but hypersensitivity pneumonitis is almost always associated with a negative history.

Family history of ILD or chronic lung disease occasionally is a useful finding, as genetic factors contribute to the development of some types of ILD.

The heterogeneity of the disease encountered continues to pose a diagnostic challenge.

Chest Radiographic Pattern

The chest x-ray is a useful diagnostic tool for many types of ILD. The x-ray can help define pulmonary infiltrates according to lung compartment involvement (interstitial, alveolar or both), and by pattern (reticular, nodular, recitulonodular, ground glass or honeycomb) and by the predominance of upper vs. lower lobe involvement. However, the chest radiograph proves to be normal in about 10% of cases and correlates poorly with clinical and functional impairment. In a National Jewish study of 48 pediatric ILD patients, chest x-rays were abnormal in all cases, with 75% of the patients having interstitial infiltrates.

Other Diagnostic Tests

High-resolution computed tomography (HRCT) has proven useful in the assessment of adults with ILD. HRCT has demonstrated good diagnostic accuracy for specific diseases, including UIP, but the imaging technique has shown the most value in the identification of specific disease patterns.

Pulmonary function tests should be performed whenever ILD is suspected. The tests typically will reveal restrictive lung impairment. Forced vital capacity and forced expiratory volume at one second are reduced proportionally in most patients. Total lung capacity, functional residual capacity and residual volume all tend to be decreased in adults, but often vary in children.

Arterial blood gases reveal hypoxemia, with exercise or at rest, in a substantial number of patients (87% in the National Jewish pediatric series).

Laboratory tests should be used as indicated to help confirm or rule out specific etiologies. CBC, sedimentation and total eosinophil count are among the most common hematologic tests. Immunologic testing, screens for infectious disease (especially HIV), urinalysis and other tests may prove useful in specific patients.

At National Jewish, cardiac evaluation has proven useful in the workup of pediatric patients. More than

40% of the first 48 patients showed evidence of pulmonary hypertension by ECG, echocardiography and/or cardiac catheterization.

Bronchoalveolar lavage has been used in adults to predict response to therapy, narrow the differential diagnosis and gain insight into the pathophysiology of ILD. However, the procedure does not enjoy universal acceptance among physicians. The procedure's role in the evaluation of pediatric patients remains undefined, primarily because of a lack of comprehensive normal values for pediatric lavage fluid. Bronchoalveolar lavage has proven useful in diagnosing infection in immunocompromised and immunocompetent children.

Transbronchial lung biopsy has proven especially useful in the diagnosis of granulomatous ILD and sarcoidosis. The procedure is limited somewhat by the amount of tissue that can be obtained via fiberoptic bronchoscopy. In addition, transbronchial biopsy has been limited in children by the lack of a suitable flexible bronchoscope.

The most invasive diagnostic option, open lung biopsy, remains the gold standard for ILD diagnosis. At National Jewish specific histologic diagnosis was made in 24 of 30 patients in whom biopsies were obtained, a diagnostic yield comparable to those reported in published series.

Treatment

A few specific therapies exist for ILD, such as interferon alpha for pulmonary hemangiomas. By and large, however, pharmacologic therapy is somewhat empirical and unproven, due to the absence of controlled clinical trials.

Corticosteroids have emerged as primary pharmacologic therapy. Steroids have been used with varying degrees of success to treat UIP, DIP, LIP, hypersensitivity pneumonitis and other forms of ILD. About 40% of patients have responded to steroids in the National Jewish pediatric series. Other investigators have reported somewhat higher response rates. The true response rate remains unknown because steroids have not been evaluated

in controlled trials of ILD. Both oral steroids and pulse therapy have been used.

A number of agents have been used as second-line therapy after corticosteroids. At National Jewish, hydroxychloroquine is used with some regularity in ILD, especially in pediatric patients, because of its relatively low toxicity. Among cytotoxic agents, cyclophosphamide, azathioprine and methotrexate are used most frequently. Although cyclophosphamide is often the drug of choice as adjunctive therapy to corticosteroids in adults, a higher than expected sterility rate limits its usefulness in children. In general, second-line pharmacologic therapies have not been evaluated in controlled clinical studies of ILD.

Attempts to define clinical responses are confounded by patterns of exacerbation and remission that commonly occur in ILD patients. Commonly used signs of improvement include decreased need for oxygen therapy, decreased respiratory rate, improvement in chest x-ray and pulmonary function, resolution of pulmonary hypertension and weight gain in children. In the National Jewish pediatric series, which has grown to 78 patients, about half improved at one-year follow-up, and two patients had complete remission.

Lung transplantation remains a final option for patients who develop end-stage ILD despite maximal pharmacologic and supportive therapy.

Supportive care remains an essential component in the treatment of adults and children. Most patients, especially children, require long-term oxygen therapy for hypoxemia. Bronchodilators should be employed as needed in specific patients with reversible airway disease. Infections should be managed aggressively. Carefully supervised fitness and exercise programs and adequate nutrition also should have defined roles, especially in children. Annual influenza vaccination is recommended.

Follow-up

ILD patients should be followed closely for signs of clinical deterioration, and supportive and pharmacologic therapy should be used aggressively and modified as necessary in response to the patient's

Supportive care remains an essential component in the treatment of adults and children.

condition. A clinical, radiographic and physiologic scoring system has been employed with some success in follow-up evaluation of adults. No well-established guidelines exist for following the progress of pediatric ILD

patients. Whether the scoring system would be useful for children remains to be seen.

ILD results in considerable morbidity and mortality, though precise figures are hard to come by because of the diversity of the disease. In the National Jewish pediatric ILD population, mortality is approximately 20%.

Conclusion

Progress has been made in the identification and characterization of ILD in adults. However, the heterogeneity of the disease encountered continues to pose a diagnostic challenge, and the absence of a clear-cut etiology in the majority of cases makes treatment problematic. Therapy remains largely empiric. Supportive care continues to play an important role in patient management. Awareness of pediatric ILD is at a more primitive stage of evolution than is the body of information on adult ILD, and closer institutional collaboration is needed to organize and perform meaningful studies and develop the necessary knowledge base.

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New Programs Expand Day Treatment Services and Foster More Cost-Efficient Care

National Jewish Center for Immunology and Respiratory Medicine has entered discussions with University Hospital, The Children's Hospital and the University of Colorado School of Medicine - all in Denver - to relocate certain clinical services among the four organizations by spring of 1995.

In light of the growing trend toward outpatient services, our small service of acutely ill respiratory, allergy and immunology patients will receive hospital inpatient care on leased National Jewish wards at University and Children's hospitals. In addition, University, Children's and the School of Medicine will relocate certain outpatient clinics for patients with respiratory and allergic diseases to National Jewish, where a \$5 million, 15,000 sq. ft. clinic addition was completed in the fall of 1994.

In each situation, physicians from the respective institutions will continue to care for their own patients. National Jewish will maintain chronic care and observation units on site.

"While inpatient census has declined in recent years, reflecting national trends, we are expanding our day treatment programs to continue offering our intensive evaluation and treatment programs while markedly reducing costs for all of our patients, including out-of-state patients, said Lynn M. Taussig, MD, president.

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