Pushing chILD Forward: The Bright Future of Children's Interstitial Lung Diseases

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It is a good thing that diffuse parenchymal lung diseases (DPLDs), more commonly known as interstitial lung diseases (ILDs), fall near the center of a major, current research effort in pulmonary medicine (1, 2). Clinical and pathophysiologic knowledge on a multitude of these orphan entities, which frequently have a debilitating course, is limited. Unfortunately, many leaders, clinicians, radiologists, and researchers in this area still have to acknowledge that beyond the diseases of adult patients, there is another broad spectrum of interstitial lung diseases, which they have not yet come across: the children's interstitial lung diseases (chILDs).

For many decades, the available adult classification systems were also applied to children, even though they do not map well across the age gap (3). In 2007, Deutsch and colleagues investigated a cohort of children with biopsy-confirmed ILD who were younger than 2 years (4). Deutsch and colleagues clearly separated from diseases that occur at all ages several entities that occur primarily in children younger than 2 years. They labeled these rare conditions "disorders more prevalent in infancy." They separated these disorders into four groups, each with several subgroups: diffuse developmental disorders including congenital alveolar dysplasia and alveolar capillary dysplasia with misalignment of pulmonary veins; growth abnormalities including pulmonary hypoplasia, chronic neonatal lung diseases, and ILD associated with trisomy 21, other genetic abnormalities, or congenital heart disease; specific conditions with poorly understood etiology, including pulmonary interstitial glycogenosis and neuroendocrine cell hyperplasia of infancy; and a large group of surfactant dysfunction disorders, including SP-B, SP-C, ABCA3, GMCSF receptor deficiency, and several others.

A clinical-radiological-pathological classification system for pediatric DPLD, used widely in Europe, integrated the system of Deutsch and colleagues for those younger than 2 years. The chILD classification expanded categories for disorders more prevalent in infancy to include DPLD not molecularly defined in the mature and almost mature neonate (5). For disorders of all age groups, the benign lymphatic disorders were separated into their own class. In addition, several diseases not included in the initial patient sample were added into the categories. Specific infections leading to diffuse parenchymal lung disorders were not included into chILD, but categorized as lung infections.

One advantage of the European system is its ability to accommodate cases without lung biopsy (6). The system is currently undergoing evaluation in the chILD-EU project (http://www.klinikum.uni-muenchen.de/Child-EU/en/index.html) (7, 8). Another recent study assessing biopsy-proven chILD in children of all ages similarly needed to extend the categories beyond infancy to accommodate the observed diagnostic spectrum (9).

In this month's issue of the *AnnalsATS,* Fan and colleagues (pp. 1498–1505) publish their experience with categorizing diffuse lung disease diagnosed in children aged 2 to 18 years based on lung biopsies and available clinical information (10). The authors used a similar methodological approach as they did in their previous publication in 2007. Teams of two pathologists reviewed the histology slides during consensus workshops, reached consensus, and assigned a final pathologic diagnosis using a modification of the chILD classification scheme. The clinical data were assessed by the Clinical Working Group and correlated with the pathologic diagnosis. With this publication, a long-anticipated systematically built clinical–pathologic classification system is now available.

An interesting feature of this system is the classification of the patient at the time of onset of symptoms or illness as either clinically immunocompromised or immunocompetent. If patients are later determined to have a nonimmunocompetent diagnosis, they are later reassigned to an immunocompromised diagnosis. Thus, this system stresses the clinical immune status at the time of diagnosis and may lead to a diverse classification of the same disease in subjects with variable immune status.

Why are classification systems so important? In particular, in the area of rare diseases, classification often comes before a definite diagnosis is made, and the class and subclass are determined (e.g., ILD related to systemic disease processes and manifestations of collagen-vascular disease). Such a nonspecific classification may help avoid the patient getting lost in a noninformative diagnosis while pursuit of a more exact diagnosis continues. When later, a more precise genetic or histological diagnosis can be

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made, a collection of such cases in the same category will determine the clinical spectrum of the condition. An example for this is a cohort of patients with different mutations in *SFTPC*, collected primarily on the basis of biochemical and histological features (11).

Last, for the evaluation of novel diagnostic and therapeutic tests in the future, larger cohorts of subjects from the same entity are needed. These can only be built if cases are collected in registers to form readily available patient groups and associated biomaterials. Such data and sample collections are an important way to build consortia. These are more likely to be successful in research or grant applications.

When caring for a child with a rare diffuse lung disease, it is desirable that a sequence of steps is realized that result in optimal patient care and at the same time allow for consultation, evaluation, and research (Figure 1). At this time, such efforts also necessitate a significant degree of altruism, as structures to pay for expert consultation are not widely available. The generation of benefit on all sides may further increase the enthusiasm to help the sick children and families with rare diseases and also help attract more young people into this emerging area of clinical and molecular pulmonary research. Finally, many children suffering from chILD will become young adults with ILD, making an approach necessary which integrates the knowledge of both adult and pediatric clinicians, radiologists, pathologists, and researchers. In particular, the genetically defined forms well known in chILD need to be identified in adults.

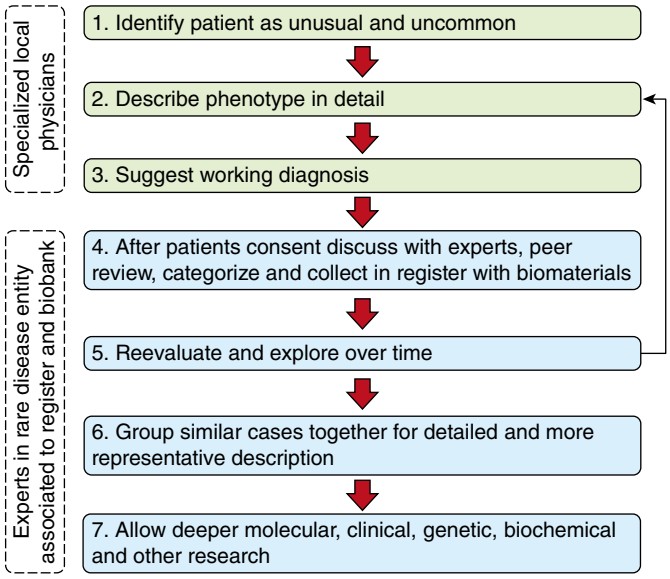

Figure 1. Desirable steps during care for patients with rare diseases. After recognizing (*1*), the phenotype is detailed by clinical, radiological, and if available, pathological, genetics, or research aspects (*2*), and a working diagnosis is suggested (*3*). The caring specialized local physicians contact experts at a register, and after receiving the patients' consent, discuss with experts the peer review, categorization, and collection in the register (*4*). Over time, reevaluation (*5*) and grouping together with similar cases are necessary (*6*). This all will make possible and lead to deeper molecular, clinical, genetic, biochemical, and other research (*7*).

Beyond programs to manage this transition clinically, it is also time to think about a common ILD classification that accommodates patients with DPLD of all ages from birth to senescence. The article by Fan and colleagues is a step toward this goal (10). I anticipate that such international cooperative research efforts and associated clinical care will guide DPLD out of its orphanage and improve the care of chILD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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