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Identifying Biomarkers in Pediatric Rare Lung Disease
chILD Grows Up

Children's interstitial and diffuse lung disease (chILD) has been recognized as distinct from adult interstitial lung diseases for nearly 2 decades after the first descriptions of disorders of surfactant metabolism and neuroendocrine cell hyperplasia of infancy (NEHI) (1, 2). In that interval, advances in clinical phenotyping, histopathology, genetic testing, and imaging have improved diagnostic capabilities and led to the discovery of novel chILD disorders (3). However, although blood- or airway-derived biomarkers can be informative in adult ILD (4, 5), similar biomarkers do not exist in chILD, and lung biopsy is often still required to make a definitive diagnosis. In recognition of these limitations, a recent National Heart, Lung, and Blood Institute workshop to advance chILD identified a "lack of validated biomarkers or outcome measures suitable for use in infants and young children" as a key gap (6). In this issue of the *Journal*, Deterding and colleagues (pp. 1496–1504) help to address this gap through the use of aptamer-based proteomics to identify proteins and related pathways in BAL fluid that distinguish two of the most common chILD disorders (NEHI and disorders of surfactant metabolism) from each other and from control individuals without chILD (7). Although this was a single-center study on a relatively small population, these findings represent a significant step forward in the study of these rare lung diseases.

The identification of unique protein signatures for both NEHI and surfactant protein deficiency could have substantial diagnostic value. Both disorders typically present similarly, with tachypnea, crackles, and hypoxemia starting before 1 year of age (8). Although findings on chest computed tomography (CT) are often diagnostic, nearly a quarter of patients with biopsy-proven NEHI have atypical findings on chest CT (9), and there are reported cases of a NEHI pattern on chest CT that were ultimately found to be caused by surfactant dysfunction (10). Genetic testing can also be informative, although approximately 25% of patients who have lung biopsy consistent with surfactant dysfunction have negative genetic studies (8). Reliance on genetic studies can also delay diagnosis and treatment, as current testing often requires up to 4 weeks for completion. This delay has meaningful treatment implications, as surfactant dysfunction is typically treated with multiple medications such as hydroxychloroquine, azithromycin, and corticosteroids (1), whereas the therapy for NEHI is supportive care. Thus, a validated BAL proteomic signature could improve diagnostic accuracy, allow more rapid intervention in critically ill children, and reduce the need for lung biopsy in those patients in whom radiologic and genetic studies are indeterminate.

The protein signatures identified in this study also offer exciting potential insights into disease mechanisms and possible new therapeutic targets. This is particularly important for NEHI, which, although relatively common (by chILD standards), is poorly understood from a mechanistic standpoint. Lung biopsies performed on patients with NEHI show increased pulmonary neuroendocrine cells, which function as innervated sensory cells within the lungs (11). However, it is unclear how abnormalities within this cell type lead to hypoxemia, as the lung parenchyma in patients with NEHI is almost normal on biopsy (2). The cell signaling and metabolic pathways identified in this study offer new pathways to investigate and may provide mechanistic insight. Interestingly, the proteomic signatures suggested two distinct endotypes in NEHI. This may indicate that NEHI represents two separate disorders, although both had similar clinical outcomes. In surfactant protein deficiency, the identification of pathways involved in fibrosis offers hope that work in adult inflammatory-fibrosis lung models may be relevant to these rare disorders. This is particularly important, as many patients with surfactant dysfunction, particularly those with pathologic variants in *ABCA3* (ATP-binding cassette subfamily A member 3), have significant mortality (12), and therefore medications that slow progression are needed. Also, most patients with surfactant dysfunction that present in childhood have progressive disease, so antifibrotic medications developed for adult ILD may be beneficial.

Although the findings of this study represent an exciting advance in chILD, the conclusions must be viewed with some caution, as the study was small (understandable, given the low prevalence of chILD) and lacked an independent validation cohort. Although the authors used appropriate statistical methods to minimize bias, the relationships between the identified pathways and disease pathophysiology will remain uncertain until validated through independent study. Furthermore, many of the markers elevated in the surfactant dysfunction group have also been associated with neutrophilic airway inflammation in other diseases (13), which was elevated in this cohort. Further investigation will be needed to identify which are specific to surfactant dysfunction.

Overall, this study by Deterding and colleagues offers an exciting first step toward developing biomarker-based evaluation of chILD. Although bronchoscopy and BAL is not without risk, it offers a significant benefit over lung biopsy, particularly in critically ill children. With appropriate validation, this study could represent a critical first step toward developing improved biomarker-based diagnostic and treatment strategies for pediatric rare lung disease. ■

Originally Published in Press as DOI: 10.1164/rccm.201908-1594ED on August 27, 2019

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

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Nintedanib and Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

Echoes of the Past, Lessons for the Future

Pulmonary hypertension (PH) commonly complicates the course of patients with idiopathic pulmonary fibrosis (IPF). It is associated with impaired functional ability and worse survival (1). The prevalence of PH has a variably reported range between 15% in those with mild to moderate restriction and 84% in those with more advanced disease (2, 3). The high end of this range underscores that most patients are likely to develop PH as their disease progresses. The increasing armamentarium of drugs to treat pulmonary arterial hypertension has raised the notion of therapy for PH complicating IPF. It remains uncertain whether the presence of PH is the driver of worse outcomes or whether it is a surrogate for disease severity. If it is indeed an adaptive phenomenon, then ameliorating this may not result in benefit and, worse yet, might result in harm. In contrast, if PH in this setting is a maladaptive response, then targeting it may result in beneficial outcomes.

The INSTAGE (Efficacy and Safety of Nintedanib Co-administered with Sildenafil in Idiopathic Pulmonary Fibrosis Patients with Advanced Lung Function Impairment) study was a prospective, double-blind, randomized clinical trial comparing the benefits of nintedanib with those of nintedanib plus add-on sildenafil in patients with IPF with single-breath D_{LCO} <35% predicted (4). This major inclusionary criterion replicated that of the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) study, which examined the effects of sildenafil versus placebo in patients with IPF (5). Among patients with IPF with D_{LCO} <35%, the prevalence of PH is about 50%, and in this regard, this cutpoint represents an enrichment strategy for underlying resting PH (6). The INSTAGE study failed to meet its primary endpoint of a change in the St. George's Respiratory Questionnaire at 12 weeks, but there was a favorable trend in a number of secondary endpoints, including the University of California, San Diego, Shortness of Breath questionnaire, as well as a salutary effect on FVC change. Therefore, although it was a negative study based on the chosen primary endpoint, the INSTAGE study was suggestive of a possible benefit, perhaps best demonstrated in a further enriched population.

In this issue of the *Journal*, Behr and colleagues (pp. 1505–1512) present a *post hoc* analysis of the INSTAGE cohort, categorized by the presence or absence of echocardiographic evidence of right heart dysfunction (RHD) (7). This parallels a subgroup analysis of the STEP-IPF study, which demonstrated a significant improvement in 6-minute-walk distance of 99 m in the sildenafil patients who had evidence of RHD on echocardiography (8). Thus, the current subgroup analysis was eagerly anticipated, with the hope that this too might demonstrate a similar difference.

Originally Published in Press as DOI: 10.1164/rccm.201908-1510ED on August 19, 2019