Chronic Obstructive Pulmonary Disease Endotypes in Low- and Middle-Income Country Settings: Precision Medicine for All

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease marked by largely irreversible airflow obstruction due to small airway obstruction and emphysema that results from complex gene–environment interactions over the lifespan of an individual. Although the clinical definition of COPD has existed for more than 50 years, there have been limited advances in therapeutic modalities as a result of heterogeneity in disease expression and natural history. COPD has historically been subcategorized into phenotypes based on pathology (macroscopic emphysema) and clinical presentation (chronic bronchitis, frequent exacerbator, rapid decliner, and asthma–COPD overlap) with an aim of improving treatment outcomes (1). Endotyping has been proposed to identify subgroups of COPD based on shared biologic underpinnings of pathology with the aim of identifying precision therapies. Furthermore, the classification of COPD and therapeutics to treat and manage this disease have been studied almost exclusively in high-income settings. Over 90% of COPD-related morbidity and mortality occurs in low- and middle-income countries (LMICs) where a significant proportion of those with COPD are never-smokers (2). We propose two potential COPD endotypes based on distinct exposures and related histopathology in LMICs: biomass- and tuberculosis (TB)-associated COPD.

Globally, nearly 3 billion people rely on solid fuels (biomass, which includes wood, dung, and agricultural crop waste, or coal) for cooking and heating (3). Although the association between COPD and biomass has not been consistent, individuals with biomass exposure and COPD have a unique presentation and inflammatory profile when compared with tobacco-mediated COPD (3–8). Phenotypically, biomass-associated COPD is characterized by increased cough and phlegm on respiratory symptom questionnaire, as well as higher rates of bronchodilator reversibility and hyperresponsiveness, signifying an elevated degree of airway inflammation (3, 5). Biomass exposure additionally results in distinct inflammatory profiles and dysregulation in innate immunity among those with COPD, with higher circulating levels of type 2 immunity mediators (IL-4 and IL-10) compared with tobacco-related disease (7). Furthermore, those with biomass-related COPD have higher levels of malonylaldehide and superoxide dismutase, measures of oxidative stress that correlate inversely to FEV_1 (9). On computed tomographic imaging, those with biomass-related COPD have less emphysema and more air trapping due to small airway disease compared with those with tobacco-related disease (6). On histopathology, individuals with COPD and lifelong biomass exposure have distinct patterns of airway disease, which may be related to the size of particles deposited in the airways during biomass exposure (10). Those with biomass-related COPD demonstrate increased anthracosis, small airway thickening, and peripheral fibrosis on lung biopsy compared with individuals with tobacco smoke–mediated COPD (8).

In addition to biomass-associated COPD, post-TB COPD also represents a major contributor to the burden of obstructive lung disease in LMICs. TB is the leading infectious killer worldwide with more than 10 million new cases and 1.5 million deaths (11). Pulmonary TB is associated with lung injury, which can persist despite microbiological cure (12). Post-TB lung disease is an important contributor of excess morbidity and mortality. Although population-based studies have found a high prevalence of COPD in individuals with prior TB (13), recent studies have shown considerable heterogeneity in the phenotype of post-TB lung disease (14). In contrast to smoking-associated COPD, a restrictive spirometry pattern, with or without airflow obstruction, that is largely unresponsive to bronchodilators is the predominant phenotype of post-TB lung disease (15). Furthermore, bronchiectasis is a common manifestation of treated TB, which is distinct from smoking-associated COPD (16). Although the host inflammatory response during TB therapy has been extensively studied, the biological mechanisms of lung injury and post-TB lung disease have received insufficient attention. Tumor necrosis factor-α and matrix-metalloproteinases have been implicated in lung tissue destruction and cavitary disease in TB (17). However, their association with long-term lung impairment is unclear. High levels of profibrotic cytokines, such as transforming growth factor-β, have been associated with excessive lung fibrosis in animal models and may be the key driver of a restrictive spirometry pattern in human TB (A. Gupte and colleagues, unpublished results) (18). Importantly, the host immune response in TB is dynamic over the course of therapy with implications for biomarker measurement and the optimal timing for therapeutic intervention. Future studies identifying the underlying immune mechanisms for TB-associated lung injury, relative to the natural history of TB disease, will help inform prognostic and therapeutic strategies for post-TB lung disease.

Although there have been a number of studies that have aimed to identify risk factors and presentation of COPD in LMICs, there has been a paucity of clinical trials examining the efficacy and effectiveness of COPD treatment specific to resource-limited settings. Management of COPD in LMICs is largely based on the Global Initiative for Chronic Obstructive Lung Disease classification, using data among COPD populations exposed to tobacco smoke. The mainstay of the current COPD guidelines remains inhaler-based therapy, which is neither available nor affordable in LMICs. There are a number of ongoing trials related to prevention of lung injury and treatment of symptomatic COPD, although many are preliminary. Ramirez-Venegas and colleagues examined the efficacy of tiotropium and indacaterol among those with biomass-associated COPD and found improvements in FEV_1 and FVC (19). An ongoing trial in Uganda (NCT03984188) aims to assess the clinical and cost effectiveness of low-dose

Originally Published in Press as DOI: 10.1164/rccm.202001-0165ED on May 12, 2020

theophylline for the management of biomass-associated COPD. Similarly, ongoing trials are evaluating pravastatin (NCT03456102), metformin (1 U01AI134585–01A1), and imatinib besylate (NCT03891901) as adjunctive host-directed therapies in patients with TB. In addition to TB treatment outcomes, these trials also plan to assess the antiinflammatory and immunomodulatory role of these therapies in reducing TB-associated lung injury.

These findings suggest that individuals with COPD with biomass exposure and/or history of TB present with a different mechanism of injury compared with tobacco, with potentially different longitudinal outcomes and response to therapeutic interventions (7). Beyond biomass exposure and TB, individuals living in LMICs have a range of unique risk factors for COPD over their lifespan. Intrauterine and early childhood exposures such as nutritional deficiencies and recurrent respiratory infections can attenuate maximal lung function development, thus accelerating the time point at which physiologic lung function decline over time results in abnormal lung function in adulthood (20, 21). Given the high burden of disease globally, there is an urgent need for further research combining distinct exposures in LMICs with systems biology to develop classification models of COPD with the aim of informing precision disease management. ■

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

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