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Editorial

Rare Disease Registries: Steps Forward

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Abbreviations: acute respiratory distress syndrome, **ARDS**; chronic obstructive pulmonary disease, **COPD**; computed tomography, **CT**

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Introduction

Progress in defining the pathogenesis of rare lung diseases comes in many forms. Unfortunately, at a macroscopic level the lung responds to injury with injury patterns that are not distinguishable from patient to patient on clinical features alone. Furthermore, rare diseases often have a heterogeneous mix of features that makes the classical description important, but incomplete.

The Bronchiectasis Research Registry

The COPD Foundation-sponsored Bronchiectasis Research Registry was initiated in 2008[1] with a goal of improving the understanding and pathophysiology of the disease. In addition, the repository of individuals willing to participate in bronchiectasis clinical trials has been helpful. On a modest budget, patients were enrolled at 13 clinical sites and data from previous medical evaluations were entered by coordinators. Yearly longitudinal reporting was encouraged.

Unfortunately, the many tests required to obtain a specific cause of bronchiectasis remain costly to obtain. Like acute respiratory distress syndrome (ARDS) and emphysema, ascertainment of specific causation requires testing. In ARDS, we stumble onto rare cases of connective tissue disease-associated alveolar hemorrhage or acute eosinophilic pneumonia when ARDS does not follow the expected course. In emphysema, we sometimes neglect to check an alpha-1 antitrypsin level or genotype. In bronchiectasis, the number of required tests jumps exponentially.

The data collection forms for the Bronchiectasis Research Registry are published online at https://www.bronchiectasisandntminitiative.org/Registry/Registry/Bronchiectasis-and-NTM-Research-Registry. There is a challenge to be comprehensive in diagnostic testing for rheumatoid airways disease, non-tuberculous mycobacteria, alpha-1 antitrypsin deficiency, cystic fibrosis (even in older adults), common variable immunodeficiency, severe gastroesophageal reflux, allergic bronchopulmonary aspergillosis and primary ciliary dyskinesia. However, times are changing. We have therapies for each of the conditions mentioned and more therapies are in the pipeline. Making a correct diagnosis is important.

The paper by Eden et al[2] in this current issue of the Journal presents clinical messages for bronchiectasis associated with alpha-1 antitrypsin deficiency, common variable immunodeficiency, and primary ciliary dyskinesia. There are always limitations to registry data. Age at presentation of any disease is subject to ascertainment bias. Lung function

correlates poorly with the extent of bronchiectasis on imaging. Presence or absence of staphylococcal and/or *Pseudomonas* species is likely related to duration of disease, severity of airways pathology, and number and types of antibiotics given. But the most compelling issue may be that complete datasets were available for 615 respondents of the 2170 participants in the registry. The hidden message is that as a community we are not comprehensive when we evaluate the cause of bronchiectasis.

Looking Forward

My wish list is that we design and fund the studies that advance the concept that a computed tomography (CT) scan is needed for every patient with chronic obstructive pulmonary disease (COPD) to personalize care and find the bronchiectasis that is present in 27%-58% of COPD cases.[3] In these patients we would obtain more cultures for non-tuberculous mycobacteria, and move the specific diagnosis of bronchiectasis from the domain of the university hospital to the broader pulmonary community. We will need cheaper panel diagnostics for the causes of disease. The early result may be that we use more inhaled and oral antibiotics. However, we would then be able to harness the observations that come from a larger group of individuals that today do not have a diagnosis. We would advance a platform able to better understand the connective tissue matrix of the airway, generate and come to consensus on more robust CT measurement tools for bronchiectasis scoring, better understand the microbiome of bronchiectasis, and refine our therapeutic trials.

The lessons from cystic fibrosis bronchiectasis suggest that early diagnosis results in improved survival. Bronchiectasis is a disease in which early and specific diagnosis makes a difference. Although antibiotics and airway clearance tools are the mainstays of symptom relief, getting to the cause of airways disease will make a difference.

Declaration of Interest

Dr. Strange has grants with the Alpha-1 Foundation, CSL Behring, Grifols, MatRx, Takeda/Shire and Vertex on emphysema due to alpha-1 antitrypsin deficiency. He consults for AstraZeneca and GlaxoSmithKline on COPD. He is a medical director at AlphaNet, a disease management company for alpha-1 antitrypsin deficiency.

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