A New Bronchiectasis Endophenotype: Immunoallertypes

More than 30 years ago, Dr. Cole described the "vicious circle" of host-mediated, inflammatory tissue damage, a paradigm of bronchiectasis pathogenesis in which an amplified, poorly controlled, and chronic inflammatory response to an "incursion" occurs (1). Since then, substantial progress has been made in elucidating aspects of this inflammation, most notably the aberrant behavior of neutrophil inflammation in bronchiectasis (2, 3).

In this issue of the *Journal*, Mac Aogáin and colleagues (pp. 842–853) shift the focus from neutrophilic inflammation to the connection between atopy and sensitization (4). This connection has been developed in respiratory diseases such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis (CF). Outside of allergic bronchopulmonary aspergillosis, little attention has been given to its presence in bronchiectasis. Investigation of atopy in bronchiectasis (5) predates the publication of Cole's "vicious circle," but only sparse evidence to support its role has been obtained (6).

The current study cohort is unique: subjects were derived from the CAMEB (Cohort of Asian and Matched European Bronchiectasis) study, a collaboration between bronchiectasis researchers in Asia and Dundee, Scotland. This is perhaps an unexpected collaboration, given the geographic disparity, but it is testament to the fact that the collegiality of the bronchiectasis community spans continents. Patients with stable bronchiectasis from Singapore and Kuala Lumpur, Malaysia (SG-KL), were matched by age, sex, and bronchiectasis severity score with patients with stable bronchiectasis from Dundee, Scotland (DD). After excluding confounding etiologies (allergic bronchopulmonary aspergillosis, asthma, chronic obstructive pulmonary disease, and CF), the investigators measured sensitization to multiple environmental allergens such as the house dust mite (HDM) and recombinant allergens of *Aspergillus* fumigatus (rAsp f) and *Alternaria alternata* (Alt a). A separate cohort of 149 patients with allergic rhinitis but no bronchiectasis served as a high-allergic-sensitization comparator group.

There are three distinct results to be highlighted. First, a surprisingly high frequency of sensitization was identified in the combined Asian and European cohort of patients with bronchiectasis: 57.6% mounted class 3 or higher sensitization to at least one allergen (significantly higher than the 26.9% observed for the comparator allergic rhinitis group). HDMs were the most common allergens to incite sensitization, and the highest IgE titers were seen in patients with sensitivity to two or more allergens.

Second, there appeared to be a geographical influence on sensitivity: subjects from the SG-KL contingent manifested higher responses to HDM allergens and a single *Aspergillus* allergen, rAsp 1, whereas the DD contingent manifested higher responses to the *A. alternaria* and *Aspergillus* allergens, with the exception of rAsp 1. These associations held up in the SG-KL group after matched analysis, whereas the DD group maintained a significantly higher sensitization to just one of the fungal allergens: rAsp17.

Third, Mac Aogáin and colleagues correlated the level of sensitization patterns to clinical outcomes such as lung function and the bronchiectasis severity index. Looking at the CAMEB as a whole, patients with sensitization to three or more allergens had the poorest lung function and greatest disease severity. Taking into account geographic patterns of sensitization, poorer lung function was noted in SG-KL subjects with sensitivity to HDM and in DD subjects with sensitization to rAsp f 1. Additionally, SG-KL subjects who demonstrated sensitization to rAsp f 17, albeit at a lower frequency than the DD cohort, had more frequent exacerbations. This signal was not seen in the overall group when both geographic groups were analyzed on the basis of high sensitization levels, and higher sensitization to three or more allergens was not associated with exacerbation frequency.

Further analyzing sensitization patterns, Mac Aogáin and colleagues applied multiplex sputum cytokine and chemokine profiling to the sensitization and clinical phenotype patterns to yield "immunoallertypes," demonstrating both fungalus- and HDM-driven patterns. Using hierarchical cluster analysis, they identified two distinct immunoallertypes that were independent of geography and instead were characterized by distinct sensitization patterns and immune profiles. First, patients with high sensitization to HDM allergens exhibited a chemokine-dominant airway profile with high GRO (CXCL1), MCP-1 (CCL2), and eotaxin-1 (CCL11) in addition to anti-inflammatory elements (IL-1RA, IL-10, and G-CSF). Meanwhile, the fungal-driven proinflammatory group with marked responses to the fungal allergens was characterized by elevated airway tumor necrosis factor-α, IL-1α, and IL-1β. The fungal proinflammatory group demonstrated worse disease as indicated by the bronchiectasis severity index and lower FEV_1. Next, Mac Aogáin and colleagues used a Markov blanket approach to identify features shared among sensitization pattern, immune cytokine/chemokine profile, and geographic origin to reveal "*intra*-immunoallertypes." By this route, they were able to identify subgroups of immune signatures unique to a geographic origin. This important finding provides the first data to suggest that the clinical heterogeneity of bronchiectasis may be due to specific immune profiles. The authors' Table 1 presents sensitization patterns, immune profiles, and notable clinical outcomes in a consolidated fashion.

Overall, this comprehensive study produces a multiplicity of results that are complex, if not somewhat heterogeneous themselves, but this may be unavoidable at this early stage of endotyping a disease that is more syndrome than disease and includes

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heterogeneity in its definition. Longitudinal data would be informative with regard to whether sensitization has a role in bronchiectasis pathogenesis or the bronchiectasis state predisposes the host to atopy. The study is notable on several levels. The international collaboration is, again, remarkable. The study moves the field of bronchiectasis forward in two significant ways: first, it describes atopy and sensitization in bronchiectasis on a large, multicenter scale that has not been done before. Second, it identifies sensitization as an "endophenotype" of bronchiectasis. The need for endophenotypes in bronchiectasis was born out of failed trials that sent a painful but clear message that non-CF bronchiectasis not only is not CF but also will not behave like CF in response to therapies with proven efficacy in CF. These data may in part explain the baffling failures of large-scale therapeutic trials to demonstrate improvement in exacerbation frequency from inhaled antibiotics despite a decrease in bacterial burden. With further study, the sensitization patterns and immune profiles identified in this work will mature as guides to categorization and therapy. No doubt Mac Aogáin and colleagues have gotten off to a productive start. ■

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HDL Cholesterol: A "Pathogen Lipid Sink" for Sepsis?

The lack of a specific medical therapy for sepsis, a dysregulated response to infection that is responsible for up to half of all inpatient deaths (1), plagues critical care. Numerous clinical trials have failed to improve mortality (2, 3). Furthermore, the failure of many anticytokine therapies challenges the classic paradigm of observing an association between plasma levels of a purported marker and sepsis mortality, testing the marker's causality and modifiability in animal models, and then moving toward clinical trials to test marker blockade. Correlation does not equate with causation, and strategies to modify a correlated but noncausal biomarker are unlikely to improve sepsis survival. Although controlled interventional trials provide strong evidence for causality, it is frequently unethical or impractical to randomize subjects to high- or low-biomarker infusions, leaving us to bridge this gap with observational designs. Our field needs smarter tools to dissect correlation from causality and identify the causal biomarkers of sepsis to speed the development of sepsis therapy.

Fortunately, tools to infer causality from observational data do exist. Classically, such methods have been applied to avoid making policy decisions based on biased or inconsistent association estimates (4) due to measurement error, uncontrolled confounding, or reverse causation. One potential solution is to use an instrumental variable analysis. This approach is valid if the instrument, or reliably measured variable, has a strong association with a potential mediator variable, and there is no correlation between the instrument and the outcome being studied (5). For example, if distance from a grocery store reliably predicts intake of fresh produce, then the association between grocery store distance and lean weight can be used to infer whether produce intake has a causal relationship with weight. Genetic researchers extended this approach by using genotype(s) to predict biomarkers, testing the association between biomarker-predicting genotypes and disease, and inferring whether the biomarker has a causal relationship with disease. Called Mendelian randomization (MR) analysis, this genetic instrumental variable strategy is attractive because genotypes are assigned at random by gametogenesis and genotype assignment always precedes outcome. Such MR analyses have provided evidence that low-density lipoprotein cholesterol (LDL-C) plasma concentrations are causally related to cardiovascular disease and mortality (6), whereas markers such as C reactive protein are not (7), thus focusing therapeutic efforts on modifying plasma LDL-C. Furthermore, MR has enabled the identification of novel genetic regulators of LDL-C, which has translated to a new class of lipid-lowering agents (8).

Could similar strategies be applied to identify key causal intermediates for sepsis death? In this issue of the *Journal*, Trinder

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