

as to cross-sectional and longitudinal (1-yr) follow-up data on asthma control and exacerbation frequency. In addition, it will be of interest to use the CT-based model to connect changes in airway caliber in different locations of the reconstructed bronchial tree to other small airway parameters such as multiple breath nitrogen washout, FEF, alveolar nitric oxide, and lung hyperinflation. This will improve understanding of how currently available physiological and imaging tests reflect small airway disease in different locations of the bronchial tree, and may identify new small airway disease subtypes with possible clinical relevance in the context of treatment such as biologicals. The ongoing discussion of proving the added value of extra-fine particles, and a range of particle sizes in an administration, could also profit from this new technique. ■

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⊗ Stratifying Bronchiectasis: Getting to within a Zone's Throw

Bronchiectasis is a chronic, progressive, and irreversible dilatation of the airway that exhibits geographic variation, contrasting endophenotypes, and involvement in “overlap” states (1–4). Its clinical heterogeneity and etiological complexity are compounded by our incomplete understanding of its pathogenesis. This leads to difficulties with clinical trials and therefore a lack of evidence-based treatments for patients (5).

The archetype “Cole’s vicious cycle” model of pathogenesis has formed the basis for emerging concepts such as the “vicious vortex,” which offers a more holistic view of the disease, reaffirming its key interrelated components: infection, inflammation, epithelial-

immune dysfunction, and lung destruction (6, 7). All of these components interact and are influenced by one another, perhaps to different extents, in different patients and etiologies and at various disease severities, including exacerbations. Consequently, improving patient stratification and identifying “high-risk” bronchiectasis endophenotypes are key focuses of ongoing research (5, 8).

Although airway infection incites and propagates disease, the immune-inflammatory consequences (even in the absence of infection) have a strong influence on disease outcomes. Neutrophils in particular are the hallmark airway inflammatory cells and a source of protection against infection, but when excessive in number and response, they can induce further airway damage and bronchiectasis. Neutrophils have important roles in severe asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), where airway-dominant phenotypes are associated with poor disease outcomes. Airway and systemic neutrophils are dysfunctional in bronchiectasis, and although immune dysregulation is a recognized feature in disease, the mechanisms by which neutrophilic inflammation is linked to impaired immunity, particularly in the context of infection, remain poorly understood (1, 5, 9, 10). This is exemplified by the paradoxical strong, cellular-abundant, and sustained neutrophilic response observed with persistence of airway infection. Acute infections in bronchiectasis are cleared by

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phagocytosis, apoptosis, and efferocytosis; however, when chronic infection ensues, features that limit phagocytosis, such as high bacterial loads and biofilm formation, promote shifts toward infection-containment strategies such as neutrophil extracellular trap (NET) formation and the development of immune tolerance to infecting offenders.

In this issue of the *Journal*, Finch and colleagues (pp. 992–1001) identify PZP (pregnancy zone protein) in the bronchiectasis airway as associating with disease severity, frequent exacerbations, and infection with *Pseudomonas aeruginosa* (11). PZP is a high-molecular-weight glycoprotein whose synthesis is estrogen dependent. By means of its immunosuppressive capability and antiproteinase activity, PZP functions as an immune regulator during pregnancy; however, its mechanisms, functions, and structure have yet to be elucidated. Dysregulated PZP has been described in association with inflammatory diseases such as Alzheimer's, diabetes, and inflammatory bowel disease but not previously in association with the human airway and airway disease.

The relationships identified by Finch and colleagues illustrate a unique airway-related association between PZP and airway infection from *P. aeruginosa* as well as other pathogens, such *Moraxella catarrhalis*, *Haemophilus influenzae*, and Enterobacteriaceae (by culture), and Proteobacteria dysbiosis (by microbial sequencing). PZP is linked to frequent exacerbations in bronchiectasis, but importantly, its detection is predictive of severer exacerbations (i.e., necessitating hospitalization) and an increased production and volume of mucus secretion. Using an elegant translational, multimodal experimental approach that includes proteomics, microbiome analyses, *in vivo* animal studies, and *ex vivo* neutrophil immunology, Finch and colleagues show that during neutrophilic inflammation (acute and chronic), PZP is released at degranulation and is detectable with NET formation. The airway PZP concentration therefore identifies patients with bronchiectasis, airway infection, and significant NET-mediated inflammation. NETosis remains a central pathophysiological mechanism in bronchiectasis, and with its established immunosuppressive effects, PZP provides the first concrete link between chronic neutrophilic inflammation and impaired host immunity in bronchiectasis. The presented science is further complemented by robust clinical studies illustrating PZP's relationship with 1) airway bacterial load (irrespective of the infecting pathogen), 2) response to antibiotic treatment (PZP decreases after treatment), and 3) lower levels in COPD (consistent with lower levels of NETs compared with bronchiectasis).

Collectively, this work has several implications for bronchiectasis. First, the usefulness of PZP as a “stratification tool” should be examined in a manner akin to point-of-care neutrophil elastase testing to identify high-risk exacerbators (12). Quantifying airway PZP may allow selection of “high-risk” NET-driven bronchiectasis endophenotypes; however, the comparable staining of eosinophils in this study should be noted. Although inflammation in bronchiectasis is generally neutrophilic, eosinophilic (and sensitized) phenotypes do exist (5, 13). Second, the identified relationship between PZP and NETs has therapeutic implications. Targeting neutrophils (and specifically NETosis) and monitoring treatment response through PZP are plausible approaches that may be extended to include COPD and CF, both of which are chronic inflammatory conditions in which mucus production and exacerbations are relevant (5, 8). Third, immunomodulation is a promising avenue for future bronchiectasis therapeutics. Although no direct correlation between airway and

systemic PZP concentrations was observed in this study, previous studies showed that systemic neutrophils are inherently dysfunctional in bronchiectasis (9, 10). Systemic neutrophils are rarely exposed to infection in bronchiectasis, a key inducer of PZP release. Systemic infection is a rare manifestation of bronchiectasis (and CF) in which patients usually succumb to respiratory failure rather than sepsis, which may explain the lack of PZP correlations observed in this work.

Several avenues should be pursued in future studies to fully exploit the data presented by Finch and colleagues. The precise signaling mechanisms associated with airway PZP should be elucidated to determine whether PZP is simply a marker of chronic neutrophilic inflammation or has a direct role in the pathogenesis of chronic infection in bronchiectasis. Longitudinal variation in PZP across different geographic regions and bronchiectasis etiologies should be investigated. Although no sex differences were described in this work, bronchiectasis remains a “postmenopausal” disease, and therefore PZP here is potentially “less influenced” than that in the “premenopausal state” (where its synthesis is estrogen driven) (14). In parallel, estrogens in CF have independent effects on *P. aeruginosa* in promoting mucoid conversion (15, 16). Studies of younger patients (pre- and postpuberty) with bronchiectasis, combined with a complementary use of animal models of infection, may better reveal the true sex- and hormone-related associations with airway PZP. The work of Finch and colleagues clearly gets us to within a *zone's* throw of next-generation stratification in bronchiectasis, heralding a new and exciting era for research into this underrecognized disease. ■

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⊗ Breathing and Ventilation during Extracorporeal Membrane Oxygenation: How to Find the Balance between Rest and Load

In theory, the application of extracorporeal membrane oxygenation (ECMO) in severe respiratory failure allows lung treatments varying from a lung at rest (continuous positive airway pressure) to all different levels of ventilatory support or even pure, spontaneous breathing. Although ECMO is increasingly used worldwide, very little is known about the respiratory settings applied during the course of ECMO, and even less is known about the optimal “balance” of ventilatory and extracorporeal support to minimize ventilator- or ventilation-induced lung injury, and the optimal conditions for lung healing and repair. In this issue of the *Journal*, Schmidt and coauthors (pp. 1002–1012) present an international, multicenter, prospective cohort study (LIFEGARDS [Ventilation Management of Patients with Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome]) in which data from 350 patients with ECMO in 23 international ICUs were collected during a 1-year period (1). In addition to demographics, the authors carefully compiled data regarding the ventilator settings applied before and during ECMO, the use of adjunctive therapies, and ICU and 6-month outcomes. The authors and their participating centers should be congratulated for providing the community with such sound data from different countries and ICUs, as well as the preferential ventilator settings used before and during the application of ECMO. The primary outcome measured was 6-month mortality, but the study also provides data on the type and use of adjunctive therapies, as well as the changes in driving pressure and mechanical power before and during the ECMO run. Some of these observational data are in part confirmatory and quite striking (2, 3). This study included only ICUs with an annual ECMO volume of more than 15 cases, and all of the participating centers treated a median of 30 patients with ECMO in the year before the study. Therefore, they could be clearly

classified as “experienced.” In this context, it is more than striking that the prone position was not used in more than 26% of the patients, especially when a plateau pressure of 32 cm H₂O was applied. Instead, the fact that a reported 15% of patients were turned to prone even during the ECMO course gives reason to hope that proning will be more regularly applied also in patients without ECMO. In contrast, with a V_T of 6.4 ± 2.0 ml/kg, patients were ventilated close to the magic “protective” value. However, the ventilatory setup as a whole led to a plateau pressure of 32 ± 7 cm H₂O, a ventilatory rate of 26 ± 8, a driving pressure (ΔP) of 20 ± 7 cm H₂O, and a mechanical power of 26 ± 12.7 J/min. It is interesting to note that after the ECMO initiation, while the reduction in DELTAP was only 30%, the reduction in mechanical power was as great as 75%, reflecting the importance of the frequency for energy transmission. With an overall 6-month survival of 61%, the study presents impressive outcome findings. The changes in respiratory settings after ECMO initiation resulted in both ΔP and power values below the thresholds that have been considered “critical” in both experimental and clinical studies (4–7). It is thus not surprising that the ventilator settings applied during the first 2 days after ECMO onset had no impact on survival, whereas age, immunocompromised state, extrapulmonary sepsis, and lactate and fluid balance—all of which could be considered indicators for the general severity of disease—were positively correlated. Given the ΔP and power values observed before ECMO was initiated, it is not unexpected that each day of delaying intubation to ECMO was also positively correlated with a higher 6-month mortality. Moreover, higher spontaneous respiratory rates during the first 2 days of ECMO were associated with higher 6-month mortality.

The strength of this study, which used data from different ICUs in 10 different countries, lies in the amount and quality of the data and the homogeneity of the treatment, including the use or nonuse of adjunctive measures. At the same time, this is also a limitation, as these data certainly do not reflect the real world of patients with ECMO treated in non-university hospitals or in hospitals with lower ECMO volumes and less experience in treating patients with severe respiratory failure and/or acute respiratory distress syndrome. In addition, the study describes how the patients were ventilated after

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