



## “Can’t Stop the Feeling”: Symptoms as the Key to Trial Success in Bronchiectasis?

Bronchiectasis, which is characterized by chronic, inflammatory, and irreversible airway dilatation, has a considerable disease burden, complex clinical heterogeneity, and broad etiology, and often has no identifiable cause (1, 2). Recognizable endophenotypes are emerging that may explain difficulties encountered in clinical trials (3, 4). Exacerbation frequency and associated symptoms are central to a clinician’s approach to caring for patients with bronchiectasis; however, assessing symptom burden, frequency, and variation among patients and even within an individual patient remains challenging.

In a study presented in this issue of the *Journal*, Gao and colleagues (pp. 1499–1507) addressed this issue by examining data from 333 patients with bronchiectasis from a single center in the United Kingdom (5). The authors assessed bronchiectasis symptoms according to St. George’s Respiratory Questionnaire (SGRQ) symptom scores and the Leicester Cough Questionnaire (LCQ), using the former to classify patients as having a high, moderate, or low symptom burden. At baseline, patients with a high symptom burden exhibited more exacerbations in the preceding year, higher rates of bacterial isolation (especially *Pseudomonas aeruginosa*), higher body mass index, lower FEV<sub>1</sub>, and worse cough-related quality of life (lower LCQ score), suggestive of a relationship between symptom burden and more severe disease. Importantly, patients with a high symptom burden at baseline also experienced approximately twice the number of exacerbations per patient per year, a sixfold increase in hospitalizations, and shorter times to first exacerbation than patients with a low symptom burden, even after adjustment for confounding variables such as age, sex, radiology, bacterial infection, and bronchiectasis etiology. The authors extended these findings by reporting a comparable association between symptoms and the risk of future exacerbations. Interestingly, Gao and colleagues reanalyzed results from a previously published, unsuccessful randomized clinical trial of inhaled mannitol, which failed to reduce bronchiectasis exacerbations compared with placebo (6). Although the original trial recruited patients with a history of multiple exacerbations, intriguingly, by classifying the patients’ symptom burden at study entry (using the SGRQ symptom score), the authors were able to show that highly symptomatic patients (i.e., those with high baseline symptom burdens) in the

mannitol-treated group had a significant reduction in exacerbation frequency and longer times to first exacerbation (5). This critically implies that future trials of mucoactive therapies in bronchiectasis should consider baseline symptoms, which if applied here, may have resulted in a different outcome for mannitol.

The study of bronchiectasis is a complex field littered with numerous but unsuccessful clinical trials despite meticulous planning, investment, and high expectations. It is hypothesized that (at least) some of these trials failed because of their inability to recruit the most appropriate “target” patient group. In agreement with this hypothesis, recent studies have further underscored the inconsistent effects of inhaled antibiotics on exacerbations and their corresponding symptoms (7, 8). One interesting consideration arising from the work of Gao and colleagues is the notion that enrichment strategies for clinical trials in bronchiectasis should emphasize the importance of a complete and thorough assessment of symptoms (including cough, dyspnea, and mucus production) rather than an overreliance on exacerbation history, which in itself has a checkered past. This is conceptually comparable to the risk assessment strategy for chronic obstructive lung disease (COPD) developed by the Global Initiative for Chronic Obstructive Lung Disease, in which exacerbations and symptoms are independently assessed to predict future risk (9). Another attractive hypothesis is that highly symptomatic bronchiectasis corresponds to a specific disease endotype, possibly characterized by a higher mucus concentration and different composition (10). Treatments that promote mucus clearance, such as physiotherapy and mannitol, would thus reduce exacerbations and their associated symptom burden in highly symptomatic patients, whereas interventions that specifically target infection (e.g., long-term macrolides) appear to be less dependent on baseline symptoms (5, 11, 12). Collectively, these observations suggest that not all bronchiectasis exacerbations are the same. Each likely has independent (and possibly co-occurring) biological mechanisms, including infection, inflammation, and mucus production, that underlie the different and heterogeneous exacerbation subtypes, each of which likely requires a specific targeted therapeutic approach.

Importantly, this work does have limitations. First, the authors propose the hypothesis that “targeting daily symptoms reduces exacerbations,” which raises the “at what threshold?” question with regard to bronchiectasis. Although the hypothesis is interesting, the authors did not assess daily symptoms but rather relied on questionnaires that assessed symptoms over months (for SGRQ) or weeks (for LCQ), both of which are subject to recall bias. Testing such a hypothesis requires the use of symptom diaries, such as the Exacerbations of Chronic Obstructive Pulmonary Disease Tool: Patient-reported Outcomes (EXACT-PRO), which was developed for COPD (13).

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Although this dataset clearly illustrates that high SGRQ symptom scores were associated with higher exacerbation rates in the preceding year, and can predict the risk of future exacerbations, it remains unclear whether this relationship is independent of exacerbation history, as that in itself has been shown to be a strong predictor of future exacerbations (14). Only 42% of patients fell within the high SGRQ symptom group in the mannitol study (even though the original inclusion criteria focused on multiple prior exacerbations), suggesting that the relationship between symptoms and exacerbations is not solely related to exacerbation history and includes other components of the SGRQ symptom assessment, such as cough, dyspnea, and mucus production. Importantly, work in COPD has suggested strong relationships between chronic cough, mucus production, and a history or future risk of exacerbations (15, 16). Whether such a relationship exists in bronchiectasis requires further study.

Cough and mucus production are cardinal bronchiectasis symptoms, and mucus exhibits distinct properties in bronchiectasis (10). Whether the composition and/or characteristics of mucus in bronchiectasis drives this relationship with symptoms is an important question, and if proven would provide a more objective and viable measure than the subjective measures of symptomatology. Should mucus properties now become an endpoint for clinical trials in bronchiectasis? Established evidence from other respiratory diseases, including COPD and cystic fibrosis, indicates a key role for mucus accumulation in disease pathophysiology, and existing therapeutic interventions focused on mucus have only limited effects on accumulation. As Alfred Adler, an Austrian doctor, psychotherapist, and founder of the school of individual psychology, once said, “Never neglect the patient’s own use of symptoms”—a statement now evidenced in bronchiectasis by the work of Gao and colleagues. ■

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