Understanding the Role of *Staphylococcus aureus* in Non–Cystic Fibrosis Bronchiectasis: Where Are We Now?

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Staphylococcus aureus is a Gram-positive bacterium that is a commensal and major pathogen in humans (1). *S. aureus* colonizes and infects the airways in persons with chronic lung diseases such as cystic fibrosis (CF) or other forms of bronchiectasis. *S. aureus* has been studied for its multitude of virulence factors, ability to form biofilms *in vitro*, persistence in the airways, and phenotypic diversity, such as its ability to form small colony variants (2, 3). In CF, *S. aureus* is among the earliest detected organisms in infants and children, partly attributed to host defense abnormalities (4, 5). Further, the increasing prevalence of methicillin-resistant *S. aureus* (MRSA) in recent decades is a point of concern (4). Although research on the effect of methicillin-sensitive *S. aureus* infection in CF has generated divergent results (4), both small colony variants and MRSA have been associated with worsened clinical outcomes (6), with the latter identified as an independent predictor of CF mortality (7). The relationship between *S. aureus* and clinical outcomes is even less clear when one examines non-CF bronchiectasis. *S. aureus* is less commonly detected in non-CF bronchiectasis, with variation in reported frequencies (8), and its detection occasionally may signify undiagnosed CF or allergic bronchopulmonary aspergillosis (9). Given the paucity of data in non-CF bronchiectasis and the potential for deleterious outcomes by extension from CF, discerning the epidemiology and outcomes of *S. aureus* infection in non-CF bronchiectasis is a worthy pursuit.

In this regard, in this month's issue of the *AnnalsATS,* Metersky and colleagues (pp. 365–370) undertook a retrospective cohort study using the U.S. Bronchiectasis Research Registry to assess the prevalence, epidemiology, and outcomes of *S. aureus* infections in persons with non-CF bronchiectasis (10). This registry was developed in the last decade as a COPD Foundation Initiative to collect demographic and clinical data of persons with non-CF bronchiectasis and nontuberculous mycobacterial (NTM) disease for use in research and clinical trials, consisting of 13 participating sites with 2,000 patients. Consenting adult patients with a physician-defined diagnosis of non-CF bronchiectasis, a minimum of one respiratory culture (and maximum of three cultures) in the predefined baseline period of 2 years before and 90 days after enrollment, and a minimum of one follow-up clinical encounter during a 3-year period were included for analysis. Based on culture results focusing on *S. aureus, Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex (grouped together as glucose nonfermenting Gram-negative bacteria, NF-GNB), patients were categorized into one of three cohorts as follows: positive for *S. aureus*, negative for *S. aureus* and NF-GNB, and negative for *S. aureus* but positive for at least one of the other NF-GNB. Patients were also stratified in their cohorts on the basis of NTM status, and the *S. aureus* group was divided into those with methicillin-sensitive *S. aureus* and those with MRSA for additional analysis. Patients who were unable to be categorized and who met diagnostic criteria for CF or had no respiratory cultures in the baseline period were excluded from analysis. In addition to descriptive epidemiology and clinical characteristic comparisons by cohort, outcomes included hospitalization, pulmonary exacerbation frequency, and lung function (FEV_1% predicted [FEV_1pp]) change after enrollment.

A total of 830 patients with non-CF bronchiectasis (82% women), with a mean age of 64 years (standard deviation, 14 years) and mean a FEV_1pp of 70%, were analyzed. Of these, 94 patients (11.3%) had a positive culture for *S. aureus,* 437 patients (52.6%) had no positive cultures, and 299 patients (36%) had a positive culture for NF-GNB. Notably, more than a third of patients in the *S. aureus* group were also positive for NF-GNB. The most frequent etiology was NTM disease (59%). Patients with *S. aureus* at baseline more likely had a pulmonary exacerbation in the preceding 2 years and an FEV_1pp that was mildly decreased when compared with patients with no positive cultures for the target organisms. Susceptibility results were available for 67 patients, of whom 22 (33%) had at least one positive culture for MRSA; no baseline demographic or clinical differences were identified between these subgroups. Univariate analyses suggested that the group of patients with *S. aureus* had an intermediate frequency of exacerbations and hospitalizations between the rates of the group with no positive cultures for the target organisms and the group with NF-GNB without *S. aureus*. However, in the multivariable models

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adjusted for a number of demographic and clinical confounders, there were no significant differences between the *S. aureus* and the other two groups. This result was robust to analyses that excluded the 32 patients with NF-GNB coinfections from the *S. aureus* group. Further, no differences in clinical outcomes between patients with methicillin-sensitive *S. aureus* and MRSA were identified. As patients with non-CF bronchiectasis and *S. aureus* had baseline characteristics between those with no positive cultures and those with NF-GNB, the authors suggested that *S. aureus* colonization or infection may be associated with more severe disease. Based on the multivariable analyses, however, the authors conclude that *S. aureus* detection may be a marker, rather than a cause, of more severe disease.

To date, most inferences regarding *S. aureus* in non-CF bronchiectasis have been extrapolated from CF because of pathophysiologic similarities in the development of bronchiectasis, but the diversity between the two entities in genetics, etiology, and patient characteristics highlights the need for focused study of non-CF bronchiectasis. The limited available data describing *S. aureus* in non-CF bronchiectasis before this study indicated that this organism may be associated with disease severity (11). In contrast, the work by Metersky and colleagues is one of the first large population-based studies to examine both the epidemiology and effects on clinical outcomes (10). However, a number of limitations must be considered. The investigators report a *S. aureus* prevalence of 11.3% (33% MRSA), which is similar to some prior reports suggesting a prevalence of 4–10% (8). As a maximum of three respiratory cultures were abstracted, and susceptibility testing was available in only two-thirds of *S. aureus* isolates, it is possible that some cases were missed and that MRSA was overrepresented. Similarly, one-third of patients with *S. aureus* also were positive for a NF-GNB, which may have affected both the baseline characteristics and outcomes. Airways infections are frequently polymicrobial, and, specific to *S. aureus* and *P. aeruginosa*, studies suggest that the interactions between the two organisms can result in different outcomes with coinfection, such as generation of small colony variants based on *in vitro* studies (12), and worsened clinical outcomes in CF on the basis of *in vivo* studies (13). As patients may have had only one baseline culture and one follow-up encounter, granular assessments of pulmonary microbiology health are challenging and may also be subject to misclassification and missingness. Although the investigators assessed number of organisms, others such as *Haemophilus influenza*, which has been linked to infections in non-CF bronchiectasis (14), and coexisting NTM infection were not specifically examined. In addition, factors such as non-CF bronchiectasis etiology and antimicrobial therapies, which in turn can select for specific organisms, may all have further confounded the results. Last, and perhaps most important, the investigators had limited power to identify meaningful differences between groups, thus representing results that are perhaps more of a starting point in our understanding of *S. aureus* in non-CF bronchiectasis.

Use of a registry to conduct population-based studies of non-CF bronchiectasis will enable improved understanding of the epidemiology and outcomes of this diverse patient population, and successful use of registries has already been well demonstrated in CF (15, 16). *S. aureus* is an important human pathogen and is prevalent in non-CF bronchiectasis, with some suggestion of negative association with pulmonary health. As both our understanding of the airway environment and microbiology evolve, future non-CF bronchiectasis studies must account for the complex interplay between infecting organisms and their effect on clinical disease. ■

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