Non-Cystic Fibrosis Bronchiectasis: Microbiology, Clinical Outcomes, and Pharmacotherapy Practices

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Recommended Reading from the Johns Hopkins University Pulmonary and Critical Care Fellows; Mark T. Jennings, M.D., M.H.S., Faculty Reviewer; Henry E. Fessler, M.D., Pulmonary and Critical Care Fellowship Director

Metersky ML, et al. The Prevalence and Significance of *Staphylococcus aureus* in Patients with Non-Cystic Fibrosis Bronchiectasis. *Ann Am Thorac Soc* (1)

Reviewed by Kristina Montemayor

The incidence and prevalence of non-cystic fibrosis bronchiectasis (NCFB) are increasing (2).

Data extrapolated from the cystic fibrosis literature show an association between methicillin-resistant *Staphylococcus aureus* (MRSA) infection and mortality (3, 4). However, the epidemiological and clinical implications of infection with *S. aureus* in the NCFB population has not been adequately studied.

To address this gap, Metersky and colleagues (1) conducted a retrospective cohort analysis of the U.S. Bronchiectasis Research Registry (5). Eight hundred thirty adult patients with a documented diagnosis of NCFB were included. Eighty-two percent of the population was female, with a mean age of 64 ± 14 years and a mean FEV₁ of 70% predicted. Up to three respiratory cultures were obtained 2 years before and 90 days after patient enrollment into the registry, and patients were grouped based on microbiology results. Among these patients, 52.7% ($n = 437$) had no prior *S. aureus* or nonfermenting gram-negative bacilli (NF-GNB) (*Pseudomonas*, *Stenotrophomonas*, or *Burkholderia*), 36% ($n = 299$) had a culture positive for NF-GNB, and 11.3% ($N = 94$) had a culture positive for *S. aureus*, with 34% of patients also having at least one culture positive for NF-GNB.

Individuals with *S. aureus* identified at enrollment had intermediate rates of pulmonary exacerbations compared with those individuals with no growth of targeted pathogens and those with NF-GNB in the 2 years before enrollment. At 1-year follow-up, the *S. aureus* cohort had higher rates of exacerbations and hospitalizations after univariate analysis, but there were no

differences after adjustment for baseline characteristics in multivariable models. The authors further stratified the *S. aureus* cohort, with 33% of patients ($n = 22$) having MRSA isolated on at least one culture. There were no significant differences in baseline demographics or number of pulmonary exacerbations, hospitalizations, or change in FEV₁ between patients with MRSA versus methicillin-susceptible *S. aureus*.

The establishment of a U.S. NCFB registry will be instrumental for future research in the field. Metersky and colleagues conducted one of the first national cohort studies using this registry to examine the clinical significance of *S. aureus* in NCFB (1). Important study limitations include lack of reported antibiotic use during the study period, small sample size resulting in limited statistical power, and that 40% of participants were lost to follow-up or had missing data in the study. Overall, the results of this study highlight the presence of *S. aureus* pulmonary infection in NCFB. Further data are needed to identify additional clinical outcomes and treatment practices associated with this pathogen. ■

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Araújo D, et al. The Independent Contribution of *Pseudomonas aeruginosa* Infection to Long-Term Clinical Outcomes in Bronchiectasis. *Eur Respir J* (6)

Reviewed by Aparna Balasubramanian

Among patients with bronchiectasis, colonization with *Pseudomonas aeruginosa* has been associated with worse outcomes, but whether this is merely a marker for lung disease severity remains unknown (7–10). Araújo and colleagues address this question in a multicenter, prospective study of patients with bronchiectasis with and without chronic *P. aeruginosa* infection to assess mortality (6).

A total of 2,596 participants with non-cystic fibrosis bronchiectasis were enrolled from 10 clinical centers. Participants were followed for up to 5 years, with a primary endpoint of mortality. Secondary outcomes included exacerbations and quality of life (measured by St. George's Respiratory Questionnaire). Chronic infection was defined by two positive cultures of the same pathogen obtained 3 months apart within a 12-month period.

Baseline median values for participants included age 67 years, FEV₁ of 73.8% predicted, and two exacerbations in the previous year. For groups with no chronic infection, chronic nonpseudomonal infection, and chronic *P. aeruginosa* infection, median bronchiectasis severity index was 5, 8, and 13, with 22.3%, 63.3%, and 86.1% classified as severe (bronchiectasis severity index > 9), respectively. In unadjusted analysis, those with chronic *P. aeruginosa* infection had higher mortality (hazard ratio [HR], 2.02; 95% confidence interval [CI], 1.53–2.66; $P < 0.0001$), but the effect did not persist in multivariable analysis adjusting for variables associated with mortality (HR, 0.98; 95% CI, 0.70–1.36; $P = 0.89$). Compared with those with fewer than two exacerbations per year and no *P. aeruginosa*, participants who had two or more exacerbations per year without chronic *P. aeruginosa* infection had an increased risk of mortality (HR, 1.74; 95% CI, 1.28–2.38; $P < 0.001$). Mortality risk was higher still among those with both chronic *P. aeruginosa* infection and two or more exacerbations annually (HR, 2.03; 95% CI, 1.36–3.03; $P < 0.001$). Having chronic infection with *P. aeruginosa* was associated with increased odds of hospital admission (odds ratio, 2.28; 95% CI, 1.69–3.08; $P < 0.001$) and worse quality of life (β , 7.46; 95% CI, 2.93–12.00; $P = 0.001$).

In this study, chronic *P. aeruginosa* infection was not independently associated with mortality, but exacerbation frequency was. The highest-risk participants were frequent exacerbators with chronic *P. aeruginosa* infection. In conjunction with observations on the frequent exacerbator phenotype (11), these results support interventions targeting exacerbation prevention. Results are limited by a lack of data on antibiotic resistance, treatment with antibiotics, and cause of death. In summary, the authors offer evidence that the effect of exacerbation frequency on

mortality is worsened by chronic *P. aeruginosa* infection, but results will need to be confirmed by prospective interventional studies. ■

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Henkle E, et al. Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results from an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. *Chest* (12)

Reviewed by Catherine E. Simpson

Bronchiectasis management strategies include use of antibiotics and inhaled steroids to suppress infectious causes of exacerbations and attenuate airway inflammation. However, there is little high-quality evidence available to guide selection of pharmacotherapies. Small randomized trials have demonstrated reductions in exacerbation rates over 6 to 12 months with chronic macrolide therapy (13–15), but a Cochrane review of inhaled corticosteroids (ICSs) found no benefit (16). Although European guidelines exist (17), there are no U.S. guidelines addressing NCFB management, and there is significant heterogeneity in U.S. prescribing practices (5).

Henkle and colleagues describe patient characteristics and associated patterns of antibiotic and ICS use in two U.S. NCFB registries, the Nontuberculosis Mycobacteria (NTM) Info and Research (NTMir) registry and the U.S. Bronchiectasis and NTM Research Registry (BRR) (12). Twenty-six percent of NTMir patients responded to an e-mail survey, with 40% of respondents reporting chronic azithromycin use, 15% reporting inhaled tobramycin use, and 55% reporting ICS use. Among BRR patients without NTM, 14% used chronic macrolides, 10% used inhaled antibiotics, and 42% used ICSs; 57% of ICS users had comorbid asthma or chronic obstructive pulmonary disease. Multivariable logistic regression models adjusting for variables significant in univariable analysis, including exacerbation history, lung function, and presence of *P. aeruginosa*, showed characteristics associated with macrolide use were *P. aeruginosa* isolation (adjusted odds ratio [aOR], 2.2; 95% CI, 1.4–3.4; $P < 0.05$) and age older than 65 years (aOR, 0.6; 95% CI, 0.4–0.9; $P < 0.05$); characteristics

associated with inhaled antibiotic use were *P. aeruginosa* isolation (aOR, 5.9; 95% CI, 3.4–10.5; $P < 0.05$) and prior hospitalization for exacerbation (aOR, 2.6; 95% CI, 1.1–5.9; $P < 0.05$); and characteristics associated with ICS use were *P. aeruginosa* isolation (aOR, 1.8; 95% CI, 1.2–2.6; $P < 0.05$) and comorbid asthma (aOR, 3.1; 95% CI, 1.2–4.3; $P < 0.05$).

This study provides insight into the real-world pharmacologic management of NCFB in the United States. The results demonstrate a high rate of ICS use in patients with NCFB without asthma or chronic obstructive pulmonary disease and relatively low rates of chronic macrolide use and suppressive inhaled antibiotic use, despite a stronger evidence base to support their use. These results also demonstrate an association between *P. aeruginosa* and all pharmacotherapies. Study limitations include use of self-reported data from the NTMir registry and exclusive enrollment of centers with expertise in bronchiectasis management in the BRR registry, which may limit the generalizability of results. With this report of contemporary pharmacotherapy practices in NCFB, Henkle and colleagues provide a springboard for future comparative effectiveness studies to refine best practices for management of this disease (12). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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