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# Early Aspergillosis in Cystic Fibrosis and Air Trapping: Guilt by Association?

In this issue of the *Journal*, Breuer and colleagues (pp. 688–696) report their findings of *Aspergillus* species in BAL specimens collected longitudinally from young children with cystic fibrosis (CF), examining association with a range of radiologic and clinical markers of pulmonary disease (1). This work is part of the AREST-CF (Australian Respiratory Early Surveillance Team for Cystic Fibrosis) program, which serves as an informative example of integrating research with distinct regional clinical practice patterns. CF clinical providers and researchers continue to debate how best to surveil and monitor both lung disease and airway microbiology in children. Publications from the AREST-CF program, including this one, are relevant to these discussions, as surveillance bronchoscopy and computed tomography (CT) chest imaging have been included in the care of hundreds of children over several years.

The authors report relatively high prevalence of airway infection with *Aspergillus* species (mostly *Aspergillus fumigatus*) in children with CF younger than 5 years. Multiple cross-sectional studies have similarly reported that *Aspergillus* is present in many of our patients, often at earlier ages than previously recognized (2, 3). The term "infection" in this context is more challenging and perhaps controversial, but the investigators demonstrate, through longitudinal data collection, that children with *Aspergillus* in the airway have greater abnormalities on CT imaging at the time of infection and in the years following (specifically, more air trapping). Increased air trapping and bronchiectasis have been seen in older populations with *A. fumigatus* infection, as well as allergic bronchopulmonary aspergillosis (4–6). Others have shown that older individuals with CF infected with *A. fumigatus* often have lower pulmonary function and greater rate of decline in $FEV_1$% predicted (pp) (7). Another Australasian research group recently reported similar findings to Breuer and colleagues, identifying increased air trapping, but not bronchiectasis, on CT in 5-year-olds with CF who grew *Aspergillus* from BAL specimens (3).

CT abnormalities associated with *Aspergillus* culture positivity suggest a host response to infection, despite the lack of abnormally elevated serum IgE typical of sensitization. CF care providers will know the challenges in diagnosing allergic bronchopulmonary aspergillosis, and it appears that validated biomarkers or diagnostic criteria for *Aspergillus* bronchitis may be even more limited. A phenotyping classification distinguishing allergic from infective aspergillosis in adults with CF based on blood and sputum biomarkers was proposed, but recent follow-up studies suggest further development is necessary (8, 9). The present study did not find significant differences in traditional inflammatory markers in BAL specimens between individuals with *Aspergillus*, *Staphylococcus aureus*, *Haemophilus influenzae*, or *Pseudomonas aeruginosa*. It is interesting that a majority of BAL fluid samples did not grow any of these four microbes, and coinfection rates between *Aspergillus* and the three keystone bacterial pathogens reported were remarkably low. When *Aspergillus* was identified, one of these three bacteria was also cultured only 29% of the time. This is somewhat surprising but may strengthen the premise that *Aspergillus* itself is contributing to pulmonary injury and signs of disease in these children. It is likely that more aggressive antibiotic strategies contribute to lower prevalence of traditional bacterial pathogens (10). It is also possible that antibacterial treatment or inhaled medications themselves increase risk for *Aspergillus* airway infection, although indication bias must be understood.

Similar to bronchoscopy, CT imaging has not been universally applied as a surveillance tool in young (or older) children with CF. Because of this, the clinical importance of changes in CT scores can be difficult to understand. The authors report the median CT scores for the entire population at the end of study (5–6 yr old), providing context for the changes associated with *Aspergillus* infection (*see* Table E2 in the online supplement of Reference 1). The study population median percentage of lung scored abnormal was 0.06% for bronchiectasis, 2.93% for air trapping, and 3.92% for total disease score. In the most conservative model (*see* Table E3 of Reference 1), *Aspergillus*



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positivity at any point during the study was associated with 2.2% increased air trapping and 1.0% increased total disease score at the end of the study (vs. those without *Aspergillus*). Given the median values, these differences in CT abnormality associated with *Aspergillus* appear to be relevant.

It is interesting that *Aspergillus* positivity did not affect $FEV_1$pp at age 5 to 6 years. Harun and colleagues also reported no association between *Aspergillus* in BAL cultures at age 5 years and $FEV_1$pp at that time or decline in $FEV_1$pp between ages 5 and 14 years (3). Indeed, the strongest factors adversely affecting lung function were nutritional status and pulmonary exacerbations requiring hospitalization (3). Inhaled antipseudomonal or chronic macrolide antibiotics may result in greater absolute or relative prevalence of *Aspergillus* but have also been shown to reduce exacerbations and improve nutritional status (11, 12). This further complicates attempts to decipher the role of *Aspergillus* bronchitis in pulmonary outcomes in young children with CF. Ultimately, a randomized interventional trial may be necessary to clearly determine the success rates and potential benefits of eradication. If such a trial requires repeated invasive sample collection under anesthesia or radiation exposure in young children, then the authors are correct in including an assessment of feasibility in broader discussions of future research plans.

In summary, Breuer and colleagues provide substantial further evidence for relatively high prevalence and potential pathogenicity of early lower airways *Aspergillus* infection without allergic sensitization. The longitudinal patterns of association and a clear dose–response between *Aspergillus*-positive cultures and CT abnormalities are compelling (*see* Figure E1 of Reference 1). We are encouraged by reports indicating that effective CFTR (cystic fibrosis transmembrane conductance regulator) modulator drugs significantly reduce *Aspergillus* positivity in respiratory cultures, and the years ahead may allow us to test the effect of early introduction of these therapies in young children with CF (13, 14). Despite anticipated advances in care, it is important to continue to wrestle with how best to detect, diagnose, and treat lower airway infections in young children with this disease. An increased appreciation for the role of nonallergic fungal infections appears to be an important part of that discussion. ■

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