

## Shifted Landscape of Airway Infection in Early Cystic Fibrosis

Airway infection plays a critical role in the pathogenesis and progression of cystic fibrosis (CF) lung disease (1). Historically, we believed that CF airway microbiology followed a reasonably predictable course of infection, commencing with *Staphylococcus aureus* and *Haemophilus influenzae* soon after birth and continuing into early childhood, then progressing to persistent infection with gram-negative organisms, most notably *Pseudomonas aeruginosa* (2). We have witnessed dramatic changes in CF care and treatment over the last 20 years, and it is reasonable to speculate that current clinical practice has influenced the prevalence and types of infections we are observing in our young patients with CF.

In this issue of the *Journal*, Breuer and colleagues (pp. 590–599) reexamine the epidemiology of lower airway infection in a modern cohort of almost 400 infants and young children diagnosed by newborn screening, followed at two Australian CF centers (3). During the 18-year study period, detection of *P. aeruginosa*, *S. aureus*, and *H. influenzae* by BAL decreased significantly, and these changes appeared to be associated with the increased use of oral and inhaled antipseudomonal antibiotics (ciprofloxacin and inhaled tobramycin), azithromycin, and inhaled mucolytic therapies (hypertonic saline and dornase alfa). In the United States, early diagnosis of CF by newborn screening is also temporally associated with reductions in *P. aeruginosa* infections (4).

One additional treatment strategy that likely had an effect on the microbiology results is the routine use of chronic antistaphylococcal antibiotics at both participating sites. Amoxicillin–clavulanic acid, which all patients received from diagnosis to 2 years of age, may have altered not only the detection of *S. aureus* but also that of *H. influenzae*, which is usually susceptible to this antibiotic (5). This certainly limits the generalizability of these results, as U.S. CF Care Centers rarely prescribe antistaphylococcal prophylaxis to infants and young children. Although prior studies have suggested the use of antistaphylococcal prophylaxis leads to an increase in the prevalence of *P. aeruginosa* (6), this was not observed within the Australian cohort (3). However, this may have been mitigated by the frequent use of antibiotics targeting *P. aeruginosa* over the study period. At one of the Australian sites, for example, treatment of pulmonary exacerbations routinely included antipseudomonal antibiotics, regardless of whether patients were culture positive for *P. aeruginosa*.

Advances in CFTR (CF transmembrane conductance regulator) modulators are likely to further affect airway microbiology. Highly effective CF transmembrane conductance regulator modulators offer significant promise for altering infection in CF. The GOAL (G551D Observational) study found that initiation of ivacaftor therapy was associated with a reduction in culture positivity of both *P. aeruginosa* and *Aspergillus* (7). Similarly,

reductions in *P. aeruginosa* infections have been reported in other studies after treatment with ivacaftor (8, 9). In 2019, the CF community is anticipating the approval of a triple combination of highly efficacious CF transmembrane conductance regulator modulators that could eventually benefit more than 80% of people with CF (10). With the intentions of studying and ultimately prescribing these modulators early in infancy, it is very likely that the epidemiology of early infection will be changed to an even greater extent.

In their cohort, the reduction in the prevalence of the bacterial pathogens has led to the emergence of *Aspergillus* as the most commonly detected pathogen from the lower airways among young children with CF (3). This study raises important questions regarding the increased prevalence of *Aspergillus* and the clinical implications of this finding. Certainly, the sampling technique affects the rate of isolation of fungi such as *Aspergillus*, with BAL and sputum being far superior to oropharyngeal (OP) swabs (11). In fact, many microbiology laboratories do not routinely test for fungi in OP swabs because of low diagnostic yield. Because most CF centers rely on OP samples for pathogen surveillance in younger children with CF, fungi such as *Aspergillus* will not be detected. This raises the question of whether bronchoscopy and BAL should be performed more routinely to survey for airway infection in infants and young children with CF. Although the arguments for and against this surveillance approach are beyond the scope of this editorial, one randomized controlled study did not provide clear evidence to support the routine use of BAL for the diagnosis and management of pulmonary infection in preschool children with CF compared with the standard practice of providing treatment based on results of OP cultures and clinical symptoms (12). Regardless, there is a need to optimize standardized protocols to identify fungi in respiratory samples including OP swabs collected from younger children. Recent advances in mycological culture and culture-independent molecular methods have led to the increased detection of a range of fungal species in CF respiratory samples (13). However, beyond the difficulties of detecting fungi such as *Aspergillus*, the more challenging issue is determining their clinical significance. Tracy and Moss recently proposed a set of practical diagnostic criteria for differentiating colonization from infection and active lung disease (13). This is an important distinction, as treatment approaches would likely differ. Another consideration that might explain the increased prevalence of *Aspergillus* in their cohort is that the use of chronic oral antibiotics, including azithromycin, and inhaled antipseudomonal antibiotics, is associated with an increased prevalence of fungi from CF respiratory samples (14, 15).

The CF Foundation is launching an Infection Research Initiative, committing at least \$100 million during the next 5 years as part of a sweeping effort to address the chronic and intractable infections that are a hallmark of CF. The findings from this study support the need for targeted research focused on the acquisition and evolution of airway pathogens early in life, and their relationship with clinical outcomes and treatment. It is vital to have a better understanding of airway infection to optimize treatment and alter the cycle of infection and inflammation and subsequent lung function decline and disease progression in patients with CF. ■

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Jordana E. Hoppe, M.D., M.S.C.S.  
 Scott D. Sagel, M.D., Ph.D.  
 Department of Pediatrics  
 Children's Hospital Colorado and University of Colorado School of Medicine  
 Aurora, Colorado

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## ⊕ CC16: A Biomarker of Pollutant Exposure and Future Lung Disease?

Birth cohort studies of lung function assessed longitudinally have identified that deficits in lung function from very early in life are carried into adulthood (1, 2). This can result in a failure to achieve optimal lung function and consequently a premature lung function decline leading to the development of respiratory symptoms and early death (3). These studies have identified the prenatal and early postnatal period as a critical window within which lifelong lung health can be determined. Therefore, factors that impact lung function at this early stage are likely to play a critical role in the development of lung disease.

Lung function deficiencies in early life most often result from preterm birth (4) or specific health conditions such as asthma (5, 6) and cystic fibrosis (7). However, environmental factors such as acute respiratory infections and inhaled

pollutants (e.g., tobacco smoke, particulates, and toxin exposure) (8) may also contribute. Due to the high frequency of individual diagnoses and environmental exposures (such as tobacco smoke) within populations, their potential impact on lung function trajectories have mostly been studied in combination. Furthermore, as a result of the confounding of multiple pollutant exposures with socioeconomic status, the evidence for the impact of specific pollutants on the development of life-long lung function deficits in healthy children and adults is limited.

Guerra and colleagues first demonstrated that reduced circulating CC16 (club cell secretory protein 16) levels in both early and later life were associated with lung function deficits longitudinally in several community-representative populations (9). Further research by Zhai and colleagues identified an association between CC16 levels and lung function both before and after airway responsiveness to albuterol as well as to methacholine in one of these population-based longitudinal cohorts, the Tucson Children's Respiratory Study (10). In this issue of the *Journal*, Beamer and colleagues (pp. 600–607) now show in this cohort that NO<sub>2</sub> exposure at birth is associated

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