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Reply to Turnbull et al. and to Hulme et al.

From the Authors:

In a recent issue of the Journal, we reported a change in infection  
prevalence observed over the 18 years of the AREST CF (Australian  
Respiratory Early Surveillance Team for Cystic Fibrosis)  
prospective study, specifically, a reduction in the prevalence of  
bacterial infections (Pseudomonas aeruginosa, Staphylococcus  
aureus, and Haemophilus influenzae), which resulted in Aspergillus  
species becoming the most prevalent lower respiratory  
infection cultured in recent years (1).

In a letter to the editor, Hulme and colleagues present  
infection prevalence data from a 6-year BAL surveillance  
program (SHIELD CF [The Study of Host Immunity and Early Lung  
Disease in Cystic Fibrosis]) in preschool-aged children with  
cystic fibrosis (CF) conducted at three specialist CF centers in Ireland.  
Differences in the prevalence of lower respiratory infections  
between their cohort and our Australian cohort, as well as  
possible explanations for these differences, are discussed in the letter.  
The Irish data show a much higher prevalence of lower respiratory  
S. aureus and H. influenzae infections and a much lower prevalence  
of Aspergillus species infections. These differences are striking,  
especially in the younger age group (0–2 yr).

Differences in the prevalence of bacterial infections between  
CF centers are not surprising. Even within the AREST CF  
cohort, significant differences between the two participating  
centers were reported (2). There could be numerous reasons  
for such differences, including antibiotic stewardship, practices  
involving antibiotic prophylaxis, varying protocols for the treat-  
ment of pulmonary exacerbations and environmental factors (as  
discussed by Hulme and colleagues), and patient adherence to  
treatment, infection control, and airway clearance routines.

The decrease in the prevalence of S. aureus and  
H. influenzae infections over the 18 years of the AREST  
CF study coincided with an overall more aggressive treatment  
approach. Specifically, use of chronic antibiotics increased  
considerably. Between 2004 and 2018, the percentage of  
preschool patients treated with long-term azithromycin and any  
use of inhaled tobramycin increased from 0% to 30% and 4.7%  
to 44%, respectively, possibly influencing the prevalence of  
bacterial infections. Interestingly, prophylactic treatment with  
amoxicillin–clavulanate did not change over the study period. In  
their letter, Hulme and colleagues do not provide specific  
information regarding antibiotic use in their patients, which  
makes it difficult to compare treatment effects on bacterial  
infection prevalence between the cohorts.

In a different letter, Turnbull and colleagues raise concern  
that infection prevalence in our study does not represent the  
full picture of CF airway microbiology in preschool children  
owing to a lack of report on samples obtained during  
pulmonary exacerbations, such as oropharyngeal swabs and  
induced sputum. We agree that it is possible that samples  
obtained during exacerbations might have increased the incidence  
of positive bacterial cultures. However, we aimed to report  
lower airway infection prevalence. Including upper  
airway samples, which have been shown to have a low  
positive predictive value for detecting lower airway infection during  
both exacerbations and clinical stability (3–5) (regardless of the  
test’s sensitivity), would lead to an overestimation of the  
prevalence of lower airway infection. Furthermore, including  
samples obtained during exacerbations would introduce a  
selection bias, which would also cause an overestimation of  
infected. Thus, although we do agree that it is important to  
understand exacerbation microbiology, it’s questionable  
whether such data should be included in an epidemiological  
study describing lower airway infection prevalence trends in  
relatively well preschool children with CF. In addition, and  
most importantly, exacerbation microbiology would not change  
the significant prevalence of lower respiratory Aspergillus  
species infections reported in our study.
The U.S. Cystic Fibrosis Foundation recently recognized that "new and/or validated ways to better classify and distinguish Aspergillus lung phenotypes" are an unmet need in CF care, limiting diagnosis and treatment of Aspergillus infections. As also presented in the letter by Hulme and colleagues, the prevalence rates of Aspergillus infections in patients with CF vary wildly among studies, mainly because of differences in the culturing methods and sample-processing techniques used, but also because of the different routines used for nebulized antibacterial therapies (6). Furthermore, bacterial infections may inhibit culture growth of Aspergillus species, which would also influence the reported prevalence (6). Our cohort showed an overall 40% incidence of Aspergillus species infection in the first 6 years of life, which is similar to what has been reported in other studies (7–9).

Hulme and colleagues pose the question, "Which is the greater evil, a higher prevalence of bacteria or a higher prevalence of Aspergillus?" There is little doubt that lower respiratory infections with bacteria cause lung damage. However, despite current aggressive antibiotic treatment regimens, preschool-aged children are still showing significant structural lung disease by 6 years of age (10). Thus, it is essential to understand the implications of Aspergillus infections, as they are not routinely treated. The use of molecular techniques to better identify fungal infections in patients with CF is critical for assessing the true prevalence of Aspergillus species infections (6), and programs like AREST CF and SHIELD CF provide opportunities to further elucidate the clinical consequences of Aspergillus infections in early CF lung disease. ■

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

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