Barry Linnane, M.B. B.Ch. B.A.O., D.C.H., M.R.C.P.I., M.R.C.P.C.H., M.D.
Our Lady's Children's Hospital, Crumlin
Dublin, Ireland
and
University of Limerick
Limerick, Ireland

Paul McNally, M.D., F.R.C.P.I.
Our Lady's Children's Hospital, Crumlin
Dublin, Ireland
and
Royal College of Surgeons in Ireland
Dublin, Ireland

*Corresponding author (e-mail: khulme@uni.sydney.edu.au).

References

1. Breuer O, Schultz A, Turkovic L, de Klerk N, Keil AD, Brennan S, *et al*. Changing prevalence of lower airway infections in young children with cystic fibrosis. *Am J Respir Crit Care Med* 2019;200: 590–599.
2. Warrier R, Skoric B, Vidmar S, Carzino R, Ranganathan S. The role of geographical location and climate on recurrent *Pseudomonas* infection in young children with cystic fibrosis. *J Cyst Fibros* 2019;18: 817–822.
3. Harun SN, Holford NHG, Grimwood K, Wainwright CE, Hennig S; Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study group. *Pseudomonas aeruginosa* eradication therapy and risk of acquiring *Aspergillus* in young children with cystic fibrosis. *Thorax* 2019;74:740–748.

Copyright © 2020 by the American Thoracic Society

Check for updates

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 treatment 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 infection. 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.

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

AREST CF is supported by Cystic Fibrosis Foundation Therapeutics, Inc., and Cystic Fibrosis Australia, and National Health and Medical Research Council grants APP1000896 and 1020555. A.S. is supported by a Translating Research into Practice fellowship from the National Health and Medical Research Council (APP1168022). None of the funding bodies were in any way involved in the data collection, interpretation of the data, or writing of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201911-2213LE on November 26, 2019

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 widely 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.

Oded Breuer, M.D.*
Telethon Kids Institute
Perth, Australia
Perth Children's Hospital
Perth, Australia
and
Hadassah-Hebrew University Medical Center
Jerusalem, Israel

Andre Schultz, M.B. Ch.B., Ph.D.
University of Western Australia
Perth, Australia
and
Perth Children's Hospital
Perth, Australia

Lidija Turkovic, Ph.D.
Nicholas de Klerk, Ph.D.
University of Western Australia
Perth, Australia

Anthony D. Keil, M.B. B.S.
Perth Children's Hospital
Perth, Australia
and
PathWest Laboratory Medicine WA
Perth, Australia

Siobhain Brennan, M.B. Ch.B., Ph.D.
University of Western Australia
Perth, Australia

Joanne Harrison, M.B. Ch.B., M.Clin. Ed.
Colin Robertson, M.B. B.S., M.Sc.(Epi.), M.D.
Philip J. Robinson, B.Med.Sc., M.B. B.S., M.D., Ph.D.
University of Melbourne
Melbourne, Australia
Murdoch Children's Research Institute
Parkville, Australia
and
Royal Children's Hospital
Parkville, Australia

Peter D. Sly, M.B. B.S., M.D., D.Sc.
The University of Queensland
Brisbane, Australia

Sarath Ranganathan, M.B. Ch.B., Ph.D.
University of Melbourne
Melbourne, Australia
Murdoch Children's Research Institute
Parkville, Australia
and
Royal Children's Hospital
Parkville, Australia

Stephen M. Stick, M.B. B.Chir., Ph.D.
University of Western Australia
Perth, Australia
and
Perth Children's Hospital
Perth, Australia

Daan Caudri, M.D., Ph.D.
Telethon Kids Institute
Perth, Australia
Perth Children's Hospital
Perth, Australia
and
Erasmus University Medical Center
Rotterdam, the Netherlands

On behalf of AREST CF‡ and the all authors

ORCID ID: 0000-0002-4775-9095 (O.B.).

*Corresponding author (e-mail: odedbreuer@gmail.com).
‡The full membership of AREST CF is available at www.arestcf.org.

References

1. Breuer O, Schultz A, Turkovic L, de Klerk N, Keil AD, Brennan S, *et al*. Changing prevalence of lower airway infections in young children with cystic fibrosis. *Am J Respir Crit Care Med* 2019;200: 590–599.
2. Ramsey KA, Hart E, Turkovic L, Padros-Goossens M, Stick SM, Ranganathan SC. Respiratory infection rates differ between geographically distant paediatric cystic fibrosis cohorts. *ERJ Open Res* 2016;2:00014-2016.
3. Breuer O, Caudri D, Akesson L, Ranganathan S, Stick SM, Schultz A; AREST CF. The clinical significance of oropharyngeal cultures in young children with cystic fibrosis. *Eur Respir J* 2018;51: 1800238.
4. D'Sylva P, Caudri D, Shaw N, Turkovic L, Douglas T, Bew J, *et al*. Induced sputum to detect lung pathogens in young children with cystic fibrosis. *Pediatr Pulmonol* 2017;52:182–189.

5. Kidd TJ, Ramsay KA, Vidmar S, Carlin JB, Bell SC, Wainwright CE, *et al*.; ACFBAL Study Investigators. *Pseudomonas aeruginosa* genotypes acquired by children with cystic fibrosis by age 5-years. *J Cyst Fibros* 2015;14:361–369.
6. Liu JC, Modha DE, Gaillard EA. What is the clinical significance of filamentous fungi positive sputum cultures in patients with cystic fibrosis? *J Cyst Fibros* 2013;12:187–193.
7. Saunders RV, Modha DE, Claydon A, Gaillard EA. Chronic *Aspergillus fumigatus* colonization of the pediatric cystic fibrosis airway is common and may be associated with a more rapid decline in lung function. *Med Mycol* 2016;54:537–543.
8. Harun SN, Wainwright CE, Grimwood K, Hennig S; Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study group. *Aspergillus* and progression of lung disease in children with cystic fibrosis. *Thorax* 2019;74:125–131.
9. el-Dahr JM, Fink R, Selden R, Arruda LK, Platts-Mills TA, Heymann PW. Development of immune responses to *Aspergillus* at an early age in children with cystic fibrosis. *Am J Respir Crit Care Med* 1994;150: 1513–1518.
10. Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA; Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Early lung disease in infants and preschool children with cystic fibrosis: what have we learned and what should we do about it? *Am J Respir Crit Care Med* 2017;195:1567–1575.

Copyright © 2020 by the American Thoracic Society