How Can Understanding the Phenotype of Pseudomonas aeruginosa Lead to More Successful Eradication Strategies in Cystic Fibrosis?

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(See the Major Article by Mayer-Hamblett et al on pages 624–31.)

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As children with cystic fibrosis (CF) age, an increasing number are infected with Pseudomonas aeruginosa in their lungs. Persistent, mucoid P. aeruginosa pulmonary infection is associated with more rapid lung function decline and increased mortality in CF [1–3]. The standard of care is therefore to try to eradicate new P. aeruginosa acquisition, usually with inhaled tobramycin treatment, to prevent its long-term deleterious effects [4, 5]. However, in 10%–40% of patients, eradication treatment fails [6, 7]. The reasons for these failures are poorly understood.

The in-depth study by Mayer-Hamblett et al in this issue of Clinical Infectious Diseases sheds some light on the subject. Using a cross-sectional cohort study design that elegantly leverages the large number of first-time P. aeruginosa isolates collected as part of the Early Pseudomonas Infection Control (EPIC) trial, the authors identified wrinkly colony surface and irregular colony edges as P. aeruginosa phenotypes independently associated with eradication failure. These 2 colony phenotypes have previously been associated with altered quorum sensing and increased biofilm formation [8, 9]. A surprising number of baseline isolates were also mucoid and had defects in motility and protease production, reflecting more of a chronic, adapted CF strain, rather than an initial, presumably environmentally acquired strain, which typically possesses the virulence factors frequently seen with acute infections. These findings are consistent with those of a previous study of 92 initial infecting P. aeruginosa isolates from children diagnosed with CF by newborn screening; in a multivariate regression model, persistent strains showed significantly lower pyoverdine, rhmannolipid, hemolysin, total protease, and swimming and twitching motility compared with strains successfully eradicated by aggressive antibiotic treatment [10]. Outside of early eradication and newborn screening studies, it is difficult to obtain large collections of initial P. aeruginosa isolates given the unpredictable nature of first-time P. aeruginosa colonization in CF. Unlike other studies that were limited by a small number of isolates [11], the study by Mayer-Hamblett et al was able to identify bacterial characteristics significantly associated with eradication failure because they had the largest published collection to date (N = 284).

The natural question arising from these results is why are some children with CF infected with P. aeruginosa isolates that have a chronic phenotype? It is unlikely that certain environmental strains have this specific phenotype, as it is known to occur as an adaptation to the CF lung environment [12]. It is possible that the initial P. aeruginosa infection occurred a significant time period prior to first detection, especially given that, according to this trial design, there could have been an interval of up to 12 months since the last P. aeruginosa–negative respiratory tract culture [13]. Longitudinal cohort studies have shown that P. aeruginosa antibody titers can rise, indicative of infection, up to 12 months prior to first-time isolation of the organism in respiratory specimen cultures [14]. Aggressive lower airway sampling in the form of routine bronchoscopic alveolar lavages in young children with CF, however, has not been shown to improve the culture rate of P. aeruginosa or improve the success rate of eradication therapy [15]. Culture-independent molecular methods
may be a more sensitive way of detecting initial \textit{P. aeruginosa} infection, although this has yet to be established [16]. Another possible explanation for first-time infection with a chronic phenotype, as pointed out by the current authors, is that initial infection may have occurred due to transmission from another CF patient with persistent \textit{P. aeruginosa} infection. Potential transmission, in shared clinic space, of \textit{P. aeruginosa} from older CF patients to infants and young children with CF identified through newborn screening, for example, has been previously described [17]. The enhanced infection control precautions recently recommended by the US Cystic Fibrosis Foundation may aid to address some of these concerns.

Can the knowledge that specific \textit{P. aeruginosa} phenotypes are associated with eradication failure help us to develop better treatment strategies? In the study by Mayer-Hamblett et al, 34% of cases of incident \textit{P. aeruginosa} infection failed eradication therapy with high-dose inhaled tobramycin. The addition of oral ciprofloxacin to tobramycin inhalation solution did not influence the prevalence of \textit{P. aeruginosa} positivity in those subjects randomized to this treatment arm during the EPIC trial [13]. Prolonging antibiotic treatment course does not improve \textit{P. aeruginosa} eradication in a child with CF and allows higher intrapulmonary concentrations of drug, would result in more successful eradication [25]. Although there may be an inclination to treat an initial \textit{P. aeruginosa} infection with a chronic phenotype using intravenous antimicrobial therapy, there are no studies comparing intravenous with inhaled eradication treatments to demonstrate its superiority. Intravenous administration of antibiotics generally does not achieve as high intrapulmonary concentrations as does nebulized drug administration. The development of newer aerosolized formulations may thus be required to effectively penetrate the biofilm structure and allow eradication of organisms with a chronic phenotype.

Bacterial characteristics are clearly not the only factor to influence the success of \textit{P. aeruginosa} eradication in CF. Host factors are likely to play a role in the patient’s capacity to clear the bacteria. Although the EPIC trial did not identify any baseline patient characteristics as significant predictors of \textit{P. aeruginosa} eradication success, previous studies have shown genetic determinants, related to degree of cystic fibrosis transmembrane conductance regulator function, and female sex to be implicated in earlier time to first \textit{P. aeruginosa} acquisition [5, 26–28]. Unfortunately, these factors are not modifiable. Additionally, the pulmonary microbiome, into which \textit{P. aeruginosa} is introduced at the time of first infection, may also influence its ability to establish chronic infection. Antimicrobial treatment of other coinfecting organisms within this polymicrobial community may improve the success of eradication attempts and deserves further study.

To conclude, given the lasting negative effects of \textit{P. aeruginosa} infection on clinical outcomes in CF, an eradication failure rate of >30% in young children with CF is too high to accept. To develop better treatment strategies to improve eradication success rates, we must first understand why these efforts fail in the first place. To that end, the study by Mayer-Hamblett and colleagues is a significant step in the right direction.

\textbf{Note}

\begin{itemize}
  \item \textbf{Potential conflicts of interest.} Author certifies no potential conflicts of interest.
  \item The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
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\textbf{References}