Pseudomonas aeruginosa Eradication: How Do We Measure Success?

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(See the Major Article by Mayer-Hamblett et al on pages 707–15.)

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Lung disease remains the major cause of morbidity and mortality for people living with cystic fibrosis (CF) [1]. Dysfunctional chloride conductance in the airways results in impaired mucus clearance, which drives a vicious cycle of infection, inflammation, and airway destruction. *Pseudomonas aeruginosa* (*Pa*) is a bacterial pathogen largely feared by the CF community as its chronic presence is associated with lung damage, a more rapid decline in lung function, and earlier mortality [2–6]. Unfortunately, *Pa* in airway secretions will be cultured in 80% of people with CF by age 18 years.

INITIAL *PA* ACQUISITION LEADS TO CHRONIC AIRWAY INFECTION

Surveillance airway cultures utilizing oropharyngeal swabs or sputum specimens are recommended quarterly in all people with CF starting in infancy, with a primary goal of detecting and eradicating initial *Pa* acquisition. Initial *Pa* infection in the CF airway is thought to be transient, reflecting a window of opportunity to eradicate this low-density, nonmucoid, antibiotic-sensitive pathogen [7]. Once chronic *Pa* airway infection, particularly with the mucoid phenotype of *Pa*, has been established, the therapeutic approach shifts from eradication toward suppression [8]. Previous work reflects the successful ability of inhaled and/or oral antibiotics to eradicate initial *Pa* infection, utilizing microbiological endpoints as primary outcome measures [9–12]. Consequently, the Cystic Fibrosis Foundation recommends the use of inhaled tobramycin as the primary means by which to eradicate initial or new *Pa* growth, and this is standard of care in CF care centers worldwide [7].

CLINICAL IMPACT OF *PA* ERADICATION

Although there is consensus regarding the importance of attempting to eradicate initial *Pa* acquisition and delay chronic airway infection, there are limited data regarding the clinical impact of successful eradication, and comparison studies are limited as placebo-controlled studies are considered unethical [13, 14]. Healthcare providers work largely on the assumption that *Pa* eradication will allow for improved quality of life and longer life expectancy. The largest US clinical trial of *Pa* eradication, EPIC (Early *Pseudomonas* Infection Control), confirmed the microbiologic success of eradication; follow-up of this pediatric cohort has provided a valuable look at clinical outcomes [9]. From the EPIC study, using 2.5 years of follow-up data, no association was found between initial *Pa* acquisition and a more rapid decline in lung function or change in growth parameters in children [15]. Although initial *Pa* acquisition was associated with more frequent physical examination findings of lung disease and the presence of additional bacterial pathogens in the airway (ie, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and methicillin-resistant *Staphylococcus aureus*), suggesting the potential for worsening clinical outcomes, this has yet to be confirmed [15]. Additional studies from other cohorts have also revealed conflicting results regarding the long-term impact of eradicating *Pa* infection on lung function and nutritional outcomes [16, 17].

In this issue of *Clinical Infectious Diseases*, Mayer-Hamblett and colleagues use data from the EPIC observational study, a follow-on to the EPIC clinical trial, to extend our understanding of long-term outcomes following *Pa* eradication [18].

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Clinical and microbiologic outcomes were compared between children who achieved a sustained eradication of *Pa* (defined as *Pa*-negative cultures for the final 12 months of the EPIC trial) with those children who did not achieve sustained eradication. As expected, children who did not achieve sustained eradication had a shorter time to chronic *Pa* infection and to first mucoid *Pa* infection. However, when clinical outcomes were examined, over a median follow-up of 5 years, there were no differences in any of the clinical outcomes measured, including lung function decline and rate of pulmonary exacerbations. Perhaps it should not be surprising that clinical outcomes were similar between groups. The children studied were young (mean age 7.2 years), had mild lung disease with a mean forced expiratory volume in 1 second (FEV_1) of 98%, and were born in an era of improved nutrition and other therapeutic advances. Children who did not achieve sustained eradication received more courses of anti-*Pa* antibiotics, potentially ameliorating the harmful impact of *Pa* infection. In addition, natural history studies of *Pa* in CF suggest that mucoid *Pa* is more clinically impactful than nonmucoid *Pa*; thus, the difference in clinical outcomes between these groups may only become apparent after the development of mucoid *Pa* [4]. Given that time to mucoid *Pa* was delayed in sustained eradicators, we can speculate that, if followed for a sufficient period of time, the outcomes within the 2 groups would diverge, with those who develop earlier mucoid *Pa* suffering more rapidly progressive disease. Even in the nonsustained eradicators, mucoid *Pa* was detected in only one-third of children over the 5 years of follow-up. This suggests that eradication approaches, even with early *Pa* recurrence, might delay the conversion to mucoid *Pa*, and that longer follow-up may be necessary to detect clinical impact. Importantly, this study did not find a difference at study entry between children who achieved sustained eradication and those who did not; thus, at this time, we are still not able to predict those children at risk of early *Pa* recurrence.

MEASURING SUCCESS—OPTIMAL OUTCOME MEASURES IN CHILDREN

Reassuringly, all children in the study remained remarkably well, with a mean decline in FEV_1 of only −0.1% per year, a slow decline compared with historical controls in this age group prior to widespread adoption of *Pa* eradication approaches and other advances in management [2]. However, this highlights the key need for more sensitive outcome measures and biomarkers of disease activity given that differences in FEV_1 decline may not be apparent for many years. Although lung function and number of pulmonary exacerbations did not differ between these groups, there may be more subtle changes in airway structure or function, and indicators of these changes could detect differences in disease progression between groups. In addition, other factors including genetic modifiers, airway microbiome communities, or host inflammatory response may impact the risk of early *Pa* recurrence in children with CF.

FUTURE DIRECTIONS

This study confirms that early eradication approaches are effective in delaying time to chronic infection and mucoid *Pa*. It is encouraging that the duration of effect of *Pa* eradication was sustained in a substantial number of patients, with a median time to the next *Pa*-positive culture of 3.5 years in those who were classified as sustained eradicators. Extending the time to chronic *Pa* in this study did not confer a measurable clinical benefit over 5 years; however, as few children in either group developed infection with mucoid *Pa*, longer follow-up and more sensitive outcome measures may be needed to detect a significant difference. Although we expect that clinical benefit will follow from delayed chronic and mucoid *Pa* infection, there is the possibility that our assumptions are incorrect, reminding us of the importance of carefully designed longitudinal studies, the selection of appropriate outcome measures, and development of novel, sensitive biomarkers.

This study also suggests the need to further improve our eradication strategies given that 1 in 3 children did not achieve sustained eradication. Although antibiotic resistance did not emerge during this study, the increased use of anti-*Pa* antibiotics among those who did not achieve sustained eradication suggests that those children are at increased risk for antibiotic resistance with time. As people with CF live longer, judicious use of antibiotics will be increasingly important, and balancing this with the need to delay lung disease development will be challenging [19]. This study supports our current clinical practice while highlighting the need for improved eradication approaches and more sensitive outcome measures in children.

Note

Potential conflicts of interest. Both authors: No potential conflicts of interest.

Both authors have 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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