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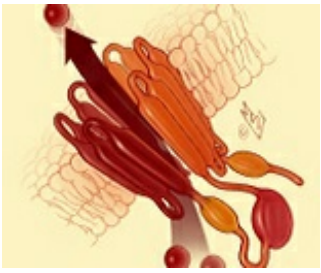

Pseudomonas aeruginosa Eradication and Outcomes: Key Questions

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In this Issue...

Chronic airway infection with *Pseudomonas aeruginosa* (PA) is associated with increased morbidity and mortality, and the eradication of early PA infection has been a therapeutic goal for decades. But vital questions remain unanswered: Why do some patients fail eradication? Are there host or pathogen factors that can predict eradication success or failure? What is the best approach to failed eradication or early PA reemergence? What data demonstrate short or long-term clinical benefits resulting from eradication?

In this issue, Dr. Christopher Oermann from the Department of Pediatrics at Children's Mercy Kansas City reviews the recent literature describing attempts to provide some answers.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Compare current evidence-based practice guidelines for early *Pseudomonas aeruginosa* eradication.
- Define *Pseudomonas aeruginosa* phenotypes associated with eradication failure.
- Discuss the impact of sustained *Pseudomonas aeruginosa* eradication on long-term cystic fibrosis outcomes.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

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Guest Faculty Disclosure

Dr. Christopher Oermann has disclosed that he has received royalties for written material from UpToDate® Pediatrics

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unlabeled/unapproved use of inhaled antibiotics specifically labeled for use in eradication protocols but not labeled for children less than 6 years of age, as well as the use of inhaled colistin.

IN THIS ISSUE

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COMMENTARY

A large body of literature spanning decades clearly demonstrates an association between chronic *Pseudomonas aeruginosa* (PA) infection and increased morbidity and mortality among patients with cystic fibrosis (CF).[1] We have a growing understanding of the underlying host and PA-specific factors that promote chronic lower respiratory tract infection in CF, but key unanswered questions remain.[2] Although several antibiotic eradication therapy (AET) regimens have proved successful in treating early PA infection, up to 40% of treated patients experience failed eradication. Although no host factors predicting AET failure have been identified, recent studies have identified specific PA phenotypes that may place patients at increased risk for failure. Some benefits of sustained PA eradication have been described, but improvements in long-term clinical outcomes have yet to be determined. Finally, crucial questions regarding appropriate therapy for patients with failed eradication or early reacquisition of PA remain unanswered.

The papers by Mogayzel and colleagues for the Cystic Fibrosis Foundation and Langton-Hewer and Smyth for Cochrane both provide comprehensive reviews of the evidence supporting AET. Both reviews focus on seven reports describing different AET regimens. Each trial included various combinations of inhaled, oral, or intravenous antibiotics compared to placebo, usual treatment, or another combination of inhaled, oral, or intravenous antibiotics. The conclusion of both reviews was that AET is indicated in early PA infection among patients with CF. The reviews differed in that the Cystic Fibrosis Foundation review stated that inhaled tobramycin (300 mg twice daily) for 28 days was the favored therapy. The Cochrane review sited insufficient evidence to recommend one AET regimen

over another. Similarly, the European consensus conference on the treatment of lung infections in patients with CF stated that although inhaled tobramycin is a recommended treatment strategy, other treatment regimens have been shown to be of similar ineffectiveness and an optimal AET regimen is not known.[1] Hence, consideration can be given to inhaled tobramycin as previously described, a combination of inhaled colistin and ciprofloxacin as reported in the above trials, or inhaled aztreonam as reported by Tiddens and colleagues.

The studies by Mayer-Hamblett and colleagues (2014) and Vidya and colleagues independently identified PA phenotypes that may be associated with increased risk of failed eradication. Mucoidy, which is often associated with chronic infection, was relatively uncommon in the Mayer-Hamblett study and not associated with increased risk of AET failure. Conversely, mucoidy was associated with failed eradication in the Vidya study. Decreased motility, specifically twitch motility, was common among patients who had failure to eradicate in both studies. Mayer-Hamblett identified only wrinkly colony surface and irregular colony edges as associated with significantly increased risk of failure to eradicate after AET. Neither study found increased prevalence of genetic defects suggesting altered quorum sensing. These two studies suggest that PA isolates with specific phenotypes, which are easily recognized in basic microbiology laboratories, may place patients at increased risk for failure to eradicate following AET. Coordination of care between clinicians and microbiology laboratories may provide an opportunity to identify patients at increased risk for AET failure and allow development of eradication protocols designed to decrease risk of failed eradication. Additional research is clearly needed in this area.

Many of the clinical trials reviewed by Mogayzel and Langton-Hewer, as well as the individual reports by Mayer-Hamblett and Vidya, have failed to identify improvements in long-term clinical outcomes resulting from successful AET. However, there is some evidence of short-term benefit as discussed in a second paper (2015) by Mayer-Hamblett and it is, perhaps, not unreasonable to extrapolate potential long-term benefit based on existing epidemiologic data. As previously stated, there is irrefutable evidence associating chronic PA infection with increased morbidity and mortality. Data from the Cystic Fibrosis Foundation Patient Registry (CFFPR)[3] indicate that the prevalence of PA infection had decreased from 60.7% in 1997 to 47.5% in 2014. Further review of CFFPR data suggest that the age of peak prevalence of PA infection has been gradually increasing; in 2003, peak prevalence occurred prior to 25 years of age, by 2006 it had increased to 25-34 years, and had increased further to 35-44 years by 2014. Furthermore, the age cohort by which 50% of patients were PA-positive has increased from < 11 years to 11-17 years, and > 17 years over the same CFFPR reported time frame. The CFF suggested in the 2014 report that these trends may “in part relate to widespread implementation of therapy to eradicate initial acquisition of *P. aeruginosa*.” Analysis of additional data from observational trials and the CFFPR database may allow identification of not-yet-evident long-term benefits of PA eradication.

While the articles reviewed herein have significantly increased our understanding of the feasibility of antibiotic eradication therapy for early PA infection, potential PA-specific risk factors (ie, phenotype) for eradication failure, and possible midterm microbiologic benefits of eradication, many important questions remain unanswered. With similar rates of eradication having been reported for several different AET regimens, is one truly preferred over another? Should issues such as cost, treatment burden, and patient preference be considered in recommending one regimen or another? Are there as yet unidentified clinical or patient-specific risk factors for eradication failure? If such risk factors exist, what is the best approach to identifying them?

Should all microbiology laboratories routinely report PA phenotypes associated with increased risk of eradication failure? Would this information alter care or dictate a more

intensive eradication regimen? If so, what would that be?

If chronic PA infection is clearly associated with increased morbidity and mortality and overall PA infection prevalence is declining, surely eradication must yield better long-term clinical outcomes. But what are they and how do we identify them?

Perhaps the most critical question is: what is the best approach to failed eradication or early PA reemergence?

None of the reviewed articles addresses this crucial question. The Artimino Algorithm from the 2012 European Consensus Conference suggests that failed eradication or early reemergence should prompt a second attempt at AET and "optimization of adjunctive therapy."[1] The guideline does not, however, recommend specific AET regimens or define optimization of adjunctive therapy. The algorithm then recommends "aggressive third line clearance" for persistent PA infection, but again does not offer guidelines regarding what this therapy would involve. Clearly, additional clinical trials or database analyses are needed to answer these vitally important questions.

References:

1. Döring G, Flume P, Heijerman H, Elborn JS; Consensus Study Group. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros*. 2012 Dec;11(6):461-479.
2. Staudinger BJ, Muller JF, Halldórsson S, et al. Conditions associated with the cystic fibrosis defect promote chronic Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med*. 2014 Apr 1;189(7):812-824.
3. Cystic Fibrosis Foundation Patient Registry. 2014 Annual Data Report and 2012 Annual Data Report to the Center Directors. Bethesda, Maryland. © 2012 and 2015 Cystic Fibrosis Foundation.

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CF Foundation Eradication Guidelines

Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al; Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Foundation pulmonary guideline. Pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. *Ann Am Thorac Soc*. 2014 Dec; 11(10):1640-1650.

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The Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee recently completed an evidence-based literature review of the treatment of early *Pseudomonas aeruginosa* (PA) infection and, based on this review, developed guidelines. The CF Foundation strongly recommends inhaled antibiotic therapy for treating initial or new growth of PA from an airway culture. The recommendation received an “A” grade, indicating a high certainty of substantial net benefit.

Numerous retrospective or uncontrolled studies have suggested that the treatment of early lower respiratory tract PA infection in patients with cystic fibrosis (CF) can prevent transient infection from progressing to chronic infection.[1] Therapeutic approaches have included combinations of oral, inhaled, and intravenous antibiotics for variable periods of time and have assessed different outcomes. Most studies demonstrated treatment benefit. More recently, randomized, controlled trials (RCT) and an open-label study demonstrated the efficacy of inhaled colistin with oral ciprofloxacin, inhaled tobramycin (with and without oral ciprofloxacin), and inhaled aztreonam lysine in PA eradication. The Guidelines Committee evaluated the seven RCTs reviewed below in recommending inhaled antibiotics for treating early PA infection.

The literature search performed by the Guidelines Committee found 717 full-text articles. Of those, 699 were eliminated for various reasons, leaving 18 articles describing 13 studies. Six articles including patients with chronic PA infection were reviewed but were not included in analysis. Seven RCTs and one open-label study were considered by the Guidelines Committee in making its recommendation.

Summarizing the findings of these studies:

- At the conclusion of a 27 month trial, including 26 children with CF who received three weeks of inhaled colistin and oral ciprofloxacin twice daily vs no treatment, each time their monthly respiratory cultures grew PA, 14% of treated and 58% of untreated patients were infected with PA ($P < .05$).[2]
- In a 12-month trial including 22 patients who received inhaled tobramycin (80 mg) twice daily, 90% of treated patients vs 20% of untreated patients had negative PA cultures at the end of treatment ($P < .05$).[3]
- In a pilot study of 21 children with CF less than 6 years of age, 100% of patients treated with inhaled tobramycin (300 mg twice daily for 28 days) had negative respiratory cultures vs 8% of patients on placebo ($P < .0001$).[4]
- In a two-year trial of inhaled tobramycin (300 mg twice daily for 28 days) or inhaled colistin plus oral ciprofloxacin, 79% of the tobramycin vs 90% of the patients who received colistin were PA free ($P = .47$).[5]
- The ELITE trial revealed that no significant differences existed between 88 patients treated with 28 vs 58 days of inhaled tobramycin (300 mg twice daily); eradication rates were 93% and 92%, respectively.[6]
- In the EPIC trial, a four-armed study of inhaled tobramycin (300 mg twice daily) with

or without oral ciprofloxacin and culture-based vs cycled therapy among 304 patients, freedom from PA was similar among all treatment arms, 85%-91%.[7]

- No differences in PA negativity were seen between treatment groups in a study of 223 CF patients given inhaled colistin or tobramycin (300 mg) combined with oral ciprofloxacin, 80% and 78%, respectively.[8]
- In the ALPINE study, 89.1% of 105 patients treated with inhaled aztreonam lysine (75 mg three times per day) were free of PA at the end of 28 days.[9]

The CF Foundation has stated that inhaled tobramycin (300 mg twice daily) for 28 days is the favored antibiotic regimen for treating initial or new growth of PA from an airway culture.

References:

1. Start B, Lin JH, Mogayzel PJ Jr. Early eradication of Pseudomonas aeruginosa in patients with cystic fibrosis. *Paediatr Respir Rev*. 2010 Sep;11(3):177-184.
2. Valerius NH, Koch C, Høiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. *Lancet*. 1991;338:725–726.
3. Wiesemann HG, Steinkamp G, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatr Pulmonol*. 1998;25:88–92.
4. Gibson RL, Emerson J, McNamara S, et al. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care*. Med 2003;167: 841–849.
5. Proesmans M, Vermeulen F, Boulanger L, Verhaegen J, De Boeck K. Comparison of two treatment regimens for eradication of Pseudomonas aeruginosa infection in children with cystic fibrosis. *J Cyst Fibros*. 2013;12:29–34.
6. Ratjen F, Munck A, Kho P, Angyalosi G; ELITE Study Group. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. *Thorax*. 2010;65:286–291.
7. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, et al. Early Pseudomonas Infection Control (EPIC) Investigators. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. *Arch Pediatr Adolesc Med*. 2011;165:847–856.
8. Taccetti G, Bianchini E, Cariani L, et al; Italian Group for P. aeruginosa Eradication in Cystic Fibrosis. Early antibiotic treatment for Pseudomonas aeruginosa eradication in patients with cystic fibrosis: a randomized multicentre study comparing two different protocols. *Thorax*. 2012;67:853–859.
9. Tiddens HA, De Boeck K, Clancy JP, et al; ALPINE study investigators. Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study. *J Cyst Fibros*. 2015 Jan;14(1):111-119. (The full text of this study was not available at the time of the CF Foundation review).

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Antibiotic Strategy for PA Eradication

Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2014 Nov 10; 11:CD004197.

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The Cochrane Collaboration completed reviews of antibiotic strategies for eradicating PA in people with CF in 2003, 2006, 2009, and, 2014. The current review included randomized, controlled trials comparing combinations of inhaled, oral, or intravenous antibiotics with placebo, usual treatment, or combinations of inhaled, oral, or intravenous antibiotics. Nonrandomized and crossover trials were excluded from analysis, as were studies using historical controls.

The same seven trials considered in the CF Foundation guidelines met inclusion criteria, included a total of 744 patients, and were of 28 days to 27 months duration. Two were placebo-controlled, one compared active treatment to no treatment, and four compared different treatment regimens. Two studies included young children (< 12 years), three included older children, and two included adults. Interventions included combinations of inhaled colistin, inhaled tobramycin, and oral ciprofloxacin for periods of 28 days to 12 months. Various outcomes were assessed, including PA negativity at the end of treatment, time to PA recurrence, time to chronic PA infection, time to pulmonary exacerbation requiring intravenous antibiotics, and percentage of PA-positive respiratory cultures over the study period.

Two studies compared inhaled tobramycin (80 mg[1] or 300 mg[2] twice daily) to placebo. The study using 80 mg did not demonstrate reduced likelihood of PA positivity until six months of treatment [OR 0.06 (95% CI 0.00 to 0.92)], which was maintained through 12 months [OR 0.02 (95% CI 0.00 to 0.67)]. This finding contrasts with treatment with 300 mg, in which significantly fewer children had a PA growth from a bronchoalveolar lavage (BAL) at one month [OR 0.01 (95% CI 0.00 to 0.30)], but not at two months [OR 0.21 (95% CI 0.03 to 1.47)]. When combined data was analyzed, there were significantly reduced odds of a PA-positive culture at both one and two months, ORs 0.06 (95% CI 0.01 to 0.33) and 0.15 (95% CI 0.03 to 0.65) respectively.

A single trial comparing oral ciprofloxacin and inhaled colistin vs no treatment included 26 children.[3] Patients received three weeks of treatment with each PA-positive culture. The primary outcome was time to chronic PA infection, defined as the presence of PA-precipitating antibodies, or six consecutive months of positive cultures. The treatment group had significantly reduced odds of being chronically infected with PA at the end of the 24-month trial, OR 0.12 (95% CI 0.02 to 0.79).

Another study compared the efficacy of three months of oral ciprofloxacin and inhaled colistin (twice daily) vs 28 days of inhaled tobramycin (300 mg twice daily) among 58 children with CF.[4] Six months after treatment, there were no significant differences between groups with respect to PA positivity, lung function, weight/nutrition, or frequency of pulmonary exacerbations.

The ELITE trial compared 28 vs 56 days of inhaled tobramycin (300 mg) in 88 patients.[5] Time to PA recurrence was not different between groups (26.12 months vs 25.82 months respectively [$P = .59$]).

In a study of 223 patients receiving oral ciprofloxacin and either inhaled colistin or tobramycin (300 mg) twice daily for 28 days, 37.1% of colistin patients and 34.7% of tobramycin patients had recurrence of PA within six months of treatment.[6] This difference was not statistically significant, and none of the other outcomes assessed differed between groups.

The previously described EPIC trial was analyzed with respect to cycled (300 mg inhaled tobramycin twice daily with or without oral ciprofloxacin) vs culture-based treatment and oral ciprofloxacin vs placebo. Unlike the original manuscript, the Cochrane review reported significantly reduced odds for recurrent PA in the cycled treatment group, OR 0.51 (95% CI 0.31 to 0.82). This is attributed to differing statistical analyses. Other outcomes were not significant. When assessing ciprofloxacin vs placebo, no significant differences in outcomes were identified.

Conclusions from the Cochrane review are:

- Antibiotic therapy (inhaled or combined with oral) was better than no treatment in eliminating early PA infection.
- Eradication may be sustained in the short term.
- No clear clinical benefit was associated with eradication.
- There is insufficient evidence to state which antibiotic strategy should be used.

References:

1. Wimann HG, Steinkamp G, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatr Pulmonol*. 1998;25:88–92.
2. Gibson RL, Emerson J, McNamara S, et al. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care Med*. 2003;167: 841–849.
3. Valerius NH, Koch C, Høiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. *Lancet*. 1991;338:725–726.
4. Proesmans M, Vermeulen F, Boulanger L, Verhaegen J, De Boeck K. Comparison of two treatment regimens for eradication of Pseudomonas aeruginosa infection in children with cystic fibrosis. *J Cyst Fibros*. 2013;12:29–34.
5. Ratjen F, Munck A, Kho P, Angyalosi G; ELITE Study Group. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. *Thorax*. 2010;65:286–291.
6. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, et al. Early Pseudomonas Infection Control (EPIC) Investigators. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. *Arch Pediatr Adolesc Med*. 2011;165:847–856.

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PA Phenotypes Associated with Eradication Failure

Mayer-Hamblett N, Ramsey BW, Kulasekara HD, et al. *Pseudomonas aeruginosa* phenotypes associated with eradication failure in children with cystic fibrosis. *Clin Infect Dis*. 2014 Sep 1;59(5):624-631.

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Antibiotic eradication therapy (AET) has become the standard approach for treating early PA infection in CF. Several regimens have been shown to be effective in eliminating newly acquired PA from respiratory cultures. However, all regimens have failed to achieve eradication in some patients. The reasons for treatment failure were not specifically addressed in many of the previously described studies, and clinical or patient characteristics predicting failure were not identified. Understanding whether PA characteristics, unlike patient characteristics, can predict eradication failure would also provide valuable information.

Mayer-Hamblett and colleagues have reported data suggesting that specific PA phenotypes may be associated with a greater risk of eradication failure. Using a cohort of patients from the EPIC trial,[1] time to PA eradication failure (defined as the first occurrence of a PA-positive culture after the initial three months of AET), proportion of patients with the emergence of mucoid PA, and time to pulmonary exacerbation during the trail were assessed. All PA isolates were analyzed in a central laboratory and underwent *lasR* (a PA gene associated with abnormal quorum sensing and chronic PA infection) gene sequencing. Two hundred eighty-four isolates were available for 194 of 304 (64%) EPIC trial participants and were included in the study cohort reported.

Wild-type tan colony color (67%) and pyocyanin production (66%) were the most prevalent phenotypes seen on baseline culture. Among potential indicators of chronic infection, mucoidy was present in only 9% of isolates and auxotrophy (the inability of an organism to synthesize a particular organic compound required for its growth) in 7%. Other indicators of chronic infection, such as defects in motility, including swimming (29%) and twitching (28%), were also more commonly noted. Defective production of pyoverdine was also relatively frequent, identified among 72% of baseline isolates. *lasR* mutations were present in 24% of initial cultures and phenotypes associated with *lasR* mutations, autolysis and/or sheen, defective protease production, and increased growth in nitrate, were seen in 20%, 35%, and 22% of cultures, respectively. Other phenotypes associated with biofilm formation and/or mucoidy were relatively common and included irregular colony edges (24%), wrinkly colony surface (10%), and binding of Congo red dye (21%).

Within this study cohort, failure of eradication occurred in 79 of 194 (41%) patients. Considering the 22 PA phenotypes assessed, only wrinkly colony surface and irregular colony edges were each associated with significantly increased risk of failure to eradicate after AET (hazard ratios of 1.99 [1.03–3.83] and 2.14 [1.32–3.47], respectively). Only colony autolysis and/or sheen at baseline were associated with a significant increase in the risk of the emergence of mucoidy; 12.9% of isolates vs 2.8% of those without either phenotype (P = .035). None of the PA phenotypes assessed was associated with increased risk of pulmonary exacerbation.

The authors conclude that:

- Phenotypes typically thought to represent chronic infection are relatively common among new PA isolates.
- Two phenotypes easily identified by microbiology laboratories are associated with

increased risk of AET failure.
- Mucoidy is not associated with AET failure.

References:

1. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, et al.; Early Pseudomonas Infection Control (EPIC) Investigators. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. *Arch Pediatr Adolesc Med.* 2011;165:847–856.

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Chronic PA Phenotype and Failed Eradication

Vidya P, Smith L, Beaudoin T, et al. Chronic infection phenotypes of *Pseudomonas aeruginosa* are associated with failure of eradication in children with cystic fibrosis. *Eur J Clin Microbiol Infect Dis*. 2016 Jan; 35 (1):67–74.

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Vidya and colleagues recently reported results from a cross-sectional study of children with CF who experienced new PA respiratory infection. The study, conducted between 2011 and 2014, included patients aged 5-18 years. Data were available for 46 children with a total of 51 "incident" PA infections. Among these, 33 of 46 patients (72%) had successful eradication, whereas 13 (28%) failed AET. Isolates from patients who failed AET were less likely to be motile and were more likely to be mucoid. Additionally, they were more likely to have a tobramycin minimum inhibitory concentration (MIC) $\geq$ 128 mcg/mL. The authors conclude that initial infection with PA having characteristics of chronic infection is associated with failed AET.

In this single-center, cross-sectional study, PA isolates from patients with CF aged 5-18 years who could expectorate sputum were analyzed. Clinical data were collected to assess for risk factors that might indicate increased risk for AET failure. Two eradication protocols were used during the years of the study: (1) inhaled tobramycin solution (300 mg/5 mL) twice daily for 28 days, or (2) inhaled tobramycin solution (80 mg/2 mL) twice daily for 365 days. An "incident" PA infection was defined as a patient having a PA-positive sputum culture with a minimum of three negative cultures in the previous 12 months without AET. Standard isolation techniques were used and PA phenotypes characterized in concordance with recognized and previously reported standards.[1] Additional analyses included PA swimming and twitch motility, protease production, mucoidy status, biofilm formation, tobramycin susceptibility, and detection of quorum-sensing genes (*lasI*, *lasR*, *rhlR*, and *rhlI*).

As above, 46 children had a total of 51 incident PA infections. Among these, 33 of 46 (72%) had successful AET, while 13 of 46 (28%) had failed eradication. Baseline clinical characteristics were similar between patient groups, and there was no difference in eradication success between treatment regimens. Five hundred fifty-two PA isolates representing 86 morphotypes (65 eradicated and 21 persistent) were found. Observed morphotypes differed significantly between eradicated and persistent isolates; eradicated isolates tended to be gray and flat in appearance, with a metallic sheen, whereas persistent isolates were more commonly green and mucoid. Isolates from patients who failed AET were less likely to be motile, with significantly decreased twitch motility ($P = .001$), were more

likely to be mucoid ($P = .002$), and a higher proportion had a tobramycin minimum inhibitory concentration $\geq$ 128 mcg/mL ($P = .001$). Though not statistically significant, there was a trend toward increased presence of quorum-sensing genes in the persistent isolates. No other differences were identified.

The authors conclude that those characteristics of PA isolates typically seen in well-established chronic infections, as reported above, are associated with failed AET. They confirmed that there are no identifiable host factors that suggest an increased risk of eradication failure. Lastly, the authors pointed out that although PA eradication has not been associated with improved long-term clinical outcomes, it is reasonable to assume that the increased morbidity and mortality associated with chronic PA infection may be delayed by preventing chronic infection.

References:

1. Tramper-Stranders GA, van der Ent CK, Molin S, et al. Initial Pseudomonas aeruginosa infection in patients with cystic fibrosis: characteristics of eradicated and persistent isolates. *Clin Microbiol Infect*. 2012 Jun;18(6):567-574.

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Sustained Eradication and Outcomes

Mayer-Hamblett N, Kloster M, Rosenfeld M, et al. Impact of sustained eradication of new *Pseudomonas aeruginosa* infection on long-term outcomes in cystic fibrosis. *Clin Infect Dis*. 2015 Sep 1;61(5):707-715.

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Chronic PA infection is clearly associated with increased morbidity and mortality among CF patients. Eradication of early PA infection has been achievable using several AET protocols. However, existing trials have failed to demonstrate short- or long-term clinical benefits resulting from eradication. Long-term observational follow-up data on children participating in the EPIC trial were used to assess potential benefits associated with eradication of early PA infection. Over a median five-year follow-up period, patients who experienced sustained eradication had a 74% reduction in the risk of developing chronic PA infection. Additionally, they had a 57% reduction in the risk of developing mucoid PA. Finally, patients with sustained eradication required significantly less antipseudomonal antibiotic therapy than those without sustained eradication.

The study cohort included a subset of patients who had participated in the EPIC clinical trial and consented to participate in an ongoing observational study. Sustained eradication was defined as 12 months of respiratory cultures that were free of PA following initial eradication. Microbiologic endpoints for the study included time to first and second PA recurrences, as well as time to chronic PA infection. Chronic PA infection was defined as the third quarter in which a PA-positive culture was observed within a two-year period. Time to mucoid and resistant PA were defined, respectively, as the first quarter in which a mucoid or persistent PA culture was recorded in the CF Foundation Patient Registry.

Among the 249 patients who completed the EPIC trial and continued in the observational trial, 172 (69%) achieved sustained eradication (SE) and 77 (31%) failed to achieve

sustained eradication (nonsustained eradication [NSE]). As has been previously reported, no clinical characteristics predicted increased risk of failed eradication. Also consistent with results from the EPIC trial, more patients on cycled therapy (300 mg inhaled tobramycin twice daily with or without oral ciprofloxacin) achieved SE (93/172 [54%]) compared to culture-based therapy (29/77 [38%]). Importantly, most patients in the culture-based group responded to subsequent antipseudomonal antibiotic treatment, and the prevalence of positive PA cultures at the end of the trial was the same in both groups.

During the follow-up study period, 84% of NSE vs 60% of SE patients experienced at least one PA recurrence, with median times of one year vs 3.5 years, respectively, for the first PA recurrence. Among the patients with PA recurrence, a second PA recurrence occurred in 77% of NSE-patients vs 55% of SE-patients, with median times of 0.75 and 2.0 years, respectively. There was a significant association between NSE and the development of chronic PA infection, with 56% of NSE-patients vs 23% of SE-patients developing chronic infection. SE during the trial was associated with a 74% reduced risk of developing chronic PA infection (HR, 0.26; 95% CI, .17–.40). Importantly, the use of cycled therapy during the trial was also associated with increased risk of developing chronic PA infection during the follow-up period. SE was associated with a 57% reduced risk of developing mucoid PA (HR, 0.43; 95% CI, .25–.73), with 33% of NSE and 17% of SE-patients respectively developing mucoid PA. Overall, SE-patients had less oral and inhaled antipseudomonal antibiotic use than NSE-patients, but there were no differences in pulmonary exacerbation rates or pulmonary function changes.

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KEY TAKEAWAYS

- Current evidence supports the use of three distinct AET protocols.
- Certain PA phenotypes may be suggestive of increased risk for failed AET.
- Although existing literature has not determined specific long-term clinical benefits associated with sustained PA eradication, the potential for long-term benefit may be inferred from extrapolation of short-term benefits and analysis of epidemiologic data.

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nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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