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eLITERATURE REVIEW
eCysticFibrosis Review

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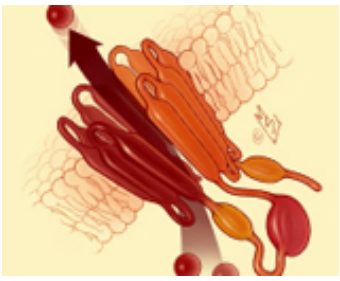

eCysticFibrosis Review VOLUME 5, ISSUE 3

P. aeruginosa eradication and reinfection

In this Issue...

Over the years, treatment of early *Pseudomonas aeruginosa* infection has become standard of care, with multiple studies demonstrating that *P. aeruginosa* can be successfully eradicated with antibiotic therapy. However, many questions remain unanswered. Are some patients at higher risk of treatment failure than others? How does this treatment perform in clinical practice? Are treatment options available other than those currently used? Can we use tests other than airway cultures to predict subsequent infection or to track patients that have been treated? In this issue, new evidence related to early *Pseudomonas aeruginosa* infection and its treatment will be discussed. This issue will address and try to find answers to these questions using new evidence that has become available through recently published study results.

LEARNING OBJECTIVES

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

- Discuss new data on the efficacy and effectiveness of eradication therapy directed against *Pseudomonas aeruginosa.*
- Describe factors affecting the success rate of eradication.
- Explain the role of anti-*Pseudomonas* antibodies in early *P. aeruginosa* infection.

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- Clinicians need guidance in understanding how new findings describing CFTR-modifying therapies may improve their treatment of patients with cystic fibrosis.
- Incomplete clinician awareness of genotype/phenotype correlations in non-pulmonary targets of CFTR-modifying therapies may limit their ability to provide optimal patient care.

Nutrition
- Clinicians lack effective guidance to increase caloric intake in patients who are nutritionally compromised.
- Clinicians do not fully understand how to manage the complexities of pancreatic enzyme replacement therapy to achieve optimal results in their patients.

Pseudomonas Aeruginosa
- Clinicians have unanswered questions about *P. aeruginosa* eradication in asymptomatic patients with positive cultures.
- New data and new choices for selecting initial inhaled anti-pseudomonal agents have created confusion.
- Conflicting data about pulmonary exacerbations has led to incorrect clinical assumptions and inappropriate treatment regimens.

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Guest Faculty Disclosures

The author has indicated that he has served as a consultant for Gilead Sciences and received grant funding from Novartis Pharmaceuticals.

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COMMENTARY

Treatment of early *Pseudomonas aeruginosa* infection has become a focus of attention over recent years. Preventing chronic infection, which negatively affects clinical status, is an important early intervention strategy that could positively affect patients' outcome. While the conventional view was that once *P. aeruginosa* is detected in airway secretions, the process is not reversible; multiple studies have now shown that eradication therapy is successful in the majority of patients. This has resulted in a recommendation for treatment in current

guidelines.[1] While in some countries in Europe eradication therapy was implemented more than a decade ago, this was primarily based on theoretical benefit of treatment rather than well-designed clinical trials. In the US, strategies for how clinicians have dealt with early *P. aeruginosa* varied greatly in the past, but treatment has now become standard of care in most centers. The recent data from the EPIC trial using a historical data set seem to reflect this change in clinical care and also support the concept that using a standardized protocol for treatment improves the chances of subsequent negative *P. aeruginosa* cultures. However, this study compared a clinical trial to another clinical care, and many aspects differed between the two settings. Nevertheless, the evidence that *P. aeruginosa* eradication therapy reduces subsequent culture positivity is rather strong. What is still missing are convincing data that these positive microbiological results translate into improved clinical outcomes. Data from our clinic suggest that patients who cleared *P. aeruginosa* infection do not differ in lung function decline over time from patients who were never infected, but these preliminary data need to be confirmed by additional studies.[2]

Currently, it is still not entirely clear which regimen is the most effective to treat early *P. aeruginosa* infection. Given the wealth of data with this treatment approach, and balancing efficacy with treatment burden, would favor the use a 28 days course of inhaled tobramycin administered as monotherapy. The ALPINE study provides evidence that inhaled aztreonam (AZLI) also is efficacious in treating early *P. aeruginosa* infection. However, the lack of a control group makes it difficult to compare this treatment strategy to other currently used regimens. It is thus unlikely that this study alone will result in a major shift of first line therapy for early *P. aeruginosa* infection from inhaled tobramycin to AZLI.

The study by Stanojevic et al, reviewed herein, did demonstrate the effectiveness of inhaled tobramycin in the clinical care setting. Assessing effectiveness rather than efficacy in clinical trials is meaningful for clinicians, as these data reflect how this treatment performs in real life. This is important as, although clinical trials rarely mimic how patients are being followed in routine care, this does not reduce their value in providing objective evidence. Thus effectiveness studies are additive in value and should not be seen as an alternative to the randomized controlled trial.

Overall, as initial eradication therapy has been shown to be highly successful, the focus of interest is shifting to patients who fail eradication therapy. The Stanojevic study also demonstrated risk factors for failure of *P. aeruginosa* eradication therapy. These risk factors largely represent clinical features that overall predict poorer outcome and may only reflect the fact that patients with a more severe phenotype have poorer mucociliary clearance and thus a higher risk of airway infection; whether this link is causally related to *P. aeruginosa* infection remains to be determined. Future studies should focus on second-line therapies for these at-risk patients so we can understand how best to use the different therapeutic options that are available and that so far have largely been studied as first-line therapy only. Potentially, cycling different agents could increase success of treatment, but evidence for this approach is currently lacking.

Finally, an additional biomarker that adds significant information to performing microbiological sampling alone could potentially improve our ability to define which patient group requires treatment of early *P. aeruginosa* infection. So far, the evidence is not supporting the routine of serum antibodies against *P. aeruginosa* in clinical care. The study by Daines et al, reviewed in this issue, nicely demonstrated that the predictive value of *P. aeruginosa* antibodies is not optimal; thus they cannot replace or add substantial value to respiratory cultures. As throat swabs have a relatively high negative predictive value, but a low positive predictive value, we currently treat a substantial number of patients with early eradication therapy who do not have lower airway infection with *P. aeruginosa*. Whether treating the upper airway with inhaled antibiotics prevents subsequent lower airway infection is an intriguing theory, but we lack evidence from clinical trials to support this hypothesis.

However, an important, well-designed randomized trial has demonstrated that guiding care of *P. aeruginosa* infection by routine bronchoalveolar lavage procedures, which are associated with substantial burden and cost, does not improve microbiological or clinical outcome.[3] Thus, while probably not optimal, current care using mostly throat swabs to diagnose *P. aeruginosa* infection may be sufficient for guiding treatment. Ultimately, CFTR modulation therapy may be the best way to reduce or prevent *P. aeruginosa* infection. Until such therapy becomes available, frequent monitoring and early initiation of *P. aeruginosa* eradication therapy remain important aspects of CF care.

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2. Amin R, Lam M, Dupuis A, Ratjen F. The effect of early *Pseudomonas aeruginosa* treatment on lung function in pediatric cystic fibrosis. *Pediatr Pulmonol*. 2011 Jun;46(6):554-558
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STANDARD CARE VERSUS PROTOCOL BASED THERAPY FOR NEW ONSET *P. AERUGINOSA*

Mayer-Hamblett N, Rosenfeld M, Treggiari MM,et al; EPIC; ESCF Investigators. Standard care versus protocol based therapy for new onset *Pseudomonas aeruginosa* in cystic fibrosis. *Pediatr Pulmonol*. 2013 Oct;48(10):943-953.

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This article represents an additional analysis of an interventional study comparing different treatment strategies to treat early *Pseudomonas aeruginosa* infection: the Early Pseudomonas Infection Control (EPIC) trial. The original trial did not demonstrate any significant differences in outcome for the treatment regimens studied; here the overall data set is pooled to assess whether treatment within this clinical trial resulted in a higher rate of *P. aeruginosa*-negative cultures compared to historical controls. The assumption was that in the historical data set, treatment was driven mainly by symptoms and not necessarily by the mere presence of *P. aeruginosa* in a respiratory culture (as was the case in the EPIC trial). The authors used data from the Epidemiological Study of Cystic Fibrosis[1] (ESCF) for the time between 1995 and 1998 as a historical control group. Outcome measures captured included: the rate of antipseudomonas therapy in response to a positive culture; hospitalization rates; and rates of *P. aeruginosa* positive cultures at follow-up.

As expected, all 304 participants of the EPIC trial received treatment after new onset of *P. aeruginosa* in respiratory cultures. This was the case in only 49% of the historical controls when a time window of 20 weeks after positive culture was chosen. Subsequent cultures were positive in 54% of the historical controls compared to 35 % of the EPIC trial participants ($P < 0.001$). Differences in hospitalization rates were not observed. The authors concluded that protocol-based therapy resulted in a lower rate of *P. aeruginosa* reoccurrence compared to the approach used in the historical cohort where treatment may be have been driven by symptoms rather than culture positivity alone.

The study asks an important question, as we need to understand whether a protocol-based treatment approach will improve outcome. However, the historical data set is likely heterogeneous as some centers may already have used a proactive approach to early *P. aeruginosa* infection while others may have used a more reactive strategy waiting for symptoms to occur. This is difficult to ascertain in a retrospective data set where symptoms are not well captured. Therefore, what has triggered physicians to initiate treatment is largely based on assumptions. Strategies may even have varied considerably between physicians at a given center. It is also unclear whether the protocol based approach has a similar success rate in clinical care where patients are less rigorously tracked compared to a controlled trial. A comparison that better reflects clinical care would therefore be to compare the historical data set to a data base analysis over recent years when eradication therapy has become standard

of care in most centers. Nevertheless, the data support the concept that a standardized eradication protocol will reduce the rate of *P. aeruginosa* positive culture on follow-up. Whether the introduction of eradication therapy into clinical practice has resulted in a lower rate of *P. aeruginosa* positive cultures cannot be proven with the current analysis of the study data, but this is highly likely based on previous observational data from Europe.

References

1. Morgan WJ, Butler SM, Johnson CA, et al. Epidemiologic study of cystic fibrosis: design and implementation of a prospective, multicenter, observational study of patients with cystic fibrosis in the U.S. and Canada. *Pediatr Pulmonol*. 1999 Oct;28(4):231-241

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EFFECTIVENESS OF INHALED TOBRAMYCIN IN ERADICATING *P. AERUGINOSA*

Stanojevic S, Waters V, Mathew JL, Taylor L, Ratjen F. Effectiveness of inhaled tobramycin in eradicating *Pseudomonas aeruginosa* in children with cystic fibrosis. *J Cyst Fibros*. 2014 Mar;13(2):172-8.

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The current evidence of efficacy of inhaled tobramycin to treat early *Pseudomonas aeruginosa* infection is largely derived from controlled clinical trials, the current standard to prove that an intervention is successful. However, it is also important to clarify whether the success rate seen in a clinical trial can be assumed to also occur in a clinical setting. In this study, the effectiveness of two eradication protocols used in the Toronto CF center was assessed retrospectively. In addition, factors predicting treatment failure were also studied in this data set.

Data from the Toronto data base for the years of 2005 to 2012 were included in this analysis; in addition a medical chart review was conducted to validate the treatment data. The two treatment strategies used included an off-label regimen of 80 mg tobramycin bid for 12 months (as used in a previously conducted double blind placebo controlled trial)[1] and 28 days of 300 mg tobramycin inhalation solution (TIS) as used in the ELITE study. [2] Effectiveness was assessed for both 1) eradication rates and 2) the development of chronic *P. aeruginosa* infection. In addition, risk factors for treatment failure were determined in the overall cohort.

Of 65 patients with incident *P. aeruginosa*-positive cultures, inhaled tobramycin treatment was effective in clearing the organism in 58 patients or 89% of cases. Eradication rates did not differ between the two treatment regimens. Only four patients (6%) developed chronic *P. aeruginosa* infection. Risk factors for recurrence or lack of clearance included female gender, poorer lung function, worse nutritional status, older age, and pancreatic insufficiency. Thus, both treatment regimens had a similar effectiveness in clinical practice compared to what was previously observed in the controlled trials. However, treatment is not universally effective, raising the question of whether a subgroup of patients should be treated more aggressively or with a different regimen.

Obtaining information of effectiveness in routine clinical care adds important additional information to that obtained in randomized control trials. Many factors differ between the two settings, with clinical trials providing a more rigid structure for both treatment regimens and follow-up. In addition, patients participating in clinical trials may not share the same characteristics as the complete clinic population, as this usually reflects a highly motivated and potentially more adherent group of patients and families. It is therefore reassuring that the success rate of *P. aeruginosa* eradication therapy is equally high in clinical practice. While defining risk factors for treatment failure is relevant, treatment is also successful in the majority of patients sharing these characteristics. Female gender and poor nutritional status are known risk factors for poorer outcome in CF; whether a lower success rate of clearing *P. aeruginosa* explains part of these differences is currently unknown. Pancreatic insufficiency, another

factor that was associated with a higher rate of treatment failure, is linked to more severe (class I to III) genotypes, and a more severe genotype may render a patient more prone to develop chronic *P. aeruginosa* infection. Finally, poorer lung function may reduce the efficacy of an inhaled medication being deposited homogeneously in the airways; whether in this scenario systemic therapy could be beneficial is currently unknown.

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2. Ratjen F et al. Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax* 2010; 65: 286-291.

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THE ALPINE STUDY: INHALED AZTREONAM FOR *PSEUDOMONAS* ERADICATION

Tiddens HA, De Boeck K, Clancy JP; for the ALPINE study investigators. Open label study of inhaled aztreonam for *Pseudomonas* eradication in children with cystic fibrosis: The ALPINE study. *J Cyst Fibros*. 2014 Aug 1.

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Different treatment regimens have been used for eradication therapy in early *Pseudomonas aeruginosa* infection, with most including an inhaled antibiotic. The best studied regimens include tobramycin in different concentrations and treatment durations and the combination of inhaled colistin (off label in the US) combined with oral ciprofloxacin. Aztreonam lysine for inhalation solution (AZLI) has been extensively studied in patients with chronic *P. aeruginosa* infection; whether it can also be used in early *P. aeruginosa* infection is currently unknown. The Aztreonam Lysine for *Pseudomonas* Infection Eradication (ALPINE) study assessed both safety and efficacy of AZLI in patients with new onset *P. aeruginosa* infection in a single-arm, open-label trial. Patients included had to be between three months and 18 years of age, have either a first lifetime *P. aeruginosa* infection or a new onset of infection after at least two years of negative cultures based on at least two cultures for a given year. Patients were treated with 75 mg AZLI three times daily for 28 days similar to the treatment regimen used in chronic *P. aeruginosa* infection. Treatment success was based on microbiological culture results of respiratory samples (throat swabs or sputum) obtained at baseline, and end of therapy at 4, 8, 16, and 28 weeks. Of 105 patients enrolled, 101 completed treatment. No relevant safety issues were identified. Eighty-nine percent were *P. aeruginosa*-culture negative at the end of treatment, 75% at eight weeks, and 58% of patients were free of *P. aeruginosa* at all post-treatment time points. The authors concluded that AZLI is safe and effective in eradicating *P. aeruginosa* in early or new infection in children with CF and that the success rate is consistent with what was previously reported for other regimens.

While the study adds to the growing body of literature on the success of eradication therapy by adding another potential treatment option, there are some limitations in performing an open-label study without a control group, be it active or placebo. Rate of adverse events cannot be compared to what is seen with other compounds; it is thus difficult to appreciate whether any drug-specific safety signals are observed. Efficacy rates have varied between different trials as have inclusion criteria; thus, comparisons between studies are rather problematic. The success rate after cessation for therapy of 75% is somewhat lower than has been reported in studies using inhaled tobramycin, but direct comparisons would require a head-to-head trial. Eradication rates were above 50% after 27 months in the ELITE trial; whether the long-term efficacy for inhaled AZLI is similar still needs to be confirmed by a data set extending beyond 6 months.

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SEROLOGY AS A DIAGNOSTIC TOOL FOR PREDICTING INITIAL *P. AERUGINOSA* ACQUISITION

Daines C, VanDeVanter D, Khan U, et al; EPIC Investigators. Serology as a diagnostic tool for predicting initial *Pseudomonas aeruginosa* acquisition in children with cystic fibrosis. *J Cyst Fibros*. 2014 Sep;13(5):542-549.

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This manuscript is also based on an additional analysis using data from the Early *Pseudomonas* Infection Control (EPIC) study. One of the challenges of defining infection status in patients with early *Pseudomonas aeruginosa* infection is that many of these patients will not produce sputum, so the microbiological diagnosis thus has to rely on throat swabs, which are unreliable in their specificity. It would thus be ideal to have additional diagnostic tools that can help in this setting. *P. aeruginosa* antibodies have been used in European centers for many years, but their diagnostic value is still controversial. Ideally, *P. aeruginosa* antibodies would predict subsequent infection as they could then be used as an early indicator to guide treatment decisions.

This study evaluated whether *P. aeruginosa* serology predicts infection in the subsequent 12 months in young patients with cystic fibrosis; the population where obtaining respirator cultures largely has to rely on throat swabs. As part of the EPIC observational study, 582 patients had annual measurements of *P. aeruginosa* antibodies performed. A commercial ELISA kit that has been used in previous studies in Europe was used to determine antibodies against three *P. aeruginosa* epitopes: alkaline phosphatase, elastase, and exotoxin A. Ninety-four healthy controls, in whom a single sample was obtained, were also included. Cutoffs for antibodies were determined using receiver operator curves. Overall, 2084 serum samples were available for analysis. While group differences could be observed between patients developing *P. aeruginosa* infection and those who did not, overlap was substantial. The maximum positive predictive value was 76 % for either using one antibody alone or a combination of antibodies; the negative predictive value was similar. No differences were seen for the six versus 12 months predictive value. Thus, *P. aeruginosa* serum antibodies were found not to be highly predictive of subsequent *P. aeruginosa* infection.

While somewhat disappointing, these results are not surprising. Previous studies have shown group differences between patients developing *P. aeruginosa* infection and those that do not, but variability was considerable and it was therefore unlikely that this test could be used to guide clinical care in individual patients. There are some limitations to this study, as a more frequent determination of *P. aeruginosa* antibodies could potentially increase the precision of the estimate, but frequent sampling is unlikely to be used in the clinic. Other antibody assays may be more sensitive, but determining specifics would require a comparative trial. Overall, these data support the concept that the superior test to diagnose infection is still to perform respiratory cultures, and that frequent sampling may be the best way to ensure that *P. aeruginosa* infection is captured early.

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PREDICTIVE VALUES OF ANTIBODIES AGAINST *P. AERUGINOSA* ONE YEAR AFTER EARLY ERADICATION TREATMENT

Kappler M, Nagel F, Feilcke M, et al. Predictive values of antibodies against *Pseudomonas aeruginosa* in patients with cystic fibrosis one year after early eradication treatment. *J Cyst Fibros*. 2014 Sep;13(5):534-541.

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This study addresses another scenario: how the assessment of *Pseudomonas aeruginosa* antibodies could be helpful in the clinical setting. A previous study had already demonstrated that in patients who clear *P. aeruginosa* from their airways, *P. aeruginosa* antibody titers

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decline, while they increase in those patients in whom eradication therapy failed.[1] In this study, the authors took this one step further and assessed how well *P. aeruginosa* antibodies predict success of eradication therapy.

Fifty-three patients who developed *P. aeruginosa* within a four-year time period in the Munich CF center were included in this analysis, reflecting an annual new infection rate of 8.5% (quite similar to what had been reported previously). Eradication therapy was successful in 60% of patients. Using the same ELISA assay as described in the analysis of the EPIC study, the authors preformed a retrospective chart review of previously obtained clinical samples obtained yearly as part of routine clinical care. The positive predictive value of P. aeruginosa antibodies was 75%; the negative predictive value was 82%. The authors concluded that *P. aeruginosa* antibodies can predict treatment success of eradication therapy.

However, while the data are consistent with the concept that *P. aeruginosa* antibodies can provide supportive evidence for eradication, their diagnostic precision is not high. In addition, the study suffers from the key problem that comparing *P. aeruginosa* antibodies to throat swabs (not considered a reliable sample in young children) does not provide comparison to the "gold standard" of respiratory cultures. It would therefore be potentially more meaningful to assess the diagnostic value of *P. aeruginosa* antibodies by comparing them to sputum or BAL samples. Thus, despite describing a positive result, this study is unlikely to change the fact that, based on the currently available data, *P. aeruginosa* antibodies are of limited additional value in guiding clinical care in CF patients with early *P. aeruginosa* infection.

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