JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eCysticFibrosis Review

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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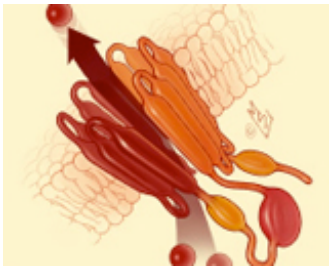

Editor's Note: Look out for eCysticFibrosis Review Special Edition; *a two-part series highlighting on some of the key information presented at the European Cystic Fibrosis Society (ECFS) Conference in Lisbon, Portugal June 12-15, 2013*.

eCysticFibrosis Review VOLUME 4, ISSUE 5

P. aeruginosa Eradication

In this Issue...

In patients with cystic fibrosis, chronic endobronchial infection with *Pseudomonas aeruginosa* (*Pa*) is associated with a greater morbidity and mortality. Early *Pa* isolates tend to be highly antibiotic-susceptible and present at low density. Thus, a "window of opportunity" exists to eradicate *Pa* before infection becomes chronic. Early *Pa* eradication is now standard of care around the world, but the most effective regimen remains a highly contested topic.

In this issue, we review the results of four important clinical trials of early *Pa* eradication therapies that, together, begin to answer the question, "How shall I most safely and effectively treat my patient who has new isolation of *Pa* from a respiratory culture?" The comparative efficacy of different treatment regimens is described, similarities and differences in study design of the four trials are identified, and potential negative consequences of early eradication therapy are discussed. Finally, suggested next steps in evaluating the safety and efficacy of early eradication therapy are outlined.

LEARNING OBJECTIVES

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

- Distinguish between existing, newly available, and investigational inhaled antibiotics for treating chronic pulmonary infections
- Identify appropriate use and selection of inhaled therapies in combination
- Evaluate current evidence describing the use of intermittent, continuous, cycled inhaled antibiotics therapies to suppress airway infections
- Recognize and apply best practices in managing pulmonary exacerbations
- Incorporate evidence-based strategies and newly available technologies to improve patient adherence to inhaled medication

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June 26, 2015

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STATEMENT OF NEED

Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

Disease-Modifying Therapies

- Clinicians may be unfamiliar with recently introduced disease-modifying therapies and how they are altering the therapeutic landscape for patients with cystic fibrosis.
- Clinicians may be uncertain how to integrate genotyping into therapeutic decisions and how to communicate with patients and families about the relationship between genotype and therapy

Nutrition

- Many clinicians lack strategies to persuade patients to adhere to CF nutritional requirements, resulting in low body weight and nutritional failure in patients with cystic fibrosis.
- Many clinicians remain uncertain how to optimize pancreatic function in patients with cystic fibrosis.

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Treating CF Patients with Inhaled Antibiotics

- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.
- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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Guest Faculty Disclosures

The author has indicated that she has received grants/research support from Vertex and has served as a consultant for Genentech.

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COMMENTARY

In patients with cystic fibrosis (CF), chronic endobronchial infection with *Pseudomonas aeruginosa (Pa)* is associated with a greater rate of pulmonary exacerbations, loss of lung function and greater mortality.[1-3] Initial acquisition of *Pa* is generally from the environment, and early *Pa* isolates tend to be highly antibiotic- susceptible and present

at low density. Thus, a "window of opportunity" exists to eradicate *Pa* before infection becomes chronic.[4] The Danish CF Clinic pioneered early *Pa* eradication therapy more than 20 years ago[5] and has demonstrated improved long-term outcomes.[6] While early *Pa* eradication is now the standard of care around the world, the most effective regimen remains a highly contested topic. In many European countries, a combination of inhaled colistin and oral ciprofloxacin, often for three months, is employed,[7] while in North America, 28 days of inhaled tobramycin is the most widely employed antibiotic, with or without oral ciprofloxacin.

Over the past several years, the results of several important clinical trials of early *Pa* eradication therapies have been published. These studies begin to answer the question, "How shall I most safely and effectively treat my patient with new isolation of *Pa* from a respiratory culture?" As the studies reviewed herein describe, the results have not necessarily been those expected in this era of ever-increasing aggressiveness of care in our CF patients. These four studies all converge on the same conclusion: that 28 days of inhaled tobramycin is in general quite effective in eradicating *Pa* and that longer or repeated courses of inhaled tobramycin, adding oral ciprofloxacin, or using three months of inhaled colistin and oral ciprofloxacin, are no more effective. All regimens were safe in the short term, though with one potential cautionary note: in both the EPIC trial (comparing four regimens all including inhaled tobramycin) and the trial by Taccetti, et al (comparing 28 days of inhaled tobramycin and oral ciprofloxacin vs 28 days of inhaled colistin and oral ciprofloxacin), up to 20% of participants developed new respiratory infection with *Stenotrophomonas maltophilia*, a tobramycin-resistant, gram negative organism of unclear pathogenicity. Interestingly, this finding was not seen in the ELITE trial comparing 28 to 56 days of inhaled tobramycin (these three trials are reviewed in this issue). Thus, as is so often the case in CF, treatment directed toward one organism probably alters the homeostasis of the complex polymicrobial community in the CF airway. The impact on clinical outcomes of this microbiologic finding is currently unclear.

It should be mentioned that a limitation of all these studies is the reliance on throat swabs to diagnose *Pa* respiratory infection, because of the invasive nature of bronchoalveolar lavage. Treatment decisions based on the results of oropharyngeal cultures may lead to "overtreatment," as the low positive predictive value of throat swabs in this population means that throat swabs tend to overestimate the prevalence of *Pa* in the lower airway.[8] Nonetheless, in many countries, treatment decisions are based on the results of throat swabs, as the presence of *Pa* in the upper airway may convey an increased risk of subsequent lower airway infection.[3]

What are the next steps in studying the safety and efficacy of *Pa* eradication regimens? First, while in general these regimens are highly effective, 10% to 30% of patients in each of these studies failed eradication therapy. Understanding how to treat these patients is critical to minimizing the burden of morbidity associated with chronic *Pa* infection. Second, and perhaps tied to the first step, is a better understanding of the role of intravenous antibiotics in early eradication therapy. In a small cohort of clinically stable children with CF and new *Pa* infection (N = 15, six of whom received IV antibiotics), Noah et al,[9] performed bronchoalveolar lavage before and four to six weeks after treatment with two weeks of systemic antibiotics or four weeks of inhaled tobramycin. While both groups had similar reductions in bacterial load after therapy, those in the systemic group had a significantly greater reduction in markers of inflammation (lower airway total cells and percent neutrophils). Though intriguing, a larger study would be required to change clinical practice. Last, longer-term follow-up of patients receiving early eradication therapy will be critical to monitoring both efficacy and safety of this approach. The participants in the clinical trials reviewed in this issue were in general healthy, with relatively preserved lung function and few pulmonary exacerbations. No differences between groups in short-term (up to two years) clinical outcomes was detected, but the effects over much longer time periods are relatively unknown.[6] Finally, long-term effects on airway microbiology (such as the finding of possibly increased prevalence of Stenotrophomonas maltophilia) must be further evaluated.

In summary, on the whole, these studies demonstrate that early *Pa* eradication regimens are relatively effective, and that "less may be more," in that 28 days of inhaled tobramycin (or possibly colistin) appears as effective as any other regimen tested. Hopefully, we are ushering in an era in which early *Pa* eradication delays or prevents chronic *Pa* infection, resulting in fewer hospitalizations and better long-term outcomes for our CF patients.[6,10]

Commentary References

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THE ELITE TRIAL: A COMPARISON OF 28 AND 56 DAYS OF INHALED TOBRAMYCIN TO TREAT EARLY *Pseudomonas aeruginosa* INFECTION

Ratjen F, Munck A, Kho P, Angyalosi G. **Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial.** *Thorax.* 2010;65(4):286-291.

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The aim of the EarLy Inhaled Tobramycin for Eradication (ELITE) study was to evaluate the safety and efficacy of two regimens of tobramycin solution for inhalation (TSI) – 28 and 56 days of TSI 300 mg 5/mL twice daily – for the treatment of early onset *Pseudomonas aeruginosa* (*Pa*) infection in patients with CF. The investigation was a two-arm, randomized

study conducted at 21 European centers between 2003 and 2008. Participants had to be at least 6 months of age with first or early *Pa* infection (defined as new isolation of *Pa* from a respiratory culture after four negative cultures in the preceding year or two years without antipseudomonal therapy). All participants received TSI for 28 days, at which point they were randomized 1:1 to either stop study drug (28-day group) or receive an additional 28 days of TSI (56-day group). In addition, patients were excluded from randomization if anti-pseudomonal serology collected at day 1 was positive (any titer ≥ 1000 for IgG against exotoxin A, alkaline protease, or elastase). Of the studies reviewed in this issue, this is the only one that incorporated *Pa* serology in the eligibility criteria. Randomized participants had regular study visits, monthly for the first year and then quarterly, until either a respiratory culture was positive for *Pa* or for 26 months. The primary outcome was the median time to recurrence of *Pa*.

A total of 123 patients were recruited into the study, and 88 were randomized (31 patients were excluded because of positive *Pa* serology and four for other reasons). Of the 88 randomized participants, 65 were included in the efficacy evaluable population, 34 and 31 in the 28- and 56-day TSI groups, respectively. The median time to *Pa* recurrence was similar between the two groups (26.1 and 25.8 months after TSI in the 28- and 56-day groups, respectively, HR 0.81, 95% CI 0.37 to 1.75, P = 0.59). At the final study visit, 66% and 69% of participants remained *Pa*-free in the 28-day (n = 36) and 56-day (n = 41) groups, respectively. Results were similar for sputum producers and nonproducers. Results were similar in participants with normal vs reduced lung function at baseline. Among the 21 patients in whom paired *Pa* isolates were available, the isolates had the same genotype in 12 and different genotypes in 9. Adverse events were similar between the two groups, as were treatment-emergent respiratory pathogens.

This study demonstrates that 28 and 56 days of TSI are both highly effective in eradicating early *Pa* infection, and there is no advantage to a longer course of therapy. Over 90% of participants had negative cultures for *Pa* one month after the end of treatment, and two-thirds were still *Pa*-negative for up to 27 months in both groups. While inhaled antibiotics may not reach all areas of the lungs because of mucus plugging or peripheral airway obstruction, in this population with relatively mild disease (mean FEV_1 ~ 83% predicted), efficacy of TSI was high. The primary endpoint was microbiologic efficacy rather than clinical outcomes. Lung function on average remained stable in both groups during the study period, but a longer term trial would be required to evaluate clinical efficacy.

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THE EPIC TRIAL: A COMPARISON OF FOUR REGIMENS INVOLVING INHALED TOBRAMYCIN TO TREAT EARLY *Pseudomonas aeruginosa* INFECTION

Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, et al. **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(9):847-856.

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The aim of the Early Pseudomonas Infection Control (EPIC) Trial was to compare the efficacy and safety of 4 anti-pseudomonal antibiotic regimens in children with CF with new *Pseudomonas aeruginosa* (*Pa*) infection. The study was a four-arm, randomized study conducted at 35 US centers between 2004 and 2009. Duration of study participation was 18 months. Participants had to be 1 to 12 years of age with new isolation of *Pa* from a respiratory tract culture within the six months preceding randomization. New isolation of *Pa* was defined as first lifetime documented *pa*-positive culture or a *Pa*-positive culture after at least a two-year absence of *Pa*. Participants were allowed one course of intravenous or inhaled antipseudomonal antibiotics before enrollment.

The study was designed to compare culture-based therapy (antibiotics administered quarterly regardless of results of respiratory cultures) vs cycled therapy (antibiotics administered only during quarters in which respiratory cultures were positive for *Pa*) as well as the addition of systemic antibiotics (ciprofloxacin) to inhaled antibiotics (tobramycin inhalation solution, TIS). Thus, participants were randomized equally to one of four groups: (1) cycled TIS and oral ciprofloxacin, (2) cycled TIS and oral placebo, (3) culture-based TIS and oral ciprofloxacin, (4) culture-based TIS and oral placebo. The antibiotic regimen administered during treatment cycles consisted of TIS 300 mg nebulized twice daily for 28 days and either ciprofloxacin 15 to 20 mg/kg twice daily or oral placebo for the first 14 days. At the beginning of the study, all participants received an initial treatment cycle according to their assigned group, and a second consecutive 28-day course of TIS if cultures obtained during the third week of the first cycle were positive for *Pa*. The primary clinical endpoint was time to first pulmonary exacerbation requiring IV antibiotics or hospital admission. The primary microbiological endpoint was the proportion of *Pa*-positive respiratory cultures among all quarterly cultures obtained after the initial treatment cycle.

A total of 304 participants were randomized equally to each of the 4 treatment groups (76 per arm) and included in the intent-to-treat population. While all study participants, as defined by the eligibility criteria, had a *Pa*-positive respiratory culture within six months before enrollment, 46% received antipseudomonal therapy during the six months preceding enrollment, and only 40% had *Pa*-positive cultures at the time of randomization. After the initial course of TSI, participants in the cycled-therapy group received on average six additional 28-day courses of TSI over the 18 month study period, while those in the culture-based group received on average only one additional course.

Overall, there was no difference between groups in the proportion of participants experiencing a pulmonary exacerbations requiring IV antibiotics or hospitalization: 24/152 (16%) in the cycled therapy group, 26/152 (17%) in the culture-based group, 29/152 (19%) in the ciprofloxacin group, and 21/152 (14%) in the placebo group. Similarly, the odds of a *Pa*-positive culture were similar between treatment groups (OR 0.78, 95% CI 0.49 to 1.23 comparing cycled vs culture-based therapy and OR 1.10, 95% CI 0.71 to 1.71 comparing ciprofloxacin vs placebo). All four regimens were effective in eradicating *Pa*. The majority of participants had no *Pa*-positive cultures after the first treatment cycle (57 to 74%, depending on the arm), and among those who did have recurrence of *Pa*, the majority had no more than two *Pa* positive cultures over the 18-month study. Growth and lung function outcomes were also similar between groups. The emergence of mucoid *Pa*, tobramycin-resistant and ciprofloxacin-resistant *Pa* was low and similar in all 4 groups (0 to 4%). Although not different between groups, the rate of treatment-emergent acquisition of Stenotrophomonas maltophilia was up to 20%. The clinical implications of acquiring this tobramycin-resistant gram-negative organism are unclear. Adverse events and safety were similar between groups, except participants assigned to ciprofloxacin had a greater frequency of cough than those assigned to placebo.

This study demonstrates that cycled and culture-based therapy are equally effective in terms of clinical endpoints (pulmonary exacerbations, growth, lung function) and microbiologic efficacy. All treatment regimens were highly effective, and the addition of oral ciprofloxacin to inhaled tobramycin did not improve outcomes. Thus, this study suggests that treatment of new *Pa* with inhaled tobramycin monotherapy is as effective as more aggressive culture-based regimens or adding oral ciprofloxacin.

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INHALED TOBRAMYCIN AND ORAL CIPROFLOXACIN FOR 28 DAYS VS INHALED COLISTIN AND ORAL CIPROFLOXACIN FOR 28 DAYS TO TREAT EARLY *Pseudomonas aeruginosa* INFECTION

Taccetti G, Bianchini E, Cariani L, et al. **Early antibiotic treatment for *Pseudomonas aeruginosa* eradication in patients with cystic fibrosis: A randomised multicentre study comparing two different protocols.** *Thorax.* 2012;67(10):853-859.

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The aim of the study by Taccetti and colleagues was to compare the efficacy of two 28-day anti-pseudomonal antibiotic regimens in children with CF with new *Pseudomonas aeruginosa* infection: inhaled tobramycin and oral ciprofloxacin (tobra-cipro) vs inhaled colistin and oral ciprofloxacin (colistin-cipro). The study was a two-arm, open-label randomized investigation conducted at 13 European centers between 2008 and 2010. Participants had to be > 1 year of age with first or new *Pa* infection, defined as a *Pa*-positive culture after three negative cultures in the previous six months.

The primary endpoint was *Pa* eradication, defined as three successive negative cultures in six months. Participants were randomized to receive oral ciprofloxacin (30 mg/kg/day in two divided doses) and either colistin (1 million IU nebulized twice daily) or tobramycin inhalation solution (300 mg nebulized twice daily) for 28 days. Participants were evaluated two, four, and six months after the study treatment and then monitored during routine clinic visits for variable periods (median length of observation 16 months, range 12-28 months).

A total of 223 patients were randomized, 105 to colistin-cipro and 118 to tobra-cipro. About half the participants in each group had previous *Pa* infection before trial entry: 54% and 47% in the colistin-cipro and tobra-cipro groups, respectively. Forty percent of participants were expectorators at enrollment. *Pa* eradication (as defined by three successive negative cultures in six months) was achieved in 63% and 65% of participants in the colistin-cipro and tobra-cipro groups, respectively. Note that the definition of eradication is stricter than in the other trials, so a direct comparison of microbiologic efficacy cannot be made. The proportion achieving eradication was similar in those with first-ever *Pa* infection (66%) and those with prior *Pa*-positive cultures (62%). Genotyping was performed on paired *Pa* isolates from 47 participants at baseline and within 6 months after treatment. The same genotype was found in 36 isolate pairs and a different genotype in 11 isolate pairs. Similar to the EPIC trial, treatment-emergent *Stenotrophomonas maltophilia* was found in 18% of participants during the follow-up period (median length of follow up 16 months) and *Achromobacter xylosoxidans* in 6%.

This study demonstrates that 28 days of inhaled tobramycin and oral ciprofloxacin or inhaled colistin and oral ciprofloxacin appear equally effective in terms of microbiologic efficacy. Efficacy of the two regimens was not significantly different in those with first-ever *Pa* infection and those with prior *Pa* infection, nor in strata of high vs lower lung function or of age. The overall microbiologic efficacy rate in this study appears lower than in either the ELITE or EPIC trials. However, this statement must be interpreted with caution because of different eligibility criteria (the ELITE and EPIC trials both required at least one year with negative cultures in those with prior *Pa* infection, whereas Taccetti and colleagues required only six months), participant characteristics and definition of microbiologic efficacy. The ELITE trial evaluated time to first recurrence of *Pa*, the EPIC trial evaluated the proportion of *Pa*-positive respiratory cultures among all quarterly cultures obtained after the initial treatment cycle, and Taccetti and colleagues evaluated *Pa* eradication, defined as three successive negative cultures in six months. In addition, similar to the EPIC trial, *Stenotrophomonas maltophilia* was newly isolated from respiratory cultures in about 20% of participants after treatment. This observation was not found in the ELITE trial, and its clinical significance remains unclear.

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INHALED TOBRAMYCIN FOR 28 DAYS VERSUS INHALED COLISTIN AND ORAL CIPROFLOXACIN FOR 3 MONTHS TO TREAT EARLY *Pseudomonas aeruginosa* INFECTION

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(1):29-34.

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The most common *Pseudomonas aeruginosa* (*Pa*) eradication regimen in Europe is inhaled colistin and oral ciprofloxacin, closely followed by inhaled tobramycin. In North America, the most common *Pa* eradication regimen is inhaled tobramycin. Proesmans and colleagues undertook a study to compare the microbiologic efficacy of these 2 regimens via a single-center open label trial conducted between 2004 and 2010. Participants were CF patients at their clinic < 18 years of age with first-ever *Pa* infection or new *Pa* infection after at least six months *Pa*-free (as documented by at least three negative cultures). Participants were randomized to oral ciprofloxacin (30 mg/kg/day) combined inhaled colistin, 2 million units inhaled twice daily for three months (cipro-colistin), or tobramycin inhalation solution (TIS) 300 mg nebulized twice daily for 28 days. Study duration was one year with follow-up for *Pa* status for two years. The primary outcome was *Pa* eradication at the end of the treatment (ie, at three months [cipro-colistin] or 28 days [TIS]). If the respiratory culture was still *Pa*-positive at the end of the treatment period, participants were changed to other treatment group.

A total of 58 participants were enrolled, 29 in each group. Ten participants in the cipro-colistin group and 8 in the TIS group had first-ever *Pa* infection, a lower proportion than in the other three studies reviewed. *Pa* eradication at the end of treatment was similar in both groups: 90% in the cipro-colistin group and 79% in the TIS group (relative risk 0.88, 95% CI 0.71-1.11). Three participants failed eradication in the cipro-colistin group and six participants failed

eradication in the TIS group. Median time to *Pa* recurrence was nine months for the cipro-colistin group and five months for the TIS group, shorter than the median time to *Pa* recurrence of 26 months in the ELITE study. In participants with successful eradication with the study drug, *Pa* status at one year after treatment was *Pa*-free/intermittent/chronic in 13/13/0 patients, respectively, in the cipro-colistin group and 13/8/1 in the TIS group (P = 0.46). Of the 47 participants followed for two years, five (10%) developed chronic *Pa* infection. There was no difference between the two groups in the number of days of either oral or IV antibiotics for a pulmonary exacerbation, lung function or nutritional status. Adverse events were not described, except for one participant who was intolerant of TIS and changed to cipro-colistin. Treatment-emergent respiratory pathogens were not described.

This study demonstrates that three months of inhaled colistin plus oral ciprofloxacin and 28 days of inhaled tobramycin monotherapy both have high and similar microbiologic efficacy, with 80-90% eradication at the end of therapy. However, median time to relapse was relatively short, nine and five months, respectively. In the ELITE trial, inhaled tobramycin for 28 days was associated with a median time to relapse of 26 months. The apparent longer duration of efficacy in the ELITE trial may be related to their entry criteria, with 60% of ELITE trial participants having first-ever *Pa* infection and a requirement for one to two years *Pa*-free and negative *Pa* antibodies for randomization. In this study by Proesmans and colleagues, only one-third of participants had a first-ever *Pa* infection, and in 25% of patients with previous *Pa* isolation this occurred < 12 months before enrollment.

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