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eLITERATURE REVIEW
eCysticFibrosis Review

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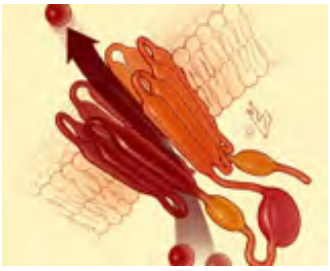

eCysticFibrosis Review VOLUME 5, ISSUE 13

Antipseudomonal agents for the management of *P. aeruginosa* infection

In this Issue...

In this issue, we describe new approaches to treatment of chronic *Pseudomonas aeruginosa* infection in people with cystic fibrosis. New research reviews:

• The role of alternative inhaled antibiotics for treatment of chronic *P. aeruginosa* infection. Two new inhaled antibiotics, aztreonam and levofloxacin, are compared in clinical trials against standard-of-care treatment with inhaled tobramycin.
• Evidence for the role of CFTR modulators in helping to treat and potentially eliminate airway infection with *P. aeruginosa*.
• The pathophysiology of CF pulmonary exacerbations and new research suggesting that exacerbations are not associated with acute increases in *P. aeruginosa* density within the airway.
• The potential for antibiotic therapy guided by biofilm susceptibility testing to improve clinical outcomes in patients with acute CF pulmonary exacerbations.

LEARNING OBJECTIVES

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

- Describe recent clinical trials of inhaled antibiotics for treatment of chronic *P. aeruginosa* infection.
- Discuss the impact potential of treatment with CFTR correctors/potentiators on chronic *P. aeruginosa* infection.
- Summarize new findings describing to *P. aeruginosa* airway dynamics and biofilm antibiotics susceptibility testing in acute CF pulmonary exacerbations.

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Length of Activity
1 hour Physicians
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Release Date
October 27, 2015

Expiration Date
October 26, 2017

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IN THIS ISSUE

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COMMENTARY

Treatment of chronic *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF) can be frustrating because in the vast majority of cases, the infection within the airways can never be eradicated[1]. Nevertheless, significant optimism was generated 15 years ago, when randomized, controlled trials of inhaled tobramycin demonstrated decreases in sputum density of *P. aeruginosa*, associated with improved FEV_1 and fewer exacerbations in patients with CF patients who received three 28 day on/off cycles of inhaled tobramycin[2]. Inhaled tobramycin therapy thus soon became a standard of care for patients with CF infected with *P. aeruginosa*. However, evidence suggests that with repeated cycles of administration, bacterial resistance to tobramycin increases, and the positive effects on lung function of inhaled tobramycin potentially wane over time[2]. Hence the need for the discovery of new inhaled antibiotics that might replace inhaled tobramycin or potentially be added to existing treatment with inhaled tobramycin.

The studies by Assael et al and Elborn et al, reviewed in this issue, address the issue of finding new inhaled antibiotics to treat chronic *P. aeruginosa* infection. Both are comparator studies that compare a new antibiotic against treatment with the existing standard therapy of inhaled tobramycin. Neither study is perfect, since both use an open-label design that is subject to potential bias in ascertainment of outcomes. The study by Assael et al suggests

that treatment with inhaled aztreonam over three 28-day alternating cycles results in greater improvements in lung function and fewer exacerbations compared to treatment with standard therapy with inhaled tobramycin. Of potential concern, the beneficial FEV_1 effect of aztreonam seemed to wane with subsequent repeated cycles. In contrast, the study by Elborn et al was not able to show a significantly greater effect of inhaled levofloxacin on lung function compared to inhaled tobramycin.

Given the evidence from these studies, it seems reasonable for clinicians to consider inhaled aztreonam in 28-day on/off cycles as an alternative treatment regimen to inhaled tobramycin for treatment of chronic *P. aeruginosa* infection. However, the question of real importance to clinicians who treat CF would be whether alternating successive 28-day therapy with tobramycin and aztreonam would be more effective than the current standard of 28 days on/28 days off antibiotic treatment cycles. Hopefully, this question will be answered in the recently completed (but results not yet available) phase 3 AZLI CAT study, which randomized patients with CF to alternating cycles of tobramycin with aztreonam compared to alternating cycles of tobramycin with placebo.[3]

Modulation of CFTR using corrector and potentiator small molecules may become "the future of CF treatment." One important question is whether CFTR modulation will have an effect on airway infection in patients who already have established bronchiectasis and chronic endobronchial *P. aeruginosa* infection. The study by Heltshe et al reviewed herein provides some hope that CFTR modulation may have an impact on *P. aeruginosa* infection. In patients with the G551D mutation, a significant proportion who were sporadically infected with *P. aeruginosa* became "sputum culture negative" after treatment with ivacaftor for one year. A smaller proportion (10%) of those with persistent *P. aeruginosa* infection became "culture negative." Although not definitive, this cohort study provides hope to patients and clinicians that CFTR modulation might improve chronic airway infection associated with *P. aeruginosa* and perhaps infections with other bacteria as well.

The last two studies in this review focus on CF pulmonary exacerbations, a daunting and important clinical problem.[4] For many years, CF pulmonary exacerbations were believed to be triggered by proliferation of *P. aeruginosa* in the airways. It was thought that increased airway density of *P. aeruginosa* would lead to airway inflammation and a clinical exacerbation[1]. However, recent studies suggest this is not the case. The prospective study by Chin et al reviewed in this journal demonstrated that respiratory viruses were associated with CF pulmonary exacerbations in 50% of instances and showed that sputum density of *P. aeruginosa* was not increased at the time of CF exacerbation. This study confirms recently published work by other investigative teams that also found no change in *P. aeruginosa* bacterial density in the sputum between steady state and exacerbation.[5-6] Given the significance of CF pulmonary exacerbations, further work is required to understand the etiology of exacerbations in patients with CF patients, since increased *P. aeruginosa* bacterial density in sputum does not appear to be responsible.

P. aeruginosa are known to grow in organized macrocolonies called biofilms within the CF airway.[7] Previous in vitro studies suggest that antibiotic susceptibilities of bacteria growing in biofilms might be dramatically different compared to susceptibilities of the same bacteria growing in free-floating planktonic states.[8] Yau et al conducted an ambitious randomized, controlled trial of patients with CF experiencing pulmonary exacerbations to determine whether antibiotics chosen based on biofilm antimicrobial susceptibility testing would result in a better microbiologic and clinical response compared to antibiotic chosen based on conventional planktonic susceptibility testing. Unfortunately, this trial, like others before it that evaluated nonconventional antibiotic synergy tests for treatment of CF pulmonary exacerbations,[9],was negative. Given this disappointing finding, adoption of biofilm susceptibility testing of *P. aeruginosa* to guide clinical antibiotic management does not seem to be warranted.

Commentary References

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AZLI VS TOBI: COMPARATIVE EFFICACY IN CHRONIC *P. AERUGINOSA* INFECTION

Inhaled aztreonam lysine vs inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. Assael BM, Pressler T, Bilton D, et al; AZLI Active Comparator Study Group. *J Cyst Fibros*. 2013 Mar;12(2):130-140.

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Inhaled tobramycin, administered in 28 day on/off cycles, has been the standard-of-care for chronic treatment of *Pseudomonas aeruginosa* infection since 1999. Newer inhaled antibiotics for *P. aeruginosa* infection such as aztreonam must therefore demonstrate efficacy when compared to placebo, as well as comparative efficacy against inhaled tobramycin. This six-month, open-label, comparative efficacy trial assessed inhaled aztreonam 75 mg TID compared to tobramycin nebulized solution 300 mg BID, both drugs were given in three 28 days on/28 days off treatment cycles.

The results of this study suggest that patients randomized to aztreonam had better short-term improvements in lung function. After one 28-day cycle, patients in the aztreonam group improved their FEV_1 by 8.35% relative to baseline, compared to 0.55% improvement in those treated with tobramycin (between group relative treatment difference = 7.80%; 95% CI: 3.86%-11.73%). The effects of both drugs seemed to wane after the first cycle, with less improvement seen in cycles 2 and 3, so that after three 28-day cycles the absolute mean change in FEV_1 was 2.05% in the aztreonam group and -0.66% in the tobramycin group (between group absolute treatment difference = 2.70%; 95% CI: 0.98%-4.43%). The time to first exacerbation needing antipseudomonal antibiotics was prolonged in the aztreonam group, and patients randomized to aztreonam experienced fewer respiratory exacerbations and hospitalizations. Both treatments were relatively well tolerated with few adverse events.

The results of this trial suggest that aztreonam is an effective alternative to tobramycin for control of chronic *P. aeruginosa* endobronchial infection. However, this study has important limitations that must be considered. The open-label design of this study could provide opportunities for bias: the study was funded and coordinated by the company that manufactures aztreonam, and therefore ascertainment of outcomes could potentially be biased to favor patients treated with aztreonam. In addition, 85% of the study population had taken inhaled tobramycin in the preceding year. Since patients were naïve to aztreonam but not to tobramycin, one would expect a greater bactericidal effect in patients treated with aztreonam; this may explain the significant FEV_1 response to aztreonam during the first cycle of treatment. This beneficial FEV_1 effect seemed to wane with repeated cycles, associated with development of *P. aeruginosa* antibiotic resistance to aztreonam.

Although the current trial suggests that aztreonam is a viable alternative to tobramycin for chronic treatment of *P. aeruginosa*, the question of real importance to clinicians who treat cystic fibrosis would be whether alternating therapy with tobramycin and aztreonam for 28 successive days each would be more effective than the current standard of 28 days on/28 days off antibiotic treatment cycles. Hopefully, this question will be answered in the recently-completed (but results not yet available) phase 3 Aztreonam Lysine for Inhalation Continuous Alternating Therapy (AZLI CAT) study, which will randomize patients with CF to alternating cycles of tobramycin with aztreonam compared to alternating cycles of tobramycin with placebo.[2]

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2. Phase 3 Study of Aztreonam for Inhalation Solution (AZLI) in a Continuous Alternating Therapy Regimen for the Treatment of Chronic Pseudomonas Aeruginosa Infection in Patients With CF (AZLI CAT). Accessed at clinicaltrials.gov on May 11, 2015.

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INHALED LEVOFLOXACIN VS TOBI FOR TREATING CHRONIC *PSEUDOMONAS AERUGINOSA* INFECTION

Stuart Elborn J, Geller DE, Conrad D, et al. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients. *J Cyst Fibros*. 2015 Jan 12.

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This trial was very similar in design to the AZLI/TOBI study reviewed herein. This 6-month open-label comparative efficacy trial assessed inhaled levofloxacin, 240 mg BID, compared to tobramycin nebulized solution, 300 mg BID. Both drugs were given in three 28 days on/28 days off treatment cycles.

The results of this study suggest that patients randomized to inhaled levofloxacin had similar outcomes (noninferior) compared to patients randomized to inhaled tobramycin. In contrast to the aztreonam study, after one 28-day cycle patients treated with levofloxacin had somewhat more modest relative changes of about 2% in FEV_1 from their baseline. The mean between-group difference (levofloxacin minus tobramycin) in FEV_1 was 1.86% [95% CI –0.66 to 4.39%, P = .15] after 28 days. An analysis of lung function changes over three cycles was not reported. The time to first exacerbation needing antipseudomonal antibiotics was similar in the levofloxacin and tobramycin-treated groups, although patients randomized to levofloxacin experienced fewer hospitalizations (17.5% versus 28.0%, P = .04). Both treatments were relatively well tolerated; however, 25% of patients treated with levofloxacin reported bad taste/taste distortion.

As with the previously reviewed AZLI/TOBI study, there are important limitations of this trial that need to be considered. The open-label design of this study could provide opportunities for bias: the study was funded and coordinated by the company that manufactures levofloxacin; therefore, ascertainment of outcomes could potentially be biased to favor levofloxacin-treated patients. In addition, each patient who entered this study had taken at least three courses of inhaled tobramycin in the preceding year. Since patients were naïve to levofloxacin-naïve but not to tobramycin, one would expect a greater bactericidal effect in patients treated with levofloxacin, and this was in fact observed during the first three cycles of treatment. However, one piece of good news was that the beneficial FEV_1 effect of levofloxacin, while quite modest and not statistically greater than tobramycin's effects, at least did not seem to wane over three successive cycles as was observed in the aztreonam trial.

Although the current trial suggests that inhaled levofloxacin is not inferior to tobramycin for chronic treatment of *P. aeruginosa*, this treatment is still probably not ready for prime time. A double-blind placebo-controlled trial would be needed to demonstrate superior efficacy of inhaled levofloxacin over placebo prior to gaining regulatory approval for this therapy in most jurisdictions.

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TREATMENT OF CFTR DYSFUNCTION AND *P. AERUGINOSA* SPUTUM CULTURE POSITIVITY

Heltshe SL, Mayer-Hamblett N, Burns JL, et al; on behalf of the GOAL (the G551D Observation-AL) Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. *Clin Infect Dis.* Epub 2014 Nov 25.

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This longitudinal cohort study enrolled 151 individuals with CF with at least one copy of the G551D *CFTR* mutation who were treated with the CFTR potentiator ivacaftor. Prior to beginning ivacaftor therapy, 59 patients (39%) had persistent *P. aeruginosa* infection (> 50% of cultures in the year grew *P. aeruginosa*) and 30 patients (20%) had intermittent infection (< 50% of cultures in the year grew *P. aeruginosa*). Median follow-up after initiation of ivacaftor was 12.5 months.

In the year after beginning ivacaftor, 70% (21/30) of those with intermittent infection became free of *P. aeruginosa* infection, and 10% (5/48) of those with persistent infection became free of *P. aeruginosa* infection. The odds of growth of *P. aeruginosa* in the year after ivacaftor compared with the previous year were reduced by 35% (odds ratio 0.65; P < .001). Ivacaftor was also associated with reduced odds of mucoid *P. aeruginosa* (OR, 0.77; P = .013) and aspergillus (OR, 0.47; P = .039), but not *Staphylococcus aureus* or other common CF pathogens.

Although this study suggests that growth of *P. aeruginosa* from airway cultures was significantly reduced following ivacaftor treatment, a number of caveats may temper the study's conclusion. This study was limited by lack of a control group: so it is difficult to know with certainty how many patients' sputum cultures might have become *P. aeruginosa*-free without treatment with ivacaftor. In addition, patients were less likely to produce sputum, and they had fewer sputum cultures in the year following initiation of ivacaftor therapy — a potential sampling bias that may have contributed to the study's results. The investigators attempted to mitigate this sampling bias by adjusting the analysis for the number of cultures performed each year and by performing a sensitivity analysis of participants with at least three respiratory cultures. Results of the adjusted analysis and of the sensitivity analysis were similar to those of the primary analysis.

Taken as a whole, this study provides intriguing data that suggests that modulation of CFTR in patients with at least G551D *CFTR* mutation may help clear the sputum of *P. aeruginosa*, especially in patients who are only intermittently infected. The mechanism of this effect remains unclear, but may reflect possible antibiotic effects of ivacaftor;[1] improvement in CFTR function leading to increased mucociliary clearance of bacteria;[2] and increased bicarbonate secretion into the airway by modulated CFTR, which may produce an antagonistic airway environment for *P. aeruginosa* by augmenting defense-related bacterial killing.[3]

It would certainly be exciting if CFTR modulation could be conclusively shown to be associated with clearance of chronic *P. aeruginosa* infection in patients with CF. Future placebo-controlled clinical trials of CFTR correctors and potentiators will hopefully evaluate sputum bacteriology as a secondary outcome to confirm the preliminary results reported in this study.

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PSEUDOMONAS AERUGINOSA BACTERIAL DENSITY DURING CF EXACERBATIONS

Chin M , De Zoysa M, Slinger R, et al. Acute effects of viral respiratory tract infections on sputum bacterial density during CF pulmonary exacerbations. *J Cyst Fibros*. 2015 Jul;14(4):482-9.

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An accepted dogma in CF clinical medicine has been that CF pulmonary exacerbations are triggered by proliferation of *P. aeruginosa* in the airways, and that this increased airway density of bacteria then leads to airway inflammation and a clinical exacerbation. This prospective cohort study examined this dogma by studying 35 adult patients who were chronically infected with *P. aeruginosa* every three months, before, during and after pulmonary exacerbations. Quantitative bacterial cultures of sputum and quantitative PCR for *P. aeruginosa* were performed at each visit, along with qT-PCR panels examining for respiratory viruses from sputum and from nasopharyngeal swabs.

Twenty-two patients experienced 30 exacerbations during the study period; 50% of exacerbations were associated with PCR confirmation of a new respiratory viral infection that had not been found during stable visits. There was no change in sputum density of *P. aeruginosa* from the stable to exacerbation state when measured by quantitative culture or by quantitative PCR. Virus-associated exacerbations did not result in significant increases in *P. aeruginosa* sputum density compared to nonviral exacerbations.

The study concluded that respiratory viruses are commonly associated with CF pulmonary exacerbations and that sputum density of *P. aeruginosa* was not increased at the time of the exacerbation and was not acutely influenced by the presence of viral infections. This study confirms results of two previous studies. The first, by Stressman et al., measured the bacterial density of *P. aeruginosa* at the time of exacerbation and weekly for three weeks prior. They found no change in sputum bacterial density.[1] The second publication by Carmody et al. found no change in total or *P. aeruginosa* bacterial density in the sputum between steady state and exacerbation.[2]

Given the significance of CF exacerbations, further work is needed to determine whether viral infections elicit an immune response that leads to exacerbation that may be independent of *P. aeruginosa* bacterial load in individuals with CF. Further investigation is required to understand the etiology of exacerbations in patients who do not have viral infections, since increased *P. aeruginosa* bacterial density in sputum does not appear to be responsible.

References

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2. Carmody LA, Zhao J, Schloss PD, Petrosino JF, Murray S, Young VB, et al. Changes in cystic fibrosis airway microbiota at pulmonary exacerbation. *Ann Am Thorac Soc*. 2013;10(3):179–187.

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USE OF BIOFILM SUSCEPTIBILITY TESTING TO GUIDE ANTIBIOTIC THERAPY FOR CF PULMONARY EXACERBATIONS

Yau Y, Ratjen F, Tullis E, Wilcox P, Freitag A, et al. Randomized controlled trial of biofilm antimicrobial susceptibility testing in cystic fibrosis patients. *J Cyst Fibros*. 14 (2015) 262–266.

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Bacteria, such as *Pseudomonas aeruginosa*, are known to exist in a biofilm, or polymicrobial community within the airways of patients with CF. This study aimed to determine whether antibiotics chosen based on biofilm antimicrobial susceptibility testing would result in a better microbiologic and clinical response compared to antibiotic chosen based on conventional planktonic susceptibility testing in the treatment of pulmonary exacerbations.

This multicenter, double-blind, controlled trial enrolled individuals with CF who were chronically infected with *P. aeruginosa* and randomized them at the time of an acute CF pulmonary exacerbation to 14 days of intravenous antibiotic treatment based on conventional vs biofilm antimicrobial susceptibility results. Over the study period there were 74 exacerbations in 39 patients. A total of 46% of the exacerbations in the conventional group compared to 40% of exacerbations in the biofilm group achieved a ≥ 3 log drop in *P. aeruginosa* sputum density (difference –0.03, 95% CI –0.5 to 0.4, P = 0.90). Lung function improvements and improvement in symptoms were similar in both groups, as were changes in inflammatory markers (sputum IL–8 and neutrophil elastase and serum WBC count, ESR, and CRP).

The results of this study suggest that antibiotic therapy chosen prospectively based on biofilm, as compared to conventional, susceptibility testing, does not result in greater decreases in pulmonary bacterial load or improved clinical outcomes as measured by lung function recovery, improvement in symptoms, or resolution of inflammatory response following exacerbation.

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This activity is supported by educational grants from AbbVie, Gilead Sciences, Inc, and Vertex Pharmaceuticals Incorporated.

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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 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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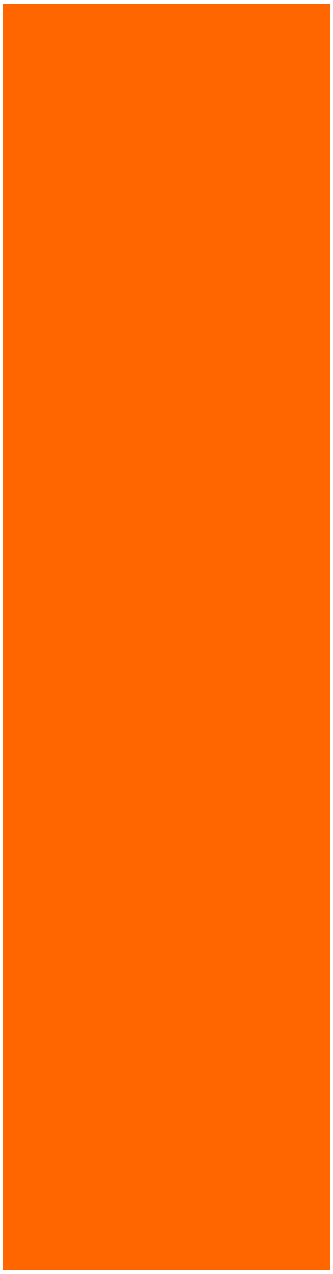
Presented by JHUSOM and IJHN in collaboration with DKBmed.



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