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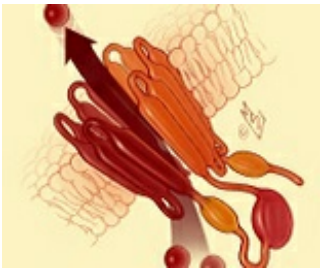



# *Trends in Inhaled Antibiotic Therapy*



## In this Issue...

*Pseudomonas aeruginosa* colonization of the cystic fibrosis airway requires chronic therapy with inhaled antibiotics for nearly all patients. Clinician options in the US, however, are limited to tobramycin nebulizer solution (TNS) and aztreonam for inhalation solution (AZLI); in the EU and many other parts of the world, colistimethate and colistimethate dry powder for inhalation (CDPI) are also available.

In this issue, Drs. Karen McCoy and Daniel Heintz from the Pediatric Cystic Fibrosis Center at Nationwide Children's Hospital in Columbus, Ohio review recent investigations describing these agents and how they are currently being used in the clinic.

## LEARNING OBJECTIVES

- Describe the clinical use patterns of the available inhaled antibiotics for managing Pseudomonas aeruginosa in patients with cystic fibrosis.
- Summarize the comparative safety and efficacy data between tobramycin nebulizer solution (TNS) and aztreonam for inhalation solution (AZLI).
- Summarize the comparative safety and efficacy data between tobramycin nebulizer solution (TNS) and colistimethate dry powder for inhalation (CDPI).

## GUEST AUTHORS OF THE MONTH

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***Guest Faculty Disclosure***

Dr. Daniel Heintz reports that he was no relevant commercial relationships with a commercial entity.

Dr. Karen McCoy reports that she has received grants from Pharmaxis, Novartis, Alcresta, and Pro-QR Therapeutics.

***Unlabeled/Unapproved uses***

Dr. Daniel Heintz and Dr. Karen McCoy have indicated that there

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will be references to the unlabeled/unapproved use of colistimethate and colistimethate dry powder for inhalation (CDPI), inhaled levofloxacin, and inhaled levofloxacin.

## IN THIS ISSUE

# COMMENTARY

Cystic fibrosis is an autosomal recessive chronic inflammatory disease that affects many organ systems, especially the respiratory system. Continuous airway inflammation leads to advanced lung disease, increasing morbidity and accelerating mortality. One of the biggest contributors to airway inflammation, which is known to decrease lung function and increase mortality, is *Pseudomonas aeruginosa* infection. *P. aeruginosa* is ubiquitous in soil and water, and attempts to eradicate these gram negative bacteria only postpone the inevitable airway colonization. Initially, colonizing Pseudomonas is nonmucoid, but eventually biofilm formation creates a mucoid "shell," leading to decreased airway clearance and decreased antibiotic/immune function effectiveness. Therefore, early, aggressive eradication is recommended for first-time pseudomonal growth.

Although pseudomonal control is paramount to better health, limited antibiotic options have complicated this endeavor. For years, tobramycin was essentially the only available option in the United States, as colistimethate had fallen from favor because of neurological effects caused by its intravenous use. In 2010, aztreonam lysine (AZLI) was approved for use in the US, giving physicians a second viable option. Previous aztreonam studies had shown that it was safe and superior to placebo for improvements in lung function, number and time between pulmonary exacerbations, and patient-reported respiratory scores, but a tobramycin comparative study had yet to be done. The study by Assael and colleagues (reviewed herein) confirms the superiority of aztreonam to inhaled tobramycin using outcomes similar to those of the placebo comparative trials.

Several other analyses were performed using the data from Assael's study. The reviewed article by Schechter and colleagues compares the economic costs associated with inhaled AZLI and tobramycin by performing a cost-utility analysis that takes into account the varying costs associated with a patient's overall health, lung function, mortality, and transplantation. Using Assael's data for the first year and extrapolating for the next two years, Schechter's team report AZLI to be cost-effective after total cost summation is completed.

However, what if the data reported in Assael's article are confounded by an agent that affects tobramycin's effectiveness? In the reviewed article by Nick et al, the authors suggest that chronic azithromycin use may have affected Assael's results. Performing a secondary analysis, these investigators showed that pulmonary function improved with tobramycin but decreased when tobramycin was combined with azithromycin. This effect has not been noted with AZLI. Even if Nick's findings prove true, AZLI still has been shown to improve lung function better than placebo, so AZLI use should not be affected.

The addition of a new inhaled antibiotic does not immediately translate into widespread use. Dasenbrook et al (reviewed in this issue) illustrate this point by demonstrating increased patient use of AZLI from 2009 to 2012 and suggesting that inhaled antibiotics (tobramycin, aztreonam, and colistimethate) were being used on a combined and presumed rotating basis. Without formal recommendations for AZLI administration (ie, through Cystic Fibrosis Foundation consensus statements), physician inexperience, combined with lack of adequate guidance, initially decreased the prescribing rate for this new medication.

Physicians can only offer regimens designed to improve health. Ultimately, in most cases, a patient's adherence rate determines the final results. Several studies have shown that adherence rates for patients with cystic fibrosis have been low. Latchford illustrated that among patients with cystic fibrosis, adherence rates for daily nebulized treatment was 57% but dropped to 32% with BID or more frequent treatment dosing[1]. Adult patients' self-reported adherence rates for nebulized treatments vs actual adherence (as downloaded from recorded nebulizer use) was 80% vs 36%.[2] Since time-consuming therapies are more likely to increase nonadherence rates,[3] and airway clearance is a time-consuming but key

component of CF therapy, attempts to decrease therapy sessions has been examined. This was the impetus for developing a tobramycin preparation that could be completed in less time than the standard 15-20 minute nebulized therapy (tobramycin powder inhalation device). This issue also affects AZLI, since TID dosing as well as a more intense cleaning regimen for the nebulizer are required, thus increasing the time demand for therapy. For these reasons, the Cystic Fibrosis Foundation's 2014–2018 Strategic Plan Report, "Our Commitment to a Cure," revealed plans to "develop and implement a validated adherence-barriers assessment with a goal of increasing adherence with prescribed therapies to 80% among at least 75% of people with cystic fibrosis."[4]

Even if adherence rates increase, the lack of available inhaled antibiotics, combined with the need for chronic use, make pseudomonal resistance inevitable. Strategies to minimize resistance development include alternating monthly administration to an on-off, 28-day cycle; or, for those who require continuous inhaled antibiotic therapy, adding a second inhaled therapy to the off cycle (ie, rotated or cycled alternating therapy).

Are fears of airway antibiotic resistance valid? Minimum inhibitory concentration (MIC) is frequently reported, but it reflects a serum achievable measurement of resistance that may not apply to inhaled antibiotics. Many physicians feel that since inhaled antibiotics are directly applied to the airways, antibiotic resistance is not the same as serum achievable MIC and serum measurements overestimate the true level antibiotic resistance. Employing inhaled antibiotics designated bacterial resistant is a strategy employed by physicians for patients who have progressed further in their CF course and for whom antibiotic options have become more limited by bacterial resistance patterns.

Development of additional pseudomonal-targeted antimicrobial agents is crucial for the future well-being of patients with cystic fibrosis. Inhaled levofloxacin has recently completed a phase III trial, while liposomal amikacin has completed a phase II study. While IV formulation of colistimethate given by nebulizer is used for pulmonary exacerbations in the United States, Europe's recent approval of colistimethate dry powder for inhalation (CDPI) may spur efforts for US approval. The reviewed article by Schuster et al demonstrated CDPI as noninferior compared to nebulized tobramycin, with a good safety profile. As European use of this drug continues, better efficacy and safety profiles may be provided that will lead to eventual approval in the US.

In conclusion, although chronic therapy with inhaled antibiotics is a mainstay of CF therapy, the lack of extensive antibiotic choices, development of pseudomonal mucoid changes, and eventual bacterial resistance make development of new therapies essential. Attention to and awareness of individual adherence is also key, as is developing less time-consuming options while still delivering effective care. Infection control practices and intervention implementation are both necessary to ensure proper care of the patient with cystic fibrosis.

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2014-2018 Strategic Plan Report, 2014;27-33. Available at: https://www.cff.org/About-Us/Assets/Strategic-Plan-Report/

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## Comparing Inhaled Aztreonam to Tobramycin

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

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Previous placebo-controlled clinical trials have demonstrated the efficacy and safety of inhaled aztreonam lysine (AZLI) in patients with varying exposure to inhaled tobramycin (TNS), finding effects were sustained for 18 months.[1-3] Assael and colleagues performed a combined European and US open-label, randomized, parallel-group study comparing the safety and efficacy of AZLI to TNS (AZLI/TNS: 136/132) across three 28-day treatment courses. The European sites also provided an optional open-labeled extension period for three additional AZLI treatment courses.

Patients randomized to the AZLI branch experienced a significant increase ($P < .001$ and $P = .0002$) in lung function improvement compared to TNS at day 28, as well as at day 140. During the extension period, TNS/AZLI patients experienced a significant increase in lung function comparable to those of the AZLI/AZLI group. AZLI-treated patients also had significant decreases in the number of pulmonary exacerbations, increased time between pulmonary exacerbations ($P = .003$), decreased need for additional antibiotics ($P < .001$), improved respiratory symptoms per CFQ-R at 28 day ($P = .005$) and 140-day ($P = .019$), and increased relative weight gain from baseline. While more adverse events were reported with AZLI, this may have been due to the investigators' more stringent reporting for a newly approved drug, as well as selection bias, as patients who had exhibited intolerance to TNS in the past were excluded from the study. Sputum PA density decreased equally between the two groups. For the optional 24-week extension period, 133 patients demonstrated comparable lung function regardless of prior antibiotic group assignment.

Several limitations were mentioned for this study. One was that it was an open-label study (because dosing frequency, taste, and approved nebulizers do not allow for a blinded study). Another was that patients with TNS experience may have been more likely to report better respiratory symptoms and treatment improvement on AZLI. Limited pediatric participation (4.9%) may also confound the results. Permitting TNS-experienced patients into the study may have affected results, but since TNS is the current standard of care, it is difficult to find TNS naïve patients.

Overall, this study demonstrated that AZLI was statistically significantly better in previously mentioned categories and is a viable option for treating chronic Pseudomonas.

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## Cost Effectiveness of Aztreonam Lysine

Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam lysine versus inhaled tobramycin in cystic fibrosis. An economic evaluation. *Ann Am Thorac Soc*. 2015;12(7):1030-1038.

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When compared to inhaled nebulized tobramycin (TNS), inhaled aztreonam (AZLI) has been shown to provide greater improvement in $FEV_1$ and to reduce pulmonary exacerbations.[1-4] But does AZLI present a cost-effective therapy that can reduce hospitalizations and add years to a patient's life, while also improving a patient's quality of life? These are the questions that Schechter and colleagues attempted to answer by performing a cost-utility analysis from the perspective of a third-party payer, using efficacy data from the comparator study (discussed above)[4] and then extrapolating for long term data.

To perform the analysis, they used a Markoff model to compare the clinical course of patients who were using either inhaled aztreonam lysine (AZLI) or tobramycin nebulized solution (TNS). Using a 28-day cycle, a specific $FEV_1$ range (> 90%, 80%-89%, etc) indicated the health of a patient after a month of either on or off inhaled antibiotics. Depending on the transition probabilities (calculated from clinical data) unique for each range of $FEV_1$, a patient could remain at, increase, or decrease their $FEV_1$ range, undergo lung transplantation, or die. Lung transplantation was a constant risk for patients with an $FEV_1$ less than 30. If lung transplantation occurred, the patient would have a perioperative mortality risk for that cycle only, and surviving patients were then moved to a post-transplant life with survival rates based on published estimates. After the comparator study data were exhausted, further data were extrapolated by determining future probabilities as the average of those calculated during the trial. The entire study scanned a three-year period for the primary analysis. According to the article: "Costs and benefits occurring beyond the first year were discounted at a rate of 3% per annum in line with current Academy for Managed Care Pharmacy pharmacoeconomic guidelines."

After 36 cycles, the AZLI branch resulted in a total cost savings of $41,947 with a small increase in life years ($P = .0162$) and quality-adjusted life-years ($P = .0286$), as well as fewer hospitalizations ($P = - 0.8377$), though the latter was not significant. To counter validity arguments, the authors ran the analysis with differences noted only in the first year and found the primary outcome results were the same. Also, the use of generic tobramycin would affect the cost analysis if the cost of generic tobramycin was under $3984.

Schechter and colleagues reported limitations that included the study being unblinded, possibly affecting hospitalization rate due to clinician bias regarding effectiveness of inhaled antibiotic, decreased TNS efficacy from prior prolonged exposure, possible increased compliance with AZLI, and blunted tobramycin response related to azithromycin use.

Finally, improvement in life expectancy since data was published, as well as overestimation of lung transplantation incidence (incidence derived from lung transplantation waiting list), may have affected mortality and lung transplantation costs and utility. Removing mortality and lung transplantation from the analysis did not, however, affect the final conclusions.

In summary, AZLI offers increased benefits to patients with CF at a price that is lower at this time.

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3. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-mo study, AIR-CF3 of the safety and improvement in pulmonary function and respiratory symptoms with repeated courses of aztreonam for inhalation solution in patients with cystic fibrosis and airway Pseudomonas aeruginosa. *Pediatr Pulmonol*. 2010;45:1121-1134.
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## Inhaled Tobramycin Affected by Chronic Azithromycin Use

Nick JA, Moskowitz SM, Chmiel JF, et al. Azithromycin may antagonize inhaled tobramycin when targeting Pseudomonas aeruginosa in cystic fibrosis. *Ann Am Thorac Soc.* 2014;11(3):342-350.

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Chronic use of inhaled antibiotics and azithromycin has been shown to improve lung function and reduce pulmonary exacerbation frequency.[1,2] But a recent study has suggested that in mice, early administration of azithromycin may antagonize the effects of tobramycin.[3] In this 2014 report, Nick and colleagues hypothesized that azithromycin may also inhibit tobramycin nebulizer solution (TNS) in patients with cystic fibrosis and lung disease, affecting patient outcomes and skewing the results of inhaled tobramycin comparison studies.

To account for concomitant azithromycin use, a secondary analysis was performed on deidentified data gathered from the comparative study by Assael and colleagues (reviewed above).[4] In that study, the investigators randomized 268 patients to receive either inhaled tobramycin or aztreonam (AZLI) for three 28-day on-off cycles, resulting in better lung function, fewer pulmonary exacerbations, increased time to need for antibiotics, and improved weight gain for the patients assigned to the AZLI group. For the optional 24-week extension period, 133 patients received one to three additional AZLI treatment cycles and demonstrated comparable lung function, regardless of prior antibiotic group assignment.

Nick and colleagues further categorized the original study's outcomes by tracking azithromycin use. Of the 263 patients with recorded azithromycin use, concomitant azithromycin use was equivalent (71% vs 67%) between the TNS (n = 128) and AZLI (n = 135) groups. Results of their secondary analysis indicated that patients using both TNS and azithromycin demonstrated significant decreases in lung function at 28 days ($P = .003$) and 140 days ($P = .007$), compared to the other groups in which lung function increased. Concomitant use of azithromycin with TNS also showed a nonsignificant ($P = .10$) lower improvement in quality of life and reduction in sputum *P. aeruginosa* density, while requiring

additional antibiotic treatment sooner and more often ($P = .01$).

Crossover patients experienced a similar increase ($P < .0001$) in $FEV_1$ when on aztreonam, but quality of life and sputum density did not reach statistical difference. In vitro biofilm testing of the 15 subjects treated with tobramycin and azithromycin showed antagonism (> 20% increase in biomass) in six, additive effect (> 20% reduction in biomass) in three, and indeterminate results in three. Contrast this to the six patients on aztreonam, who showed no antagonism and two with additive effect.

The results clearly indicate a negative association between azithromycin and tobramycin, while at the same time questioning the results of the comparator study that concluded that inhaled aztreonam is superior to inhaled tobramycin. This negative association was not seen in patients taking tobramycin alone, who instead experienced results similar to the aztreonam group (+/- azithromycin). The authors suggest several possible hypotheses for this negative association, including competitive inhibition (both azithromycin and tobramycin can disrupt the cationic bonds, allowing crosslinking in the bacterium's outer membrane), and selective induction of aminoglycoside-resistance mechanisms. Regardless, since azithromycin is concentrated in macrophages and neutrophils, it can persist in the airways, antagonizing tobramycin for weeks.

Finally, the authors point out that retrospective analyses can be misleading, in that unknown or unreported factors may confound the results. At this time, they do not advocate stopping the use of tobramycin and azithromycin in combination but instead recommend awaiting the results of a currently planned prospective clinical trial before deciding.

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# AZLI Use: Three Year Prevalence Changes



Dasenbrook EC, Konstan MW, VanDevanter DR. Association between the introduction of a new cystic fibrosis inhaled antibiotic class and change in prevalence of patients receiving multiple inhaled antibiotic classes. *J Cyst Fibros.* 2015;14(3):370-375.

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The Cystic Fibrosis Foundation Patient Registry (CFFPR) tracks a number of parameters including "reported inhaled antibiotic use." Between 2009 and 2012, the registry reported an increased prevalence of inhaled aztreonam lysine (AZLI) use, while inhaled tobramycin (TNS) prevalence remained essentially stable.[1,2] However, ascertaining how patients were using this new inhaled antibiotic for their current pulmonary regimen was difficult to determine.

After a pilot study using 2009–2012 data from their Adult CF program revealed that inhaled antibiotics rotated monthly (eg, TNS/AZLI) had doubled, Dasenbrook and colleagues tried to determine if the same was true nationwide by evaluating deidentified data from the CFFPR. Since the CFFPR does not directly track monthly rotating inhaled antibiotics, the investigators noted changes in the "annual prevalence of patients receiving more than one antibiotic" and "prevalence of multiple antibiotics at any single visit." These changes were categorized by subgroups of age, $FEV_1$, and documented growth of *Pseudomonas aeruginosa* if cultured more than once per year.

The results demonstrated that the overall prevalence of inhaled antibiotic use remained essentially unchanged (51.4% to 52.3%), but increased prevalence of patients receiving more than one inhaled antibiotic (7.3% to 17.3%; $P < .0001$) or receiving more than one class of inhaled antibiotics at any visit (6.5% to 15.7%; $P < .0001$) was noted. Area-proportional Venn diagrams illustrated decreased use of aminoglycosides (AMI) (81% to 53.8%) and colistimethate (COL) (4.1% to 2%) as the sole inhaled antibiotic, while aztreonam (AZLI) increased from 0.8% to 11.1%. The prevalence of combination therapy with AZLI increased as well (+AMI: 1.8% to 22.8%; +COL: 0.4% to 3%; all together: 0.7% to 3.5%) but decreased for the therapy AMI + COL (11.2% to 3.9%).

Analysis of the age subgroups revealed that up to 18 years of age, there was a decline in the overall prevalence of patients using inhaled antibiotics; that prevalence increased by 5.4% in patients over 18. This differs from the lung function subgroups, where the overall prevalence of patients using inhaled antibiotics remained essentially unchanged. Prevalence doubled in all lung function subgroup for patients receiving more than one class of inhaled antibiotics, with the greatest change noted in the severe lung function ($FEV_1$ < 40%) subgroup (20%; $P < .0001$). Increased use of inhaled antibiotic was most marked in those who grew *P. aeruginosa* more than once (16.3% to 38.1). These findings suggest that the use of multiple inhaled antibiotic classes for patients with chronic *P. aeruginosa* airway infections is becoming increasingly more common in the US, with indications that planned intermittent rotation of inhaled antibiotics is also increasing.

The authors reported that the limitations in their study included dependence on the accuracy of the data reported from the CF centers; the lack of description of the inhaled antibiotic regimens used (and likely variable); no reporting of other possible inhaled antibiotics use (resulting in a possible underestimation of overall inhaled antibiotic use); and no determination whether the observed increase in the prevalence of combination inhaled antibiotic class was associated with changes in health outcomes. The authors note that complex statistical modeling would be needed to handle the indication biases associated

with these observational data.

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## Comparing Colistimethate Sodium Dry Powder to Inhaled Tobramycin

Schuster A, Haliburn C, Doring G, Goldman MH. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. *Thorax*. 2013;68(4):344-350.

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Inhaled colistimethate sodium is currently not approved for use in the United States but is used widely in Europe as an agent against chronic *Pseudomonas aeruginosa* infection. But the lengthy[1] nebulization times and complex administration may affect adherence.[2,3] To counter these barriers, colistimethate dry powder for inhalation (CDPI) was created. CDPI is delivered by its own handheld portable nebulizer that requires little cleaning and maintenance; the device can be disposed of after the 28 day cycle; and the proportion of drug delivered to the lung (compared to nebulization) may possibly be increased. Schuster and colleagues investigated the efficacy and safety of CDPI compared to tobramycin nebulizer solution (TNS) in CF patients greater than 6 years old with chronic *P. aeruginosa* lung infection.

This was a prospective, centrally randomized, phase III, open label study performed at 66 European CF centers. The intention to treat group (ITT) contained 373 patients, but 81 occurrences of protocol violations led to 298 patients for the per-protocol group (PP) (CDPI 141, TNS 157). All participants were required to take two 28-day on-off cycles of TNS either previously or in preparation for the study. They were then randomized to continuous BID CDPI or to three 28-day courses of TNS. Efficacy measures included change in week 24 $FEV_1$% predicted from baseline (main efficacy measure), susceptibility testing of *P. aeruginosa* to CDPI and TNS, and changes in other spirometry measures (FVC, $FEV_1$, FEF25-75). Albuterol use 2 hours prior to spirometry was not permitted. Adverse events (AEs) and serious adverse effects (SAEs) were monitored, and data were collected on patients' views of trial treatment, preferences, and quality of life.

The results showed that CDPI was not inferior to TNS in $FEV_1$% predicted change at 24 weeks, as well as for changes in FVC, $FEV_1$, and FEF25-75 for both the ITT and PP groups. Susceptibility testing for *P. aeruginosa* resistance to CDPI and TNS were not noted during the study. CDPI had a good safety profile, with increased cough and bad taste reported most frequently in the CDPI branch; but it is typical for dry powder medications to cause mild cough, throat irritation, and unpleasant taste from deposition in the oropharynx. The large dose of CDPI may also have contributed to this irritation, but SAEs were reported more in the TNS group (6.2% to 4.3%). The CDPI inhaler was also rated as easier to use by 51.9% compared to 9.9% in the TNS group.

In conclusion, CDPI was shown to be equally effective against chronic *P. aeruginosa* infection, had a good safety profile without development of resistance during the time frame of the trial, and provided improved patient satisfaction.

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