Aerosol Antibiotics in Cystic Fibrosis

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Summary

Chronic airways infection and inflammation is the greatest source of morbidity and mortality in cystic fibrosis (CF) patients. Many organisms can be found in the lower respiratory tract of CF patients, but infection with mucoid Pseudomonas aeruginosa is common, is associated with poorer outcomes, and is the main target for antimicrobial strategies in CF. Aerosol antibiotics achieve high local concentrations in the airways, reduce systemic toxicity, and have been used successfully for chronic suppressive treatment for established P. aeruginosa infections. Eradication of early P. aeruginosa airway infection has also been tried with aerosol antibiotics, though the ideal treatment strategy is still being investigated. There are several variables to consider when choosing an antibiotic formulation to develop for topical inhalation. Tobramycin solution for inhalation (TSI) is currently the only approved inhaled antibiotic in the United States. The time burden for patients to administer TSI by jet nebulizer is substantial, so efforts have focused on more efficient, faster delivery methods. Novel formulations of aerosol antibiotics are being studied for CF, including β-lactams, fluoroquinolones and aminoglycosides. Phase-3 studies of aztreonam lysinate for inhalation delivered via a proprietary eFlow nebulizer showed improved outcomes and a short (< 3 min) delivery time. Liposome formulations are being studied as a way to penetrate mucoid biofilms and prolong the residence time of the antibiotic in the lungs. Light, porous, dry-powder formulations are also in clinical trials to reduce delivery time. These new formulations and delivery systems promise to expand our armamentarium against microbes while reducing the time burden for patients.

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Introduction

The lung disease in cystic fibrosis (CF) is characterized by endobronchial infection, exaggerated inflammatory response, progressive airway obstruction, bronchiectasis, and eventual respiratory failure. Patients with CF are particularly susceptible to endobronchial infections with several bacteria that may not cause disease in a healthy, immune-competent host. The microbes infecting the airways in CF are reviewed by Davies and Bilton in this series, and the prevalence of these bacteria found in respiratory cultures is shown in Figure 1. The most important bacterial pathogen associated with CF from the perspective of prevalence and pathogenicity is Pseudomonas aeruginosa. P. aeruginosa is found in almost 80% of patients with CF by 18 years of age; overall 54.4% of the patients are infected. Once P. aeruginosa has established a home in the respiratory tract of CF patients, the clinical course can worsen. Infection with chronic, mucoid P. aeruginosa is associated with poor growth, more rapid decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death. Therefore, effective antimicrobial therapies targeting this pathogen are central to the management of CF.

Other pathogens may also adversely affect the clinical course in CF. Burkholderia cepacia complex may be associated with a very rapid deterioration of lung health, but the prevalence is too low to design studies of treatment strategies, including inhaled antibiotics. Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) is increasing in CF and is a concern for patients and healthcare workers alike. While epidemiologic studies show that CF patients with MRSA infection tend to have lower pulmonary function than those who are not infected, it is unclear whether the MRSA is responsible for that, or if it is just a marker for more aggressive antibiotic therapy in patients with increased disease severity. Therefore, it is not yet certain that MRSA is a reasonable target for inhaled antibiotic strategies. The preponderance of evidence for using inhaled antibiotics is in treating P. aeruginosa infection, so that will be the focus in this discussion.

Antibiotics used to treat P. aeruginosa include aminoglycosides, β-lactams, polymyxins, and fluoroquinolones. Delivering antibiotics via aerosol makes particularly good sense for CF, since the infection is mostly limited to the endobronchial space. The concept of using aerosol antibiotics in CF was actually introduced in 1946, but it was not until the 1980s and 1990s, when more efficient aerosol devices became available, that they became part of CF treatment regimens. This review will detail the rationale and challenges for using inhaled antibiotics, factors in selecting candidate drugs, indications for inhaled antibiotics, current drugs in use, and novel formulations and delivery systems in development.

Evolution of Lung Infections in Cystic Fibrosis

The assumption is that the lungs of CF newborns are not infected, but they become so early in life. While Staphylococcus aureus and Haemophilus influenzae are fairly common in early childhood, P. aeruginosa can be isolated from 30% of children by their first birthday. A model for the time course of P. aeruginosa can be seen in Figure 2. Early infection typically involves P. aeruginosa in a non-mucoid or planktonic form. Following the first identification of P. aeruginosa there is a variable period of intermittent or transient infection, during which time the organism is not detectable every time the patient has a culture sent. If this is left untreated, most patients will eventually develop chronic infection with mucoid strains of P. aeruginosa, which form a structured community enmeshed in an exopolysaccharide matrix called a biofilm. A biofilm offers several protective mechanisms for bacteria such that cells in the biofilm state are several times more resistant to antibiotics than in the planktonic state. In most cases, mucoid P. aeruginosa infections cannot be eradicated, even with aggressive antibiotic regimens, so a strategy for eradication must incorporate early and frequent surveillance cultures to identify the P. aeruginosa before mucoid strains gain a foothold in the airways.

Rationale for Use of Inhaled Antibiotics

The main benefit of topical inhalation of antibiotics is the same as that for other inhaled drugs in other lung diseases: namely, to deliver relatively high doses of drug directly to the location of the disease (the airways) while minimizing the systemic exposure and toxicity. The therapeutic effect of an inhaled antibiotic depends on the amount of drug deposited in the airways, how well the drug distribution matches the location of the bacteria, and if the local concentration of antibiotic achieved is adequate to kill the microbes. The lung dose may need to be on the order of tens of milligrams in order to overcome protective mechanisms of the bacteria and other variables that interfere with antibiotic effects. Achieving high airway con-
centrations with systemic drugs (oral or intravenous) may require doses known to have systemic toxicity, so aerosolizing them makes sense. For example, intravenous aminoglycosides (eg, gentamycin, tobramycin, amikacin) are highly polar and penetrate poorly into the endobronchial space. In one pharmacokinetics (PK) study, intravenous administration of tobramycin at 6–10.8 mg/kg/d in a group of CF patients yielded an average maximum serum concentration (Cmax) of 7.5 μg/mL, with an average sputum Cmax of 100 μg/g of sputum.13 Aerosolization of tobramycin solution for inhalation (TSI) (300 mg) gave an average sputum Cmax of 1,200 μg/g sputum, (12-fold higher than intravenous) while systemic absorption yields an average serum Cmax of only 1 μg/mL.14

How can we be sure that the antibiotic is reaching the right target in the airways? The short answer is that we can’t be sure. The numerous variables that guide how an aerosol distributes in the lungs were recently reviewed.15 CF patients come in all sizes, ages, and disease severities, and there is a large amount of variability between patients in how much drug reaches the lower airways and where it distributes. For example, in a patient with severe airway obstruction, there may be infected areas with poor ventilation that are not penetrated by aerosol; bacteria in such areas may be protected from aerosol antibiotics and may repopulate the airways when antibiotics are discontinued. Also, microbes may not be evenly distributed between different lobes.16 Dosing strategies must account for these factors by using high enough doses to treat the “worst-case scenario.”

Finally, there are other considerations that may affect tolerability of inhaled antibiotics, including pH, osmolality, and chloride content. If these values are outside certain ranges, the drug may provoke coughing and bronchospasm.17,18 Historically, inhaled antibiotics were extemporaneously compounded from intravenous formulations that

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**Fig. 1.** Prevalence of bacteria species cultured from respiratory secretions in cystic fibrosis patients, from the Cystic Fibrosis Foundation 2007 registry. (From Reference 3, with permission.)

**Fig. 2.** A model of progression of pseudomonas infection from intermittent to chronic infection. Inhaled antibiotics are frequently used during the period of intermittent infection to prevent or delay the time to chronic infection. (Adapted from Reference 11.)
commonly contain preservatives, which may also provoke bronchospasm when inhaled. Though the early studies of inhaled antibiotics used these intravenous formulations, we cannot take comfort that this approach will always be effective or safe for patients. A good example is contained in the package insert of intravenous doripenem (a carbapenem similar to meropenem and imipenem) that states, “When doripenem has been used investigationally via inhalation, pneumonitis has occurred. Doribax should not be administered by this route.” The pneumonitis occurred in healthy volunteers, so one can only imagine what may happen if this were tried in a CF patient!

Antibiotic Selection: Factors to Consider

A number of factors should be considered when designing an inhaled antibiotic strategy for treating airway infections. Clearly there should be in vitro activity against the bacteria, taking into account the range of minimum inhibitory concentrations (MICs) in the CF population. The costs of goods and development, ability to aerosolize the compound, possible drug interactions, and potential toxicities are important. The time burden of drug administration is important to the patients and caregivers, and was summarized by Kesser in this series.

The presence of purulent sputum may affect the activity of some antibiotics, but not others. For example, aminoglycoside activity is significantly inhibited by mucins, DNA, and divalent cations: components of purulent sputum. By increasing the concentration of the aminoglycoside in sputum to 25 times the MIC, the antagonism from sputum can be overcome and bactericidal activity restored. The antimicrobial activities of non-aminoglycosides, such as aztreonam and levofloxacin, are not inhibited by CF sputum. Clearly the activity of the antibiotic in the presence of sputum has important implications for dosing strategies of these compounds.

Antibiotics can be categorized by the pharmacodynamic (PD) parameters that best predict efficacy. In the case of pseudomonas, most β-lactam antibiotics (synthetic penicillins, cephalosporins, monobactams, and carbapenems) display “time-dependent” killing (ie, the duration of time the drug concentration remains above the MIC of the bacteria). Conversely, aminoglycosides and fluoroquinolones display a “concentration-dependent” pattern (ie, the ratio of maximum drug concentration [or the area under the concentration-time curve] to the MIC [Fig. 3]). These agents (but not most β-lactams) also demonstrate a post-antibiotic effect with P. aeruginosa, which is a time period of bacterial growth suppression after the drug concentration falls below the MIC. Thus, β-lactams may require more frequent doses to keep the lung concentration above the MIC, whereas aminoglycosides and fluoroquinolones use “shock-and-awe” concentrations to kill the microbes, and are effective with less frequent dosing.

Possible Indications for Inhaled Antibiotics

Possible uses for aerosol antibiotics include prophylactic use to prevent infection, eradication of early infection, suppressive treatment of chronic infection, and acute treatment of pulmonary exacerbations. In 1997, the CF Foundation convened a panel of experts that concluded that there was only enough evidence to make recommendations about chronic suppression therapy. Several studies have been published since then, but the evidence still supports mainly chronic suppressive treatment, though interest in using inhaled antibiotics remains high for other purposes.

Prophylaxis

The goal of using an antibiotic chronically for prophylaxis is to prevent infection and subsequent lung damage. This strategy has been studied with oral antibiotics for S. aureus, with mixed results, as reviewed by Davies in this series. Since P. aeruginosa is associated with worse clinical outcomes, prophylaxis against P. aeruginosa has been suggested, but there are few data supporting this approach. Heinzl et al studied 28 P. aeruginosa culture-negative children over 3 years, and found that those who took inhaled gentamycin for the entire time remained culture negative, whereas 43.8% of those who stopped the
antibiotic early developed chronic \textit{P. aeruginosa} infection.\textsuperscript{27} Besides the paucity of data supporting prophylaxis against \textit{P. aeruginosa}, the risks of this approach include cumulative drug toxicity, selection of species resistant to the drug, and an incredible investment of money and time for an unproven therapeutic approach.

**Eradication**

Early isolates of \textit{P. aeruginosa} from airway secretions are usually non-mucoid phenotype, susceptible to most anti-pseudomonal antibiotics, and are present in relatively low numbers, which presents a window of opportunity to wipe out the infection before it develops defense systems and becomes chronic.\textsuperscript{11} The immediate outcome measure for aerosol antibiotics to eradicate early infection is absence of organisms after treatment (microbiologic outcome), which we hope will prevent the onset of chronic infection and its sequelae. It is now common practice to try to eradicate \textit{P. aeruginosa} from the lower airways when it is first isolated in CF patients, though there are no convincing data yet to show that early eradication of \textit{P. aeruginosa} improves the long-term prognosis. In part due to limitations of culture techniques, accurate diagnosis of early lung infection is problematic, as is determining if eradication has actually occurred.\textsuperscript{28} Nevertheless, evidence is fairly compelling, and this practice is now so ingrained in the CF community that it is unlikely that a long-term, placebo-controlled trial will ever be performed for this indication.

Several protocols for \textit{P. aeruginosa} eradication have been tried, including intravenous, oral, and inhaled antibiotics, or combinations thereof.\textsuperscript{29} An early study of intravenous azlocillin and tobramycin for first \textit{P. aeruginosa} infection showed respiratory cultures were negative at the end of therapy in 18 (64\%) of 28 subjects, but in only 5 in 14 of 15 subjects.\textsuperscript{36} The second placebo-controlled trial used a much larger dose of tobramycin (TSI, 300 mg) and showed negative BAL cultures at the end of treatment, it was unclear whether eradication or suppression of growth had occurred. A second study clarified the issue, and used open-label TSI for 4 or 8 weeks in \textit{P. aeruginosa}-positive children, with a follow-up BAL 3 months later, and an additional 3 children were culture-negative after a second eradication attempt (88\% total). Though this study used the best culture technique (BAL) to demonstrate early infection and success of eradication, it did not show which elements of the treatment were the most useful, and whether they were all necessary.

The only placebo-controlled trials of early \textit{P. aeruginosa} treatment had very few subjects and used inhaled tobramycin as a single agent. One small study of tobramycin 80 mg versus placebo inhaled twice a day for 12 months showed a reduction of positive cultures in the treated group at the end of the year.\textsuperscript{35} A follow-up, open-label study using the same treatment regimen showed negative \textit{P. aeruginosa} cultures one year after stopping the therapy in 14 of 15 subjects.\textsuperscript{36} The second placebo-controlled trial used a much larger dose of tobramycin (TSI, 300 mg) and showed negative BAL cultures at the end of only 4 weeks of treatment in all 8 of the TSI-treated children, versus only 1/13 of the placebo group.\textsuperscript{37} Since the second bronchoscopy was performed coincident with the end of treatment, it was unclear whether eradication or suppression of growth had occurred. A second study classified the issue, and used open-label TSI for 4 or 8 weeks in \textit{P. aeruginosa}-positive children, with a follow-up BAL done 1–3 months after treatment. Lower-airway eradication was successful in 63–82\% of the children at the second BAL, up to 3 months after treatment.\textsuperscript{38} Though the follow-up period after treatment was relatively short, evidence of eradication of \textit{P. aeruginosa} with TSI alone seems just as good as combinations of inhaled plus oral or intravenous antibiotics. We still lack evidence from large randomized trials to define the optimal drug(s), doses, delivery methods, and duration of treatment for early \textit{P. aeruginosa} eradication. Since many of the physicians treating CF patients utilize early intervention, the goal of treatment should be to find the least invasive, safest, and shortest-duration treatment regimen that achieves the desired microbiologic and clinical outcomes.
Two major studies were designed to answer some of these remaining questions. The ELITE (Early Inhaled Tobramycin for Eradication) study enrolled 123 subjects at sites across Europe to provide evidence for the proper duration of treatment. Of the enrollees, 88 subjects were randomized to receive either a 4-week or 8-week treatment course of TSI 300 mg twice a day. Subjects were followed for 27 months with further cultures of respiratory secretions. Both groups achieved early eradication of > 90%, and at the end of the trial, 70% of the subjects in both groups were still culture-negative. Those authors concluded that a single 4-week treatment course with TSI is just as effective as the longer treatment course for P. aeruginosa eradication.40

A second ambitious study sponsored by the CF Foundation is in progress to answer other questions about eradication treatment, including whether combination therapy is needed, and whether initial treatment should be continued after the first cycle. The EPIC (Early Pseudomonas Infection Control) trial is enrolling 300 CF patients with first-time P. aeruginosa isolation, and randomizing them to 4 treatment arms.40 All patients are initially treated with TSI for 4 weeks, and half are randomly assigned to cotreatment with either oral ciprofloxacin or placebo. The patients are then followed for 18 months, with some patients randomized to receive treatment with TSI with or without ciprofloxacin every 3 months, regardless of culture results, and the others to receive courses of treatment only when they are P. aeruginosa-positive again. Results from this trial may be available in late 2009, and will shed more light not only on the treatment strategy, but also on whether the treatment will cause selective pressure that favors resistant bacterial strains.

**Chronic Suppressive Treatment**

The most robust evidence for the use of inhaled antibiotics in CF is for suppression of chronic infection. Chronic lower airway infection with P. aeruginosa is associated with a mucoid phenotype, biofilm formation, and a more rapid decline in the clinical course.1,2,4-6 The conditions associated with chronic infection (ie, exopolysaccharide coating, hypoxic environment) protect the microbes from phagocytosis, antibiotic penetration, and killing, which makes it almost impossible to eradicate the organisms. The treatment goals for aerosol antibiotics for treatment of chronic infection are to reduce the bacterial load, improve lung function and reduce CF morbidity and mortality.

Since the early 1980s there have been several studies of inhaled antibiotics in CF, including aminoglycosides, β-lactams, and polymixins.41 Early studies had small sample sizes, different patient ages and disease severities, different study designs and treatment regimens, and no taste-masking of drug. The studies employed nebulizers with different performance levels and used extemporaneous solutions compounded from intravenous formulations that contained preservatives. Despite those drawbacks, most of the early studies showed benefits in one or more categories, including lung function, slower decline in lung function, pulmonary exacerbations and hospitalizations, clinical scores, weight gain, and P. aeruginosa sputum density.41

Further, there did not seem to be any serious safety issues with inhaled antibiotics. Many of the early studies used tobramycin, which helped to inspire the development and commercialization of TSI (TOBI), described in more detail below.

Recent guidelines regarding chronic treatments for the maintenance of lung health in CF addressed aerosol antibiotics use for chronic infections.42 These evidence-based guidelines state, “For patients with CF, 6 years of age and older, who have moderate to severe lung disease and with P. aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations.”42 In patients 6–15 years old with milder lung disease and chronic P. aeruginosa, it was found that TSI reduced the pulmonary exacerbation rate but did not improve the forced expiratory volume in the first second (FEV1), so these guidelines recommended the chronic use of inhaled tobramycin for that healthier population as well.43 As the evidence in children less than 6 years is sparse, no recommendations were made for that group. However, the new European guidelines on inhaled medications in CF state, “All patients chronically infected with mucoid P. aeruginosa should be offered this treatment (inhaled antibiotics) irrespective of lung function.”43

Inhaled colistin is also frequently used for chronic P. aeruginosa infection, though there are no randomized, placebo-controlled trials that favor its use. The only placebo-controlled trial did not show a significant difference in the rate of FEV1 decline over the 90-day treatment period between colistin and placebo.44 A comparison study between colistin and TSI was performed with 115 CF patients and a 4-week treatment course. Both treatments reduced P. aeruginosa sputum density, but only the TSI group had a significant improvement in FEV1 of 6.7%.45 The study was performed in the United Kingdom, where colistin treatment was common, but inhaled tobramycin was not used frequently. Therefore, one may expect a more robust response to TSI treatment in a naive population. The North American guidelines found insufficient evidence to recommend for or against the use of colistin for chronic P. aeruginosa infection.42 In the United States, many caregivers prescribe compounded, off-label colistin for use in the “off” months of TSI cycles, for patients with multi-resistant or pan-resistant organisms, or for those who cannot tolerate TSI.46 Use of intravenous formulations for
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Pulmonary Exacerbations
A pulmonary exacerbation occurs when new signs and symptoms occur or when chronic symptoms worsen and require intervention. The few data available on the addition of inhaled aminoglycosides to intravenous antibiotics showed no clinical benefit, and there are no data available on the use of inhaled antibiotics alone for the treatment of exacerbations. Despite the lack of evidence, inhaled antibiotics are currently used for this indication. A recent paper surveyed a large CF database in the United States and looked at practice patterns regarding inhaled antibiotics from 1996 through 2005. Not surprisingly, the use of inhaled antibiotics overall increased, from 35% to 58% of the population over the decade, coincident with the approval and adoption of TSI as a chronic therapy. However, between 2003 and 2005, inhaled antibiotics were also used in 24.3% of the exacerbation events, either alone or in combination with oral or intravenous antibiotics. In 2005, almost 40% of patients used inhaled antibiotics only on a chronic basis; 13.3% used them both chronically and for exacerbations, and 5.4% used them only for an exacerbation. Since the practice is fairly widespread with no supporting evidence, the use of inhaled antibiotics for treatment of mild out-patient exacerbations or as an adjunct to oral and intravenous antibiotics is a ripe area for further study.

Tobramycin Solution for Inhalation: Lessons Learned

The safety and efficacy of aerosolized tobramycin in CF is the most thoroughly documented of all inhaled antibiotics. A brief look at the clinical development of TSI is very instructive, as it touches upon many of the factors involved bench characterization of nebulizer devices, microbiology of P. aeruginosa, PK/PD, and clinical trials that ultimately culminated in the commercialization and approval of TSI. They accounted for many of the variables already discussed to develop a dose and delivery strategy for tobramycin. They not only recognized the inhibitory effect of sputum on tobramycin activity, but also that the inhibition differed between patients, so they sought to achieve sputum concentrations that were 100 times the MIC of the organisms (at least 400 μg per gram of spu-tum). Bench and sputum PK studies showed that the De-Vilbiss UltraNeb 100 ultrasonic nebulizer had good tobramycin delivery characteristics. The UltraNeb 100 was used in 2 studies of CF patients who inhaled 600 mg of tobramycin 3 times daily for 4 to 12 weeks. Significant improvement in lung function was seen after 2–4 weeks of treatment, but declined thereafter. Sputum density of P. aeruginosa decreased, but resistant strains of P. aeruginosa developed transiently in the 12-week study. The high, inhaled doses were safe and well-tolerated. Despite the apparent success of these studies, the high cost of the unapproved therapy, and the cumbersome, inefficient delivery system prevented its acceptance by patients and caregivers. A more convenient system was needed.

Subsequent in vitro and PK studies demonstrated that the Pari LC Plus jet nebulizer could achieve the same high sputum levels of tobramycin in most CF patients with half (300 mg) the nominal dose. The Pari LC Plus was used for the large pivotal trials of TSI (5 mL, 60 mg/mL), which was formulated as a preservative free, pH-adjusted, and chloride-adjusted solution to minimize cough and bronchospasm.

The phase-3 trials randomized over 500 CF subjects with moderate to severe lung disease, 6 years and older, to either TSI 300 mg or placebo nebulized twice daily (not 3 times daily, as in the earlier trials), in 3 cycles of 28 days on, 28 days off therapy. One would assume that twice-daily dosing was chosen because tobramycin has concentration-dependent killing, and requires less frequent dosing. By happenstance, it was also discovered that most subjects in the earlier trials of thrice-daily dosing skipped the middle dose, yet it still had clinical benefit. An alternating-month regimen was chosen because the beneficial effect of TSI on lung function appeared to peak at 4 weeks, and by allowing an “off” month the antibiotic selective pressure for resistance may be reduced. At the end of 3 treatment cycles, FEV1 improved by 11.9%, P. aeruginosa density fell significantly and there were fewer hospitalizations and courses of intravenous antibiotics in the TSI group. All subgroups showed benefit, but the group that achieved the best improvement in pulmonary function was the adolescent age group. PK analysis showed that absolute bioavailability was about 11.7%, with large variability in sputum levels. Almost all subjects had peak sputum levels more than 10 times the MIC of their organism, and 95% had concentrations more than 25 times the MIC. Systemic exposure and incidence of adverse effects were low. A 72-week open-label extension study showed that the original TSI group continued to have an FEV1 benefit of 4.7% above baseline. Of interest, even subjects with resistant strains of P. aeruginosa had clinical benefit with TSI, which argues that MIC break-points for resistance may be irrelevant for inhaled tobramycin.
In 1998 TSI was approved by the Food and Drug Administration for use with the Pari LC Plus nebulizer. Even though the time burden was reduced by going to twice daily dosing and using the jet nebulizer, the treatments were still time-consuming (almost 20 min each). To further improve delivery efficiency, newer tobramycin formulations and aerosol devices have been studied, including an experimental, breath-actuated, vibrating-mesh device,\(^6^8\) more concentrated tobramycin solutions (up to 120 mg/mL) in jet nebulizers,\(^5^9,^6^0\) the eFlow vibrating-mesh device,\(^6^1\) and the controlled inhalation Akita device (Activaero, Germany).\(^6^2\) Many of these technologies are reviewed by Kesser in this journal.\(^2^1\)

Though treatment times were reduced with these techniques, there were still device requirements for cleaning and disinfection that may impact patient adherence. Using a dry-powder-inhaler (DPI) approach for delivery can remove that barrier. Nektar Therapeutics (now part of Novartis) developed tobramycin inhalation powder, a light, porous-particle formulation delivered with a simple passive DPI.\(^2^1\) PK studies found that delivery efficiency was almost 3 times greater with tobramycin inhalation powder than the standard TSI nebulized treatment, and equivalent pulmonary delivery could be accomplished in only 3–4 min, without the need for device cleaning.\(^6^3\) Two large clinical trials have been performed, and the results from the placebo-controlled study in CF patients with moderate lung disease show lung-function improvement similar to that in the original TSI pivotal trials.\(^6^4\) Thus we see that in the decade since approval of TSI, there are ongoing efforts to improve treatment efficiency and adherence to therapy, with the goal of better patient outcomes.

**Novel Aerosol Antibiotic Formulations in Development**

Ideally, having a panel of inhaled drugs from different antibiotic classes would provide better treatment options and reduce the risk of bacterial resistance. The experience gained from TSI development has enabled others to develop new inhaled antibiotics with a more rational and streamlined approach. All of the new formulations outlined below have much faster delivery times than TSI delivered via jet nebulizer.

**Aztreonam Lysinate for Inhalation**

Of the new formulations, aztreonam lysinate for inhalation (Gilead Sciences, Seattle, Washington), a new inhaled antibiotic for treatment of pseudomonas infection in CF, has progressed the most toward regulatory licensing. During the development of aztreonam lysinate for inhalation for CF, many of the variables discussed previously (ie, activity in sputum, PK/PD, dosing intervals, delivery time) were addressed. The standard intravenous formulation of aztreonam, a monobactam antibiotic, contains arginine that has been shown to cause inflammation after chronic inhalation.\(^6^5\) Therefore, the drug was reformulated as a lysine salt for inhalation. Preclinical studies showed that nebulization had little effect on the activity of the drug, and that the presence of sputum did not interfere with bacterial killing.\(^2^3\) A proprietary eFlow nebulizer was chosen in the early stages to shorten treatment time (under 3 min). PK studies showed variable but high sputum concentrations that remained above the MIC of 90% of the pseudomonas strains for at least 4 hours.\(^2^3\) Further clinical trials demonstrated improved lung function and quality-of-life scores, reduced bacterial density in sputum, and less need for other antibiotics in the subjects who took aztreonam lysinate for inhalation, versus placebo, for 4 weeks.\(^6^6,^6^7\) Another phase-3 trial compared twice-daily to three-times daily dosing of aztreonam lysinate for inhalation and found no clinical differences after one 4-week cycle.\(^6^8\) However, an open-label add-on study showed that those patients who remained on 3 doses a day in subsequent cycles had a better clinical response, consistent with an antibiotic that demonstrates time-dependent killing, which requires more frequent dosing.\(^6^9\)

**Aminoglycosides**

A liposomal formulation of amikacin is being developed for inhalation with the eFlow (Arikace, Transave). In an in vitro model, investigators showed that the liposomes can penetrate biofilm, which is a major defense system for *P. aeruginosa*.\(^7^0\) Also, the enzymes in sputum and factors associated with *P. aeruginosa* can help release amikacin from the liposomes, thus targeting the drug to the bacterial microenvironment.\(^7^0\) Whether this occurs in vivo is still unclear, but the “Trojan horse” concept of introducing antibiotics directly into a biofilm is appealing. The liposomes release the drug over time, which prolongs the residence time in the airway and might reduce the dosing frequency to once daily or less. A European phase-2 placebo-controlled study showed that 280 mg and 560 mg daily doses improved FEV\(_1\) versus placebo after 28 days, and the beneficial effect was sustained for another 4 weeks in the high-dose group. Fewer hospitalizations were observed and there was a longer time before rescue anti-pseudomonal antibiotics were needed in the amikacin groups.\(^7^1\)

**Fluoroquinolones**

Two fluoroquinolones are in early development for inhalation in CF. These drugs also demonstrate concentration-dependent killing, and are not inactivated by the presence of purulent sputum. Levofloxacin (MP-376, Mpxe
Pharmaceuticals, San Diego, California) is being developed as a solution for use in the eFlow mesh nebulizer. Two phase-1 studies of 3 ascending doses of MP-376 showed high sputum concentrations with low systemic exposure, a decrease in sputum *P. aeruginosa* density, and good tolerability.\textsuperscript{72, 73} A larger phase-2 study is currently in progress.

Ciprofloxacin (Bayer Healthcare, Germany) has been formulated as a light, porous powder for a capsule-based DPI,\textsuperscript{74} and is also in phase-2 trials. Aradigm (Hayward, California) is developing a liposomal ciprofloxacin formulation for nebulization. In an open-label study in Australia and New Zealand, they showed that CF patients treated with liposomal cipro had a decrease in sputum *P. aeruginosa* density, and an almost 7% increase in FEV\textsubscript{1} over baseline.\textsuperscript{75} Based on the characteristics of these drugs, it may be possible to achieve therapeutic effects with once-daily dosing.

One possible criticism of liposome formulations of amnoglycosides and fluoroquinolones is that these classes of antibiotics have concentration-dependent killing, so prolonging the residence time in the airway at sub-MIC levels (toward the end of a long dosing interval) may promote the emergence of resistant bugs. On the other hand, technologies that increase residence time in the airways make perfect sense for β-lactams (time-dependent killing). The benefits and risks of liposomes will become more evident in future, larger studies.

Fosfomycin

Fosfomycin is a phosphonic-acid antibiotic with activity against both Gram-positive and Gram-negative bacteria. The growing concern about MRSA in the CF population (see Fig. 1) has encouraged discussion regarding effective treatments. Fosfomycin, in combination with tobramycin, is being developed for inhalation by Gilead Sciences, and may have activity against both MRSA and *P. aeruginosa*.\textsuperscript{76} Phase-2 trials are beginning, and the eFlow device will be used to deliver this formulation.

Non-Antibiotic Antimicrobials

Besides antibiotics, other novel formulations are being considered in CF to kill microbes in the airways. An important mechanism of virulence for *P. aeruginosa* is the attachment to host cells and injection of exotoxins into the cells. Kalobios (Pari, Palo Alto, California) has developed a recombinant, human antibody (KB001) to interfere with that process, and a phase-1 trial with single intravenous doses is under way.\textsuperscript{77}

NanoBio (Ann Arbor, Michigan) has developed a surfactant-stabilized, oil-in-water nanoemulsion that has antimicrobial effects on species of *Pseudomonas*, *Burkholderia*, and other microbes that are multiple-drug-resistant.\textsuperscript{78} The nanoemulsion was effective in vitro against bacteria in the planktonic form, in biofilms, and in the presence of CF sputum, and holds promise for the treatment of CF airway pathogens. Importantly, no resistance to the nanoemulsion has been observed so far.\textsuperscript{78}

**Risk of Antimicrobial Resistance**

The use of chronic antibiotics can cause selective pressure favoring resistant organisms, whether the antibiotic is given intravenously, orally, or inhaled. In some of the early studies of inhaled tobramycin over several weeks, a majority of the subjects developed less susceptible strains of *P. aeruginosa*.\textsuperscript{51, 79} In the pivotal trials of alternate-month TSI for 6 months, there was only a subtle increase in the *P. aeruginosa* MIC values, and there was no increase in the isolation rate of other bacteria that are inherently resistant to tobramycin.\textsuperscript{80} However, there was an increase in the isolation of *Candida albicans* and *Aspergillus* from sputum at the end of 3 antibiotic cycles.\textsuperscript{80} The clinical relevance of this finding is unknown, since there was a clinical response even in patients known to have highly resistant strains.\textsuperscript{57} It is likely that the high levels of antibiotics achieved in the airways with direct inhalation still exceed the MIC in most areas, but because of the nature of deposition patterns of inhaled drugs, there will be areas of variable antibiotic concentrations in the airways, and the areas that have low concentrations may allow selection of more resistant microbes. The strategy of alternating months of antibiotics is to reduce the selective pressure on the bacteria. The TSI studies showed that the sputum density of *P. aeruginosa* trended back to baseline in the off-months, but the benefit in pulmonary function was largely preserved.\textsuperscript{55} Studies of novel inhaled antibiotics also look vigilantly for the emergence of resistant microbes\textsuperscript{66, 68} and diminution of the clinical response over time.\textsuperscript{69} It is only with time that we will discover whether “drug holidays” or alternating chronic antibiotics will prevent the emergence of multi-resistant organisms in CF.

There may be a perceived risk of inhaled antibiotics on the patient caregivers and the environment. Family members and hospital staff are exposed to low levels of antibiotics from nebulizers, as is the surrounding environment. There are no published data to support the conjecture that low-level environmental contamination leads to pathogen resistance; this needs further study.

**Summary**

Early studies in CF showed the potential for clinical benefit with inhaled antibiotics, even though the many
variables that affect outcome were not considered. The 2 principal indications for inhaled antibiotics are for eradication of early infection, and for chronic suppressive therapy. The development of TSI illustrates how consideration of aerosol delivery and microbiological and PK/PD variables can lead to a rational dose regimen. Minimizing the treatment burden for patients is now considered very important by companies developing inhaled antibiotics. In the future this should provide more diverse treatment choices, improved delivery efficiency, shortened administration times, and better adherence and outcomes for CF patients.

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Discussion

Newton: Do you use the Pari LC Plus to deliver TOBI [inhaled tobramycin] in the hospital?

Geller: Yes, but there’s more than one answer. We ask patients to bring in their own Pari LC Plus, but if they don’t remember to, we use the disposable Pari, even though it does not deliver as much as the LC Plus; there’s no one-way valve in the disposable version. The problem is that most of the time we don’t deliver TOBI in the hospital, so it’s not a common thing because we don’t add it to intravenous therapy.

Newton: What about the pharmacy mixes for TOBI in the eFlow nebulizer?

Geller: A lot of folks compound tobramycin and colistin and a lot of other things. With compounded drugs you lose something, in that they are not regulated by the Food and Drug Administration any more; they depend on the states to regulate compounding pharmacies. At a compounding pharmacy in Orlando the top brass were hauled off to jail because of anabolic steroids.

What we’re looking for is time-savings and maybe cost-savings. Some companies are trying to compound drugs that already exist on the market and have been validated for safety and efficacy. We have none of that with a compounded product. Though the concept of compounding seems to make sense—it’s still tobramycin, it’s the same thing, and an in vitro bench study showed that you can deliver X milligrams in the respirable range with this one and it’s exactly the same as that one—the problem is that the in vitro bench results do not necessarily translate to the patient.

In some of those studies they doubled the concentration and did the study with a Mobileaire compressor and found it was exactly equivalent to the output from the LC Plus with TOBI, but we discovered that in people there was a 40% difference in the pharmacokinetics.1 And there’s the safety issue. Decreasing the aerosol administration time is desirable, but we can’t endorse a new compound of drugs unless we’re sure it’s safe.

Newton: I agree.

Geller: Cool, but I imagine that there are others who disagree. I also want to shorten delivery time—now, not 5 years from now when it might be approved. The patients want it now. I think what’s going to happen is that, if aztreonam had been approved last week, we’d be talking about this a lot more because that’s delivered with the eFlow and patients would want to use their other medications in the eFlow. So there are a lot of issues tied in with that.

Marshall: I’m struck by the marked difference in the use of colistin in the United States and the United Kingdom and other European countries. Why are practice patterns so different?
Davies: Partly the difference is historical. When I started at the Royal Brompton Hospital in 1990, Margaret Hodson had been using nebulized antibiotics for a long time, and that practice had transferred down to the pediatric clinic; it was extremely commonplace. And at the time I think there wasn’t a license for a similar type of agent in the United States. I think nebulized antibiotics have “grown up” historically in the United Kingdom and parts of Europe in that context. I think there has been a bit of a problem for some clinics with the acceptance of newer agents that, by and large, have not been compared head-to-head in any good clinical trials. I think you mentioned that one trial compared colimycin with TOBI, but in that trial all the patients were already maintained on long-term colimycin and we wouldn’t necessarily expect an FEV₁ improvement on continuation, whereas there was an improvement when they switched to TOBI. I think it probably boils down to history and licensing. It certainly seems that acceptance and widespread use of nebulized antibiotics has taken longer in the United States.

Ratjen: In mainland Europe there was more use of low-dose—the intravenous solution—of tobramycin than of colistin. But when TOBI came to the market, there was already 15–20 years of experience with inhaled antibiotics, so the feeling in the community was, “Please show us that this is really better than what we’re currently using.”

We were missing 2 important data sets: a head-to-head comparison of tobramycin and colistin, and a dose-finding study of tobramycin. The story that you presented is very nice, but you can also present it in a different way, with how the doses were developed for tobramycin, because we don’t have any good data that prove that it needs to be 300 mg and that 150 mg wouldn’t do the job.

Novartis was struggling with that when they took over the product, because they were asking, where are the data? I think people in Europe thought the existing data inadequate: comparing the new product just to placebo will not do the job. That tells us the story of how we’re going to deal with new antibiotics, because it’s nice to get some placebo-controlled data, but the important question will always be, how does it compare to current practices; without that data, uptake in the community will be slow.

Geller: In a lot of the earlier trials, the way the dose was picked had nothing to do with MIC, sputum inactivation, or anything like that. It had to do with how the drug came in the vial, so the most common TOBI dose was 80 mg, because it came in a 2-mL (80 mg) vial and you just dumped it in the nebulizer. I have heard some of the back-room stories about how they chose the TOBI dose, and it made no sense.

I was trying to present the scientific way that you might think about doing it, because TOBI is now the accepted standard because it’s the only one that’s been approved. To figure out the right dose now you might say, “That’s the benchmark, so, is our new drug inactivated by sputum?” For example, ciprofloxacin and levafloxacin are not, so, theoretically, you don’t need 300 mg of those drugs, but you still probably have to do a dose-ramping study and get toxicity data.

It’s quite complex, and there’s probably a way of figuring out whether TOBI would work once a day instead of twice a day, whether it would work at half the dose versus the full dose. But I think we can say that we have this bell-shaped curve or geometric curve of patients, and how much drug they get in and how much you need in there to kill the bacteria, and you’re trying to control for the worst-case scenario. You’re trying to get 95% of your patients covered by the drug with the factors and conditions that they have to use it. That said, you’re going to “overdose” a lot of people. So until we develop better ways of determining aerosol doses, we’ll always be looking to treat the worst-case scenario.

Davies: Why didn’t the Food and Drug Administration approve aztreonam?

Geller: I don’t know.