Inhaled Antibiotics for Lower Airway Infections

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Abstract

Inhaled antibiotics have been used to treat chronic airway infections since the 1940s. The earliest experience with inhaled antibiotics involved aerosolizing antibiotics designed for parenteral administration. These formulations caused significant bronchial irritation due to added preservatives and nonphysiologic chemical composition. A major therapeutic advance took place in 1997, when tobramycin designed for inhalation was approved by the U.S. Food and Drug Administration (FDA) for use in patients with cystic fibrosis (CF) with chronic *Pseudomonas aeruginosa* infection. Attracted by the clinical benefits observed in CF and the availability of dry powder antibiotic formulations, there has been a growing interest in the use of inhaled antibiotics in other lower respiratory tract infections, such as non-CF bronchiectasis, ventilator-associated pneumonia, chronic obstructive pulmonary disease, mycobacterial disease, and in the post-lung transplant setting over the past decade.

Antibiotics currently marketed for inhalation include nebulized and dry powder forms of tobramycin and colistin and nebulized aztreonam. Although both the U.S. Food and Drug Administration and European Medicines Agency have approved their use in CF, they have not been approved in other disease areas due to lack of supportive clinical trial evidence. Injectable formulations of gentamicin, tobramycin, amikacin, ceftazidime, and amphotericin are currently nebulized "off-label" to manage non-CF bronchiectasis, drug-resistant nontuberculous mycobacterial infections, ventilator-associated pneumonia, and post-transplant airway infections. Future inhaled antibiotic trials must focus on disease areas outside of CF with sample sizes large enough to evaluate clinically important endpoints such as exacerbations. Extrapolating from CF, the impact of eradicating organisms such as *P. aeruginosa* in non-CF bronchiectasis should also be evaluated.

Keywords: aerosol; inhaled antibiotics; lower airway infection

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The rationale for inhaling antibiotics is to maximize drug delivery to the target site of infection (i.e., the airways) and limit the potential for systemic side effects. Aerosol delivery of antibiotics was first reported in the 1940s (1), but the early use of inhaled antibiotics was hampered by the lack of reliable nebulizer systems to maximize delivery to the airway. Most of the early formulations, which consisted of reconstituting antibiotics designed for

parenteral administration, were poorly tolerated by patients due to hyperosmolality and added preservatives (i.e., phenols), which induced bronchial irritation and bronchospasm.

A major therapeutic advance took place in the 1990s, when aerosolized tobramycin was evaluated in patients with cystic fibrosis (CF) chronically colonized with *Pseudomonas aeruginosa* (2, 3). A multicenter, double-blind, placebo-

controlled, crossover trial (2) and two subsequent large randomized placebo-controlled trials (3) used preservative-free formulations of tobramycin with an osmolality that closely matched airway surface liquid. These pivotal studies demonstrated improvements in lung function, decreased exacerbation rate, and reductions in sputum bacterial load (see Table E1 in the online supplement). The U.S. Food and Drug Administration (FDA)

subsequently approved inhaled tobramycin in 1997 (4).

Today, CF remains the only pulmonary condition in which inhaled antibiotics have received FDA and European Medicines Agency approval, although randomized controlled trial (RCT) evidence is continuing to emerge and accumulate in other conditions outside of CF. This review provides an update on the current state of knowledge by examining the evidence for use of inhaled antibiotics in both CF and non-CF pulmonary disease, highlighting ongoing uncertainties and areas where additional research is needed.

Cystic Fibrosis

As reviewed by the European CF Society Consensus Group (5), the earliest studies of inhaled antibiotics in CF focused on inhaled aminoglycosides—specifically, tobramycin, gentamicin, and amikacin. Aminoglycosides were chosen because of their limited absorption across epithelia permitting high concentrations at the site of infection and minimizing systemic toxicity. Based on the landmark studies conducted on tobramycin inhalation solution mentioned above, clinical guidelines for chronic stable CF lung disease continue to note a high level of evidence supporting the use of inhaled tobramycin in chronic

P. aeruginosa infection in both the United States and Europe (6–8).

Two other antimicrobials have received extensive clinical attention in CF: inhaled aztreonam (a monobactam) and inhaled colistin (a polymyxin). Nebulized aztreonam lysine inhalation solution (AZLI, Cayston; Gilead Sciences, Foster City, CA) was approved in 2010 by the FDA with the indication to improve respiratory symptoms but not specifically for chronic use. Approval was based on two randomized, placebo-controlled phase 3 trials (Table E1) that demonstrated improved lung function (FEV₁) and respiratory symptoms and decreased sputum *P. aeruginosa* density after 28 days' administration of 75 mg AZLI either twice or three times a day as compared with placebo (9, 10). An open-label extension after the phase 3 trials involved up to nine treatment cycles, each consisting of 28 days on and 28 days off drug. Thrice-daily dosing (75 mg) was chosen as the optimal regimen because of greater improvements in FEV₁ and patient-reported respiratory symptom scores and is currently recommended for clinical care (11). Cyclic improvements in lung function and symptoms were consistently observed during on-treatment months, although the magnitude of the effects was smaller than in the earlier clinical trials (11).

Inhaled colistin, the polymyxin derivative colistimethate sodium

(Colomycin; Forest Labs, New York, NY), has been used extensively in Europe and the UK for treatment of chronic *P. aeruginosa* infection and to a lesser extent in the United States (12). In a systematic review by the Cochrane Collaboration, the authors only found two trials with 54 participants comparing colistin to placebo, both of which were problematic for interpretation (13); thus, the published evidence for efficacy and safety is limited. Inhaled colistin has recently been reformulated as a dry powder inhaler using capsules containing the equivalent of 125 mg colistimethate sodium (1,662,500 IU) in fine particle form (14). This study agent was found to be noninferior to tobramycin inhalation solution in a randomized nonblinded comparator trial in 380 patients with CF after 24 weeks of every-other-month therapy (14). The results of this study are difficult to interpret because neither inhaled antibiotic demonstrated an improvement in the primary endpoint, FEV₁, calling into question the integrity of the study. This agent has now been approved for marketing in Europe as Colobreathe (Forest Labs), but it is not FDA approved. The only FDA-approved colistimethate is colimycin, approved in 1970 as an intravenous/intramuscular formulation for treatment of susceptible gram-negative bacilli such as *P. aeruginosa*.

Table 1. Inhaled antibiotics for cystic fibrosis

Drug	FDA Indication	Established Clinical Use	Notes
Aztreonam solution (Cayston)	To improve respiratory symptoms in patients with CF and <i>Pseudomonas aeruginosa</i> infections $\geq$ 6 yr of age and FEV ₁ > 25% and < 75%	Chronic pulmonary <i>P. aeruginosa</i> infection	Alternating-month use is common
Colistin solution (Colomycin)	An intravenous/intramuscular formulation to treat or prevent acute or chronic gram-negative bacterial infection (including <i>P. aeruginosa</i>)	Chronic pulmonary <i>P. aeruginosa</i> infection	
Colistin dry powder (Colobreathe)	N/A*	Chronic pulmonary <i>P. aeruginosa</i> infection	Not FDA approved
Tobramycin solution (TOBI, Novartis)	Management of patients with CF with <i>P. aeruginosa</i> infection > 6 yr of age, FEV ₁ > 25% and < 75%. Treatment schedule is 28 d on therapy alternating with 28 d off therapy	Chronic pulmonary <i>P. aeruginosa</i> infection	Alternating-month use
Equivalent formulation: TEVA Pharmaceuticals, USA		<i>P. aeruginosa</i> eradication	
Tobramycin dry powder (TOBI Podhaler)	Management of patients with CF with <i>P. aeruginosa</i> infection > 6 yr of age, FEV ₁ > 25% and < 80%. Treatment schedule is 28 d on therapy alternating with 28 d off therapy	Chronic pulmonary <i>P. aeruginosa</i> infection	Alternating-month use Not currently used for <i>P. aeruginosa</i> eradication

Definition of abbreviations: CF = cystic fibrosis; FDA = U.S. Food and Drug Administration; N/A = not applicable.

*EMA approved but not FDA approved.

Figure 1. Drug development pipeline. Reprinted by permission from Reference 76.

Although there are several therapeutic options already approved in the United States and worldwide for CF (Table 1), additional inhaled antibiotics are in late-stage development (Figure 1), including levofloxacin inhalation solution (MP-376, Aeroquin; Aptalis Pharma, Bridgewater, NJ) (15), liposomal amikacin (Arikace; Insmad, Monmouth Junction, NJ) (65), and fosfomycin/tobramycin for inhalation (FTI; Gilead Sciences) (16). In addition, there is increasing interest in developing inhaled antimicrobial therapies for respiratory pathogens other than *P. aeruginosa*. Two examples of ongoing clinical trials in CF include the use of inhaled vancomycin (AeroVanc; Savara Pharmaceuticals, Austin, TX) (Table 2) for treatment of methicillin-resistant *Staphylococcus aureus* and liposomal amikacin (Arikace; Insmad) (NCT 01315236) for the management of chronic mycobacterial infections (Table E2).

As reviewed above, the literature supporting the use of inhaled antibiotics in CF in the setting of chronic stable disease is extensive. It is not surprising that 69% of U.S. patients colonized with *P. aeruginosa* use inhaled tobramycin and 3% use inhaled aztreonam based on data from the 2012 Cystic Fibrosis Foundation national patient registry (5). There are several important clinical questions, however, that remain in this population, including the use of inhaled antibiotics to eradicate *P. aeruginosa* in patients with recent onset of infection, the role of inhaled antibiotics in acute infection—commonly termed a pulmonary exacerbation (17)—and the optimal regimens for use given the multiple inhaled antibiotics now available.

Eradication of *P. aeruginosa* in patients at initial onset of infection has been well

studied in the young, pediatric population (18–20). These large, well-designed studies have demonstrated that *P. aeruginosa* can be eradicated in both the lower and upper airways in the majority of patients, and patients remain *P. aeruginosa* free for months (21), even with inhaled tobramycin monotherapy (18). The impact on clinical endpoints, such as frequency of exacerbations, is less clear (18), and these patients were too young to reproducibly perform pulmonary function testing. As the age of *P. aeruginosa* onset increases in the CF population, the role of *P. aeruginosa* eradication in the adult population will need to be evaluated.

The role of inhaled antibiotics for acute pulmonary exacerbation is not well studied. A recent Cochrane review found six RCTs of inhaled antibiotics in CF pulmonary exacerbations involving 208 patients with CF (22). The trials were heterogeneous in trial designs and interventions so they could not be pooled in a formal metaanalysis. The primary comparison in these trials was intravenous antibiotics with or without inhaled antibiotics for CF pulmonary exacerbation. The systematic review concluded that the

trials were not powered with large enough sample sizes to demonstrate efficacy, so that routine use of inhaled antibiotics in this setting is not recommended (22).

One of the additional key unanswered questions is how best to implement multiple inhaled antibiotics in the clinical setting. Based on the original studies of tobramycin solution for inhalation, inhaled antibiotics have been cycled every other month. The basis for this pattern of use was the concern for the development of resistance in the setting of chronic antibiotic exposure. As noted by a recent European CF Society Consensus Group, there are limited data to support this theory, and the clinical relevance of the development of resistance in an organism is far from clear (6). A common clinical practice among CF clinicians is to alternate different inhaled antibiotics, thus providing continuous suppressive antibiotics to the airway surface liquid. There are no efficacy data, however, supporting this treatment approach. There is currently an RCT that is evaluating alternating month tobramycin solution for inhalation with placebo on the off month compared with tobramycin solution for inhalation and inhaled aztreonam on alternating months (NCT 01641822), which may shed light on the benefit of this alternating antibiotic regimen.

Non-CF Bronchiectasis

The primary treatment goals for non-CF bronchiectasis are to improve symptoms, reduce infective exacerbations, and optimize health status (23). To determine if the clinical benefits of nebulized tobramycin observed in CF could be extrapolated to non-CF bronchiectasis, a few small RCTs have been conducted over the past decade. Tobramycin solution for inhalation was examined in a placebo-controlled, double-blind, randomized study of 74 patients

Table 2. Inhaled antibiotics for non-cystic fibrosis bronchiectasis

Drug	Potential Indication	Notes
Gentamicin	Chronically infected sputum with frequent exacerbations (≥ 2 in past yr) <i>Pseudomonas aeruginosa</i> eradication	Studied as continuous and not alternating-month use Clinical benefits not sustained once drug is stopped
Tobramycin	Chronic pulmonary <i>P. aeruginosa</i> infection Frequent infectious exacerbations <i>P. aeruginosa</i> eradication	Not rigorously studied but might reduce more severe exacerbations and eradicate <i>Pseudomonas</i> in one-third of cases

with bronchiectasis and grossly purulent sputum containing *P. aeruginosa* (Table E1) (24). Over the 4-week treatment period, there was a significant reduction in sputum *P. aeruginosa* density (one-third eradicated *P. aeruginosa*), but no improvement in lung function was observed, and tobramycin-treated patients were more likely to report an increase in cough, wheezing, and dyspnea.

A subsequent crossover RCT of tobramycin solution for inhalation in 30 patients with non-CF bronchiectasis and *P. aeruginosa* treated over a longer period of 6 months demonstrated a reduction in the number of more severe exacerbations requiring hospitalization but no significant change in the overall number of exacerbations, pulmonary function, or quality of life (Table E1) (25).

These two small studies examining tobramycin formed the basis for the 2010 British Thoracic Society non-CF bronchiectasis guidelines, which provided a level C recommendation for the use of long-term nebulized antibiotics in non-CF bronchiectasis (23). However, the guidelines mention that patients could be considered for long-term nebulized antibiotics if: (1) they are chronically colonized by *P. aeruginosa*, and (2) they experienced three or more exacerbations per year that caused significant morbidity (Table 2).

Shortly after publication of the 2010 British Thoracic Society guidelines, nebulized gentamicin was evaluated over a continuous treatment period of 1 year in an RCT involving 65 patients with non-CF bronchiectasis (Table E1) (26). In contrast to prior studies examining tobramycin, patients with bacteria other than *P. aeruginosa* were also included. Nearly half of patients (48%) were infected with *P. aeruginosa* at baseline, 41% had *Haemophilus influenza*, and the remainder had *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Similar to tobramycin, patients on treatment had reduced sputum bacterial density (one-third of patients with *P. aeruginosa* eradicated this organism) and symptoms but no change in lung function. Benefits were not sustained in the 3-month follow-up period off therapy (Table 2).

A number of other inhaled antibiotics, such as nebulized liposomal amikacin, nebulized aztreonam lysine, and both nebulized (27) and dry powder forms (28) of ciprofloxacin, are being investigated in

Table 3. Inhaled antibiotics for ventilator-associated pneumonia

Drug	Potential Indication	Notes
Colistin	Adjunctive therapy to intravenous antibiotics in multidrug-resistant gram-negative pulmonary infections (<i>P. aeruginosa</i> or <i>Acinetobacter baumannii</i>)	May improve microbiologic outcomes but no proven clinical benefits

both phase 2 and 3 clinical trials in non-CF bronchiectasis (Table E2).

Ventilator-Associated Pneumonia

Aerosolized antibiotics have been studied as alternative or adjunctive agents to intravenous antibiotics in patients with ventilator-associated pneumonia caused by gram-negative bacteria (29). The initial motivation for exploring inhaled antibiotics in these settings were the high rates of treatment failure reported when intravenous aminoglycosides were used alone or in combination with other intravenous antibiotics to treat drug-resistant gram-negative bacteria in intubated patients and patients with tracheostomy (30). Based on the consensus guidelines created by a joint committee of the American Thoracic Society and Infectious Diseases Society of America in 2005, aerosolized antibiotics were not considered valuable in the treatment of ventilator-associated pneumonia but “could be considered as adjunctive therapy in patients with multi-drug resistant (MDR) gram-negatives who are not responding to

systemic therapy” (Table 3) (31). Since this document was published, there have been two RCTs investigating nebulized antibiotics as alternative or adjunctive agents to intravenous antibiotics in ventilator-associated pneumonia, and both have demonstrated favorable microbiologic responses but no impact on other clinical or radiographic outcomes (32, 33) (Table E1).

Aerosolized antibiotics have also been evaluated as prophylaxis for ventilator-associated pneumonia. A metaanalysis of five RCTs involving about 400 patients demonstrated a reduction in the risk of ventilator-associated pneumonia for patients assigned to nebulized antibiotics compared with placebo, but no reduction in mortality was observed (34). Nebulized antibiotics for ventilator-associated pneumonia prophylaxis were not recommended in the 2005 American Thoracic Society/Infectious Diseases Society of America consensus document due to concerns about the promotion of antibiotic resistance and the design limitations of published RCTs (31, 35).

Table 4. Inhaled antibiotics for post-lung transplant infections

Drug	Potential Indication	Notes
Amphotericin	Routine antifungal prophylaxis post-transplant to prevent invasive aspergillosis (not universally adopted) Adjunctive treatment in post-transplant <i>Aspergillus</i> infections Adjunctive treatment in anastomotic infections by <i>Aspergillus</i> or <i>Candida</i> species	Liposomal form is comparable in effectiveness but better tolerated Not rigorously studied
Colistin	Post-transplant prophylaxis in patients with pretransplant infection with multidrug-resistant organisms (<i>Pseudomonas aeruginosa</i> or <i>Burkholderia cepacia</i>)	Not rigorously studied Typically used for 3 mo
Tobramycin	Post-transplant prophylaxis in patients with pretransplant infection with multidrug-resistant organisms (<i>P. aeruginosa</i> or <i>B. cepacia</i>)	Not rigorously studied Typically used for 3 mo

Post Lung Transplantation

Inhaled antibiotics have been used off-label to prevent and treat bacterial and fungal infections after lung transplantation over the past few decades, but rigorous RCTs evaluating their use post lung transplant have not been conducted. Despite broad-spectrum intravenous antibiotic prophylaxis, pneumonia risk is estimated at 10 to 20% within the first 30 days post transplant, with even higher rates observed among patients with CF (36, 37). As a prophylactic measure to prevent allograft gram-negative bacterial infections, inhaled aminoglycosides and colistin have been used as adjunctive agents to intravenous antibiotics in patients with CF post-transplant, especially in patients who have a history of pretransplant colonization with multidrug resistant gram-negative organisms (such as *P. aeruginosa* or *Burkholderia cepacia*) (Table 4) (38).

Lung transplant recipients have higher rates of invasive *Aspergillus* infections compared with other solid organ transplant recipients, due to more intense immunosuppression and altered mucociliary clearance (39, 40). Given the high mortality rates associated with invasive *Aspergillus* infections, routine antifungal prophylaxis is common but not universally adopted (41). Nebulized amphotericin B has been investigated as antifungal prophylaxis in a few nonrandomized, comparative studies (42–44). In two separate studies, nebulized liposomal amphotericin B was compared with nonliposomal amphotericin B deoxycholate. In both studies, rates of invasive *Aspergillus* infections were low and comparable between the two treatment groups, but the liposomal form was better tolerated (42, 43). Inhaled antifungal agents have also been used as adjunctive agents to systemic antifungals in patients with devascularized anastomotic infections caused by *Aspergillus* or *Candida* spp. In the few small, retrospective studies that have been conducted to date, the combination of systemic amphotericin B and/or fluconazole with nebulized amphotericin B resulted in favorable clinical outcomes (Table 4) (45, 46).

Mycobacterial Infections

No RCTs have investigated inhaled antibiotics in patients with tuberculous (TB) or nontuberculous mycobacterial (NTM)

Table 5. Inhaled antibiotics for mycobacterial disease

Drug	Potential Indication	Notes
Amikacin	Adjunctive therapy in treatment refractory cases of nontuberculous mycobacterial disease	Not rigorously studied in a randomized controlled trial, but improves microbiologic outcomes and symptoms

lung disease to date, but this remains a very active area of research (47, 48). Inhaled antitubercular antibiotics have the potential to be used as adjunctive agents to conventional systemic therapy to augment therapeutic drug levels or as part of second-line anti-TB regimens. Mycobacteria are prototypic intracellular pathogens that reside within alveolar macrophages. A potential advantage of inhaled antibiotics in this setting is that drug particles can be phagocytosed by alveolar macrophages within the airways and alveoli, resulting in higher drug concentrations within the macrophage cytosol than would otherwise be achieved using systemic agents, potentially overcoming drug resistance (47).

For TB, respirable insoluble micro- and nanoparticles of rifampin and isoniazid have received the most research attention but have been limited to animal studies thus far (49, 50). Liposomal forms of antitubercular medications such as amikacin and capreomycin are also undergoing development (51, 52).

For NTM lung disease, nebulized nonliposomal amikacin was added to standard therapy in a nonrandomized, uncontrolled study of 20 patients with treatment-refractory NTM disease followed at the National Institutes of Health. This adjunctive therapy resulted in improved symptoms and microbiologic outcomes, but one-third of patients had to stop treatment due to toxicity (53) (Table 5). Nebulized liposomal amikacin is currently undergoing phase 2 study in subjects with recalcitrant lung disease caused by *Mycobacterium avium* complex and/or *Mycobacterium*

abscessus on a stable multidrug regimen (NCT 01315236).

Chronic Obstructive Pulmonary Disease

There are no published RCTs examining the effects of inhaled antibiotics on health outcomes in chronic obstructive pulmonary disease, but two studies have been presented in abstract form. A phase 2 multicenter, RCT involving levofloxacin for inhalation (MP-376) (54) demonstrated that the study drug was well tolerated, but treatment did not reduce the exacerbation rate. In a small, uncontrolled study of patients with severe chronic obstructive pulmonary disease and colonization with multidrug-resistant *P. aeruginosa*, tobramycin solution for inhalation was administered at a dose of 300 mg twice daily for 14 days (55). There was a significant reduction in sputum inflammatory mediators at the end of the 2-week treatment period and a 42% reduction in the incidence of acute exacerbations in the 6 months post-treatment, when compared with the 6 months pretreatment. With these limited data, it is not possible to assess efficacy or safety of inhaled antibiotics in this population (Table 6).

Dosing and Administration

Several antibiotics, such as gentamicin, amikacin, ceftazidime, and amphotericin B, designed for parenteral administration have been repurposed for nebulization and used off-label to treat lower airway infections (Table 7). Most of these drugs have been studied in a nonrandomized, uncontrolled manner, and therefore

Table 6. Inhaled antibiotics for chronic obstructive pulmonary disease

Drug	Potential Indication	Notes
Tobramycin	Overlapping bronchiectasis with purulent sputum production and chronic infection with <i>Pseudomonas aeruginosa</i>	Not rigorously studied

Table 7. Inhaled antibiotics currently used in clinical practice

Generic Name	Brand Name	Disease Indications	Formulation	Recommended Dose/Frequency	Delivery Device	Adverse Effects
Approved use Aztreonam	Cayston	CF	Inhalation solution	75 mg nebulized three times a day	Altera eFlow nebulizer	Wheezing
Colistin	Colomycin	CF; ventilator-associated pneumonia	Powder dissolved in saline	1–2 million units (75–150 mg) nebulized twice a day	Jet or ultrasonic nebulizer	Cough Bronchospasm Throat irritation
	Colobreathe	CF	Dry powder	125 mg (1,662,500 IU) inhaled twice a day	Turbospin inhaler	Cough Throat irritation Abnormal taste
Tobramycin	TOBI*	CF	Inhalation solution (5-mL ampule containing 300 mg tobramycin and sodium chloride, pH 6.0)	300 mg nebulized twice a day	PARI LC PLUS jet nebulizer	Tinnitus Dysphonia Bronchospasm Hearing loss
	Bethkis	CF	Inhalation solution (4-mL ampule containing 300 mg tobramycin and sodium chloride, pH 5.0)	300 mg nebulized twice a day	PARI LC PLUS jet nebulizer	Tinnitus Dysphonia Bronchospasm Hearing loss
Off-label use Amikacin	TOBI Podhaler	CF	Dry powder	112 mg inhaled twice a day	T-326 inhaler	Cough
	N/A	Nontuberculous mycobacteria	Injectable solution diluted with saline	250 mg nebulized daily (up to 500 mg twice a day if tolerated)	Jet nebulizer	Hearing Loss Vertigo Dysphonia Nephrotoxicity Shortness of breath Cough Abnormal taste Bronchospasm
Amphotericin B	Fungizone	Post-transplant fungal prophylaxis or treatment	Injectable solution diluted with sterile water	Prophylaxis: 25 mg daily for 4 d then weekly for 7 wk Double dose if mechanically ventilated	Jet nebulizer	
	Abelcet	Post-transplant fungal prophylaxis or treatment	Liposomal solution	Prophylaxis: 50 mg daily for 4 d then weekly for 7 wk Double dose if mechanically ventilated	Jet nebulizer	Cough Abnormal taste Bronchospasm
Ceftazidime	Fortaz	Ventilator-associated pneumonia; CF (<i>Burkholderia cepacia</i> infection)	Injectable solution diluted with saline	Ventilator-associated pneumonia: 15 mg/kg nebulized every 3 h for 8 d CF: 1 g nebulized twice a day	Jet nebulizer	
Gentamicin	N/A	Non-CF bronchiectasis	Injectable solution diluted with saline	80 mg nebulized twice a day	Porta-Neb Ventstream jet nebulizer	Bronchospasm Unpleasant taste

(Continued)

Table 7. (CONTINUED)

Generic Name	Brand Name	Disease Indications	Formulation	Recommended Dose/Frequency	Delivery Device	Adverse Effects
Tobramycin	N/A	CF	Injectable solution diluted with saline	80 mg nebulized twice a day	Jet nebulizer	Tinnitus Dysphonia Bronchospasm Hearing loss

Definition of abbreviations: CF = cystic fibrosis; N/A = not applicable.

*Two U.S. Food and Drug Administration–approved products available: TOBI (Novartis Pharmaceuticals) and the generic equivalent to TOBI (Teva Pharmaceutical Industries, Ltd.).

optimal drug dosing remains undefined. Optimal nebulizer systems also remain indeterminate, but most studies have used jet nebulizers, which use air or oxygen under high pressure to generate the aerosol (56). During mechanical ventilation, nebulizers are connected to the inspiratory limb of the ventilator circuit, and the antibiotic can be administered continuously or only during inspiration.

A major challenge to the use of inhaled antibiotics has been the prolonged administration time (typically 15–20 min) of the jet nebulizer systems. The recent development of more efficient nebulizer systems and formulations have been a major advance for antibiotic delivery to the lower airways and should improve patient convenience and therefore adherence to therapy. Two examples of these new technologies for administration of inhaled antibiotics are provided.

First, vibrating mesh nebulizers driven by piezoelectric actuators have been developed to replace the older compressor-driven jet nebulizers. Droplets generated are similar in size to the mesh aperture (usually about 3 μm), thus reducing heterodispersion (i.e., size variability) compared with conventional nebulizers. This advance significantly increases the efficiency of drug delivery to the lower airway and shortens nebulization time (57). Vibrating mesh nebulizers are also portable devices, as they are hand held and battery powered.

Second, advances over the past decade in particle engineering technology have resulted in the development of antibiotic formulations delivered by dry powder inhalation. Most recently, tobramycin inhalation powder (TIP; Novartis Pharmaceuticals, Basel, Switzerland) (58) was created using a process known as emulsion-based “spray-drying” (PulmoSphere technology), which transforms a solution or emulsion from a fluid state into many fine, dried, porous particles with uniform size distribution (1–5 μm) (58, 59). TIP is delivered with a portable, capsule-based inhaler that does not require an external power source. In addition, the device is breath actuated with low airflow resistance, and its delivery is independent of the patient’s peak inspiratory flow rate, thus reducing variability in drug delivery (60). Data available from two different controlled clinical trials involving more than 600

patients led to its approval in Europe, Canada, and the United States (trade name, TOBI Podhaler) (61, 62). Both trials demonstrated similar efficacy and safety to nebulized TOBI but noted increased cough with the TOBI Podhaler (Table E1).

Recently, studies of inhaled amikacin (Arikace; Insmed) have focused on liposomal formulations with the goal of protecting the antibiotics from the harsh environment of the sputum, improving penetration into biofilms, and allowing for more sustained release of drug within the airway, allowing for once-daily administration (63). Based on *in vitro* studies, liposomes demonstrate excellent penetration into CF sputum and *P. aeruginosa* biofilms (63). A phase 2 clinical trial in CF supported preliminary pharmacokinetics, safety, and efficacy of this therapy; we are awaiting the results of a European/Canadian comparator trial (64).

Adverse Effects of Inhaled Antibiotics

Known or potential adverse effects of inhaled antibiotics fall into three main categories: local, systemic, and emergence of antibiotic resistant organisms.

Local Effects

As mentioned above, topical effects include transient bronchoconstriction due to osmolality and preservatives within some of the solutions (65). In one study of different preparations of inhaled tobramycin, acute drops in both vital capacity and FEV₁ were very common (in preparations with and without phenol preservatives) but normalized quickly and were usually responsive to pretreatment with albuterol (66). Experience with inhaled aztreonam has also demonstrated acute changes in FEV₁ after inhalation, with the majority recovering to within 15% of baseline by 2 hours (67). In a comparator trial of tobramycin solution for inhalation and colistimethate sodium, airway reactivity (defined by a $\geq 10\%$ loss in FEV₁ 30 min after nebulization) was recorded in 11.3% of patients in the tobramycin group and 17.7% of patients in the colistimethate-treatment group (68). Due to the frequent occurrence of bronchospasm, patients are often routinely instructed to administer bronchodilators before dose. Altered taste, dysphonia, and throat irritation are also

commonly reported side effects related to inhaled antibiotics.

Systemic Effects

Current knowledge of the systemic effects of inhaled antibiotics remains limited, particularly for antibiotics under development. Systemic effects such as ototoxicity or nephrotoxicity were not noted in either phase 2 or 3 trials of inhaled TOBI (2, 69). Although extremely rare in patients with normal renal function, case reports have noted both ototoxicity and renal toxicity in patients with and without CF treated with tobramycin solution for inhalation or colistin, primarily in the setting of diminished glomerular filtration rate resulting in systemic drug accumulation (70–72).

Emergence of Antibiotic-Resistant Organisms

The most common clinical concern with chronic inhaled antibiotic administration is the emergence of drug-resistant pathogens. In the pivotal clinical trials in CF, 25% of participants in the trial had isolates of *P. aeruginosa* that had a minimal inhibitory concentration of greater than or equal to 8 µg/ml before the start of drug therapy

increasing to only 32% at Week 24 in the tobramycin-treated group (22). No change was noted in the placebo arm. Long-term follow-up of this study in a phase 4 trial noted continued development of resistance of tobramycin; after 12 treatment cycles (2 yr), the proportion of patients with an isolate with an minimum inhibitory concentration of greater than or equal to 16 g/mL increased from 10 to 41% (69). Despite this finding, the patients still appeared to derive a clinical benefit. Follow-up of the two phase 3 clinical trials of inhaled aztreonam noted small transient increases in aztreonam resistance, particularly in the twice-daily dosing; interestingly, this was associated with a decreased rate of carrying tobramycin-resistant *P. aeruginosa* (11, 73).

One of the other concerns raised regarding the use of inhaled antibiotics is the potential increase in the rate of non-*P. aeruginosa* intrinsically resistant pathogens. In an analysis of data from both the inhaled tobramycin and aztreonam phase 3 trials (11, 74), common multidrug-resistant bacterial pathogens isolated from the CF airway, *B. cepacia*, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*, were not found more

frequently with multiple cycles of inhaled antibiotics compared with placebo. Use of both antibiotics was associated with an increase in fungal colonization, such as *Candida* spp. (11, 74).

Conclusions

Inhaled antibiotics have a long history of use in the treatment of lower airway infections. These therapies have clearly transformed the management of CF and have likely led to improved clinical outcomes, as recently demonstrated in an observational assessment (75). Data will likely evolve in the next 5 years regarding non-CF bronchiectasis, post-lung transplant management, and ventilator-associated pneumonia. The medical community needs continued innovation to reduce the burden of these therapies while using alternative antimicrobial mechanisms. The future remains promising in the arena of inhaled antibiotic development, with the potential to use novel technologies to improve both drug delivery and compliance. ■

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