Expert Opinion

Aerosolised antibiotics: a critical appraisal of their use

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Aerosolised antimicrobial agents have been used in clinical practice since the 1950s. The main advantage of this route of administration is the targeted drug delivery to the site of infection in the lung. Exploitation of this targeted delivery can yield high concentrations at the site of infection/colonisation while minimising systemic toxicities. It is important to note that the ability of a drug to reach the target area in the lung effectively is dependent on a number of variables, including the nebuliser, patient technique, host anatomy and disease-specific factors. The most convincing data to support the use of aerosolised antimicrobials has been generated with tobramycin solution for inhalation (TOBI®, Chiron Corp.) for maintenance treatment in patients with cystic fibrosis. In addition to cystic fibrosis, the use of aerosolised antimicrobials has also been studied for the treatment or prevention of a number of additional disease states including non-cystic fibrosis bronchiectasis, ventilator-associated pneumonia and prophylaxis against pulmonary fungal infections. Key studies evaluating the benefits and shortcomings of aerosolised antimicrobial agents in these areas are reviewed. Although the theory behind aerosolised administration of antibiotics seems to be sound, there are limited data available to support the routine use of this modality. Owing to the gaps still existing in our knowledge base regarding the routine use of aerosolised antibiotics, caution should be exercised when attempting to administer antimicrobials via this route in situations falling outside clearly established indications such as the treatment of patients with cystic fibrosis or *Pneumocystis* pneumonia.

Keywords: aerosolised, antibiotics, bronchiectasis, cystic fibrosis, nebuliser, *Pseudomonas aeruginosa*, tobramycin

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1. Introduction

The concept of aerosolised antibiotics and the theoretical advantages associated with this route of administration have intrigued clinicians since the 1950s. Drug administration via inhalation allows for the targeted delivery of high concentrations of antimicrobials directly to the lungs, while minimising systemic toxicities.

Historically, if a clinician sought to use an aerosolised antimicrobial, the only option was to aerosolise an extemporaneously prepared product designed for systemic administration. It is important to note that these products are not formulated for inhalation and may possess characteristics undesirable for this route of administration. Some characteristics such as foaming solutions or bad taste reflect relatively benign complications that may affect compliance. More seriously, some intravenous antimicrobial preparations contain preservatives and other additives, such as bisulfites, phenol, or disodium edentate, which may precipitate airway hyper-responsiveness, cough and bronchoconstriction [1,2]. Other factors related to airway tolerability include drug pH, osmolarity and chloride ion concentration. Cough and bronchoconstriction may occur when these values

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fall outside the conventional range [3,4]. To decrease the risk of pulmonary adverse events, an optimal solution for inhalation should have a pH of 4.5 – 8.7 and an osmolality of 150 – 550 mOsm/kg [2-5]. In addition, the chloride ion concentration should fall between 31 and 300 mM [2,3,5]. Currently, the only FDA-approved antimicrobial that is specifically formulated for inhalation is tobramycin solution for inhalation (TSI; TOBI®, Chiron Corp.). TSI addresses many of these formulation concerns. It is a sterile, preservative-free formulation and has an appropriately adjusted pH and osmolality. Although the preservative-free inhalation formulation of tobramycin may be less irritating and better tolerated than the intravenous formulation when nebulised, bronchospasm may still occur [6,7].

In addition to the aminoglycosides, many other parenteral agents including ceftazidime, colistin, polymixin B, amphotericin B and pentamidine have also been administered via aerosol. These agents have been tested in a variety of settings, including patients with cystic fibrosis and non-cystic fibrosis bronchiectasis associated with *Pseudomonas aeruginosa*, prevention of ventilator-associated pneumonia (VAP), prophylaxis against pulmonary fungal infections in lung transplant patients, and prophylaxis of *Pneumocystis jiroveci* pneumonia.

An important concern with prolonged administration of antimicrobial agents by any route is the emergence of antibiotic-resistant organisms. A number of studies evaluating the use of inhaled tobramycin in patients with cystic fibrosis and non-cystic fibrosis bronchiectasis have demonstrated a small, often nonstatistically significant, increase in resistant strains of *P. aeruginosa* and/or increases in minimum inhibitory concentrations (MIC) of fourfold or greater [8-13]. The potential for evolving resistance is concerning. The clinician must take into consideration that treatment options may be negated if patients develop acute infections with pathogens that have become resistant to traditionally used parenteral agents.

2. Drug delivery

2.1 Deposition in the lungs

In order for aerosolised antibiotic therapy to be effective, a sufficient amount of drug must reach the appropriate region of the respiratory tract and be retained there long enough to produce its effect. The delivery of aerosolised drug to the lungs is a highly inefficient means of drug delivery. Only 1 – 20% of the dose, generally < 10%, placed in the nebuliser is deposited in the lungs [14-16]. The inefficiencies associated with this delivery modality are due to a variety of factors including the nature of nebulisers and the anatomy of the upper and lower respiratory tract.

Most of the drug solution placed in a nebuliser is wasted. Because commonly used nebulisers generate aerosolised droplets continuously during the respiratory cycle, wastage occurs when aerosolised drug produced during the expiratory cycle is not inhaled. Rather, this drug is released into the environment where it can be deposited on the patient's skin, other nearby surfaces, or inhaled by other individuals in close proximity to the patient. Drug is also lost when it is inhaled but not deposited in the lower airway. This portion of drug is readily exhaled into the environment. In addition, as much as 50% of the drug solution placed in the nebuliser becomes trapped by the device and never exits the nebuliser system. Tapping the walls of a nebuliser during use and increasing the amount of drug solution (fill volume) placed in the nebuliser can reduce the percentage of drug that becomes trapped in the nebuliser [16,17].

Drug deposition in the lungs is affected by the anatomy of the airways, the aerodynamics of the particles and the delivery system. The upper respiratory tract is designed to protect the lungs from inhalation of foreign particles. One example of this protection can be found in the nasal passages. The anatomical design of the nasal passages makes them especially efficient at removing particles > 1 µm [18]. Although inhalation following oral inspiration bypasses the filtering effects of the nasal passage, some level of protection against inhalation of particles > 5 µm is afforded. However, particles ≤ 5 µm may be able to reach the lower respiratory tract following inhalation via the mouth. As a result, oral inhalation is the preferred route when drug delivery via aersolisation is attempted. Even when agents are administered via this route, proper administration techniques must be used to minimise the amount of drug deposited in the mouth during the administration process.

Because of the protection provided to the host by the anatomical structure of the respiratory tract, particle size becomes a major determinant in the pulmonary deposition of drugs. In general, aerosolised particles 1 – 5 µm are considered to be within the respirable range following oral inhalation by healthy humans [18,19]. Particles ≥ 5 µm may deposit in the mouth and throat, or never make it out of the nebuliser. Particles 1 – 5 µm deposit within the lower respiratory tract according to three size-dependent mechanisms; impaction, sedimentation or diffusion. Larger particles within the respirable range are more likely to deposit in the large central airways of the lungs by impaction, to a degree dependent on their mass and inspiratory flow rate. As the particle size decreases < 3 µm, the potential for deposition in the smaller airways increases. In this particle range, sedimentation becomes the primary mechanism for drug deposition. Sedimentation occurs when gravity causes particles to settle. Retention time is the key factor that influences sedimentation. Holding one's breath and breathing pattern can alter the deposition of particles that deposit predominantly by sedimentation. Pulmonary deposition of particles < 1 µm is affected predominantly by diffusion. Particles of this diameter exhibit poor pulmonary deposition and retention characteristics, and are readily exhaled. By carefully controlling particle size it may be possible not only to optimise drug delivery to the lungs, but also to target specific regions of the lung [18-21].

Nebulisers typically used to generate aerosolised droplets generally produce a polydispersed aerosol. This means that

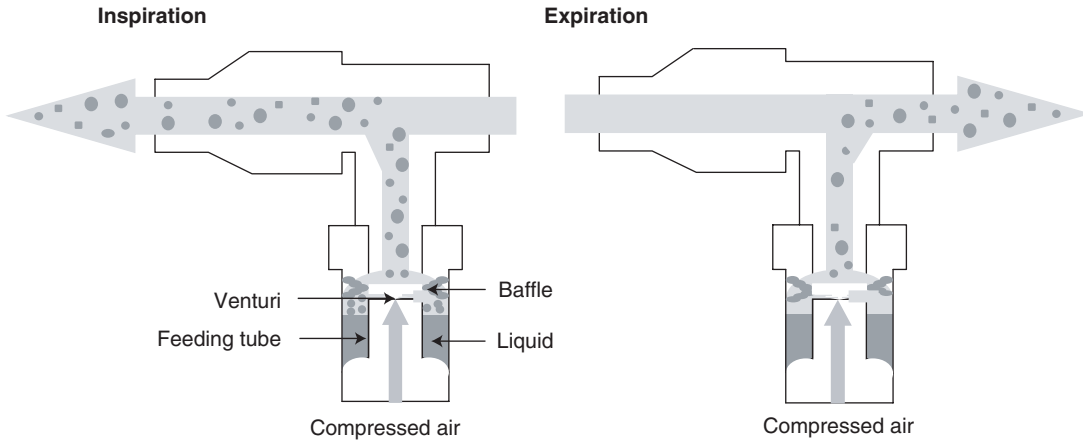

Figure 1. Conventional jet nebuliser design.

droplets of many different sizes are generated. The distribution of particle sizes in an aerosol is best described by the mass median aerodynamic diameter (MMAD). As clinicians, it is important to note that 50% of the aerosol mass contains particles smaller than the MMAD whereas the other 50% of the aerosol mass contains particles larger than the MMAD [20]. Therefore, it is important to keep the MMAD in mind when selecting a nebuliser for drug delivery. It is desirable to select a device that will generate a maximal number of droplets within the respirable range.

2.2 Nebuliser factors affecting drug delivery

There can be as much as a 10-fold difference in the amount of drug delivered between nebulisers [22], which makes proper nebuliser selection critical for optimal drug delivery to the patient. Improper selection of nebuliser and compressor combination could lead to therapeutic failure of a drug valuable in the treatment of the patient. It is interesting to note that TSI, the only antimicrobial currently FDA approved for aerosolised administration, was approved for use with a designated nebuliser (PARI LC PLUS®, PARI Respiratory Equipment) and compressor (Pulmo-Aide®, DeVilbiss) combination.

There are two common types of nebulisers, jet and ultrasonic nebulisers. Jet nebulisers are more commonly used in clinical practice than ultrasonic nebulisers. Jet nebulisers force compressed air through a small exit orifice creating a high velocity jet of air (Figure 1). As this jet of air exits the orifice it expands, creating a vacuum that pulls the drug solution up feed tubes from the nebuliser reservoir. Drug solution is sheared as it exits the feed tubes, thus creating a polydispersed aerosol. Droplets too large for inhalation are blocked from exiting the nebuliser by baffles and returned to the nebuliser reservoir for renebulisation [23]. Droplets within the respirable range may either exit the nebuliser or be pulled by gravity back into the nebuliser [24,25]. Jet nebuliser output is primarily dependent on the volume of liquid placed in the nebuliser cup (fill volume) and the flow rate of the compressed gas. Common fill volumes for jet nebulisers range from 2 to 6 ml, and most jet nebulisers require a gas flow rate of ≥ 6 l/min.

Traditional constant output jet nebulisers generate aerosolised droplets continuously during the inspiratory, expiratory and breath-holding phases of the respiratory cycle. Drug wastage occurs when the patient exhales and aerosolised droplets are pushed through the expiratory limb of the nebuliser into the ambient air. In contrast, the breath-assisted, open-vent nebuliser is a modified jet nebuliser that is designed to reduce the amount of drug wasted during the expiration phase and maximise drug deposition. A vent opens during inhalation drawing aerosolised particles through the mouthpiece. During exhalation the valve closes and prevents the output stream from exiting the nebuliser. Exhaled gas is routed out of an expiratory valve instead of through the nebuliser [24]. Nebulisers of this type have been found to have a higher output of aerosolised particles and produce more particles in the respirable range, making them a better choice for clinical application [25,26]. As nebuliser technology evolves it is likely that the efficiency of drug delivery will improve.

In contrast to jet nebulisers, ultrasonic nebulisers generate aerosol by high frequency vibration of the drug solution by a piezoelectric crystal. Like jet nebulisers, large particles are collected by baffles and prevented from exiting the nebuliser. One limitation of some ultrasonic nebulisers is the generation of heat during the nebulisation process. This temperature elevation may result in significant degradation of heat-sensitive agents [24].

With respect to jet nebulisers, particle size generated, volume of fluid placed in the nebuliser cup (volume of fill), compressed gas flow rate (flow rate), rate of output from the nebuliser, viscosity and surface tension of the solution to be nebulised are all factors that influence nebuliser performance

and pulmonary deposition of drug [5,16,22,26-28]. Unfortunately, standards have not been developed for nebulisers or compressors, making it difficult to compare systems and select the optimal nebuliser and compressor system to maximise drug delivery. In an assessment of nebuliser variability, Loffert *et al.* examined the output of normal saline with albuterol from 17 jet nebulisers [29]. In an attempt to minimise the differences between jet nebuliser operating conditions, the same flow rate (12.3 l/min) and volume of fill (2 ml) were used with all nebulisers. The authors reported a twofold (0.98 – 1.86 ml) variation in total fluid output, a ninefold (2.28 – 20.95 min) difference in time required to deliver the total fluid delivery, and a threefold (21.89 – 71.94%) difference in the percentage of fluid delivered in the respirable range among nebulisers. Although this study did not use antibiotic solutions, it clearly demonstrated the importance of the nebuliser on output variability. Another study investigated the output of gentamicin solution from four different jet nebulisers under different operating conditions [22]. Each nebuliser was operated at four different flow rates and two different fill volumes. In this study, the investigators noted a 10-fold difference in the amount of drug delivered between the least to the most efficient nebuliser system. In addition, as the flow rate was increased, droplet size and nebulisation time were decreased. These findings are clinically important because droplet size is related to drug deposition, and nebulisation time may influence absolute drug concentrations in the lung and may also affect patient compliance. The differences found in these studies are comparable to other studies that have examined nebuliser variability. Some of these studies evaluated both jet and ultrasonic nebulisers [5,14-16,26,28,30-32]. Coates *et al.* provides an excellent review of drug delivery via jet nebulisers [32].

Antibiotic output from nebulisers is highly variable and depends not only on the type of nebulising system but also on the properties of the antibiotic solution such as drug concentration in the solution [5]. A concentration-dependent increase in the viscosity of antibiotic solutions causes a decrease in the rate of solution nebulisation. Most antibiotic solutions contain a high concentration of drug causing the viscosity to increase. High viscosity solutions are especially problematic for ultrasonic nebulisers and can lead to unreasonably long nebulisation times. At high drug concentrations, some investigators have found it difficult or nearly impossible to nebulise the drug solution [5,33]. It is important to recognise that even if a solution with a relatively low starting concentration of drug is used, a reduction in nebulisation rate can occur with time as the solvent is preferentially aerosolised. As a result, the concentration of drug in solution increases with time resulting in increased solution viscosity within the nebuliser [5,22,33]. Therefore, selection of an appropriate starting drug concentration and selection of the proper administration system can be critical for the optimal delivery of an antibiotic to the lungs.

The future of aerosolised antibiotic delivery is promising. New delivery devices that work only on inspiration or eliminate the need for a traditional nebuliser are currently being researched. A passive dry powder for inhalation device using Pulmosphere™ (Nektar) tobramycin showed a ninefold improvement in pulmonary deposition over a standard nebulised treatment [34]. Another delivery system with potential is the Aerodose® 5.5 RP (Nektar): a hand-held, battery-powered, breath-actuated device. This device delivered tobramycin to the lung in < 50% of the time and with three times the efficiency of jet nebulisation [35]. These new delivery systems and others like them are likely to continue to be developed and improved, leading to better therapeutic outcomes in patients.

2.3 Patient factors affecting drug delivery

Drug deposition in the lung is also dependent on a variety of patient parameters such as tidal volume, inspiratory flow rate, breath holding pattern and airway diameter. An increase in tidal volume or in the breath-holding time results in increased deposition of particles in the terminal airways. However, inspiratory flow rate has the greatest influence on deposition in the tracheobronchial region. Overall antimicrobial deposition tends to increase when inspiratory flow is increased while controlling the number of inspirations per minute. Deposition of smaller particles, however, is reduced in the terminal airway as inspiratory flow rate is increased [16,36]. With respect to the diameter of the respiratory tract, anatomically the diameter of the bronchial tree decreases as the particle moves deeper into the lung or as a result of disease causing particle deposition to increase. However, it is important to note that larger particles may be restricted from reaching the desired region of the lung owing to the decreased airway diameter. Therefore, smaller particles may be necessary to achieve the desired delivery outcome [15,16,19,36].

Several challenges and issues exist when administering aerosolised drugs to young children and infants. Young children may be uncooperative to the nebuliser treatment. Fear of the nebuliser system may result in the alteration of patient breathing patterns or may result in improper administration technique. In addition, infants tend to breathe primarily through their nose, thus significantly reducing the amount of drug available to the lungs. A facemask is often used to aid with aerosol administration in this patient population. Use of a facemask allows drug to be administered regardless if the child breaths through their nose or mouth. Unfortunately, this dual route of inhalation can be less efficient than oral inhalation alone. Chua *et al.* found that following nasal inhalation lung deposition was 50% of that from oral inhalation in children aged 6 – 18 years, and that lung deposition was also lower in infants than in children aged 6 – 18 years following nasal inhalation [30]. However, the amount of drug deposited in the lungs of infants (3 – 24 months) could be increased using a facemask when particle size was reduced. The authors hypothesised that this occurred because the smaller particles were able to pass unfiltered through the nasal passage [15]. Although it is common practice to hold the facemask away from the face of an uncooperative child, this may reduce deposition

Table 1. Aerosolised tobramycin availability.

Study	Number of patients	Aerosolised dose	Mean absolute systemic availability
Touw *et al.* [40]	6	600 mg	17.5 ± 8.8% (SD)
Cooney *et al.* [41]	6	7.5 mg/kg/dose (mean 5.6 mg/kg/dose) Range 200 – 315 mg/dose	9.13 ± 3.82% (SD)
Geller *et al.* [39]	258	300 mg b.i.d. Three cycles of therapy 28 days on/28 days off	11.7%

SD: Standard deviation.

Table 2. Aminoglycoside sputum concentrations following aerosolised administration.

Study	Drug	Dose	Number of patients	Mean sputum concentration	Peak serum concentration	Portion of dose reaching lungs
Ilowite [16]	G	160 mg	8	376.5 ± 264 µg/ml	Undetectable	7.69 ± 3.7% (SD)
Mukhopadhyay [38]	T*	120 mg	27	400 µg/ml		6.7 ± 4.3% (SD)
Geller [39]	T	300 mg b.i.d. Three cycles of treatment 28 days on/28 days off	258	1237 ± 1090 µg/g (first dose) 1154 ± 1147µg/g (last dose)	0.95 ± 0.50 µg/ml (first dose) 1.05 ± 0.67 µg/ml (last dose)	

G: Gentamicin; SD: Standard deviation; T: Tobramycin; T*: Radiolabelled tobramycin.

and should be avoided. It has been reported that holding the facemask 1 cm and 2 cm away from the face in an *in vitro* model reduced the percentage of drug deposited by 60 and 85%, respectively [27].

Deposition of drug on the face and eyes should also be considered when selecting a nebuliser, compressor and facemask. Unintended topical exposure could increase the patient's risk for topical irritation and exposure of skin flora to the aerosolised antibiotic. A smaller particle size in combination with a vented facemask has been shown *in vitro* to reduce eye and face deposition of drug. This reduced topical exposure may reduce the potential for toxicity and undesired bacterial exposure at these areas [37].

3. Pharmacokinetics

The systemic bioavailability of an aerosolised antibiotic is dependent on the amount of drug absorbed from the lungs into the systemic circulation following inhalation, and the amount of drug swallowed due to deposition in the oropharynx. This is in turn dependent on how much of the antibiotic deposits in the lung and the degree of gastrointestinal absorption. As the amount of drug deposited in the lung can vary greatly, the relationships between dose administered, serum concentration and sputum concentration also tends to be highly variable (Table 1 and 2) [16,38,39]. Due to the inefficiency of aerosol administration, as little as 10% of the dose placed in a nebuliser is deposited in the lungs; therefore, the absolute availability would be expected to be low [40]. Whereas the systemic pharmacokinetics following inhalation have been described for some antibiotics, little data exist that describes the distribution, achieved levels and elimination of antimicrobials from the lungs.

Three pharmacokinetics studies have been published that have attempted to describe the serum pharmacokinetics of tobramycin following aerosol administration [39-41]. Not surprisingly, the authors found the absolute availability of tobramycin to be both low and variable. Two studies measured both peak serum and sputum concentrations, and found the serum:sputum ratio to be low [16,42]. Another study examined the accumulation of tobramycin in the sputum and plasma following administration of 300 mg b.i.d. for three treatment cycles (28 days on and 28 days off) [39]. The authors noted that drug accumulation did not occur in either the sputum or the plasma. In addition, the poor bioavailability noted in these studies indicates that a minimal amount of drug reaches the systemic circulation, thus implying a low risk of toxicity and adverse effects for the aminoglycosides when administered via inhalation.

Antimicrobials have the potential to bind to and/or interact with various components in the sputum, which may alter their activity in the lung [43,44]. For example, biological antagonism of aminoglycosides occurs in purulent sputum as a result of the antibiotic interacting with ions and binding to macromolecules in the sputum. As much as 52% of tobramycin in the sputum may be bound to mucin and, therefore,

biologically inactive [44]. The typical MIC for aminoglycosides against *P. aeruginosa* isolates is 4 mg/l in broth. In the presence of purulent sputum from cystic fibrosis patients, MIC values may be increased by 10- to 25-times [43,44]. Therefore, sputum concentrations ranging from 40 to 100 mg/l would be required to elicit bactericidal activity. As sputum concentrations following intravenous administration of an aminoglycoside are low relative to the target levels needed in purulent sputum (40 – 100 mg/l) [42-45], the serum concentrations required intravenously to overcome the antagonism would lead to severe toxicity. Despite differences in dose, nebuliser systems and patient populations, sputum concentrations achieved following inhalation generally exceed 100 mg/l.

Only a few studies have been carried out that look at the antibiotic levels in the sputum over time following inhalation, and most have only used tobramycin. One study determined sputum concentrations for 24 h following the administration of aerosolised tobramycin 120 mg. Although the authors of this study but did not draw any conclusions, it appear that there is highly variable clearance of drug from the lung [38]. Pulmonary pharmacokinetic data following inhalation are desperately needed. Data in this area needs to be generated to determine how the influence of disease and region of deposition within the lung affect drug levels and clearance.

4. Disease state review

4.1 Cystic fibrosis

Continued advances in the understanding and management of cystic fibrosis have led to an impressive increase in survival rates over the past decades. Currently, predicted survival age of patients with cystic fibrosis is > 32 years [46]. Although survival has increased, morbidity and mortality resulting from chronic pulmonary infections remains a critical concern. *Pseudomonas aeruginosa* is isolated in > 50% of all cystic fibrosis patients and in ~ 80% of patients over the age of 18 years [46]. Other organisms commonly recovered from cystic fibrosis patients include *Staphylococcus aureus*, which is the predominant organism in cystic fibrosis patients during the first decade of life, *Haemophilus influenzae* and *Burkholderia cepacia* [46]. The damage resulting from recurrent and chronic lung infections contributes to an average decline in forced expiratory volume for 1 s (FEV_1) of 2%/year [46].

A number of studies and review articles have been published on the use of aerosolised antimicrobials in patients with cystic fibrosis. Table 3 summarises some of the key studies evaluating the use of aerosolised antimicrobial agents in cystic fibrosis patients. Ramsey *et al.* and Burns *et al.* reported on the compilation of two parallel trials that were essential to the approval of TSI for the management of cystic fibrosis patients with *P. aeruginosa* [8,9]. The trials were identical in design. Both were multi-centre, double-blind, randomised and placebo-controlled. A total of 520 cystic fibrosis patients were enrolled in these studies. Patients received three cycles of TSI at a dose of 300 mg or a taste-masked placebo twice daily for 28 days on therapy, followed by 28 days off therapy. TSI was self-administered using a PARI LC PLUS® jet nebuliser and a Pulmo-Aide® compressor. An improvement in FEV_1 was noted by week 2 in the tobramycin group. In addition, among tobramycin-treated patients, the FEV_1 persisted above baseline during both on and off periods of administration. At week 20 of the trial, FEV_1 remained an average of 10% above baseline among patients treated with tobramycin. By comparison, the FEV_1 of patients receiving placebo had decreased by an average of 2% from baseline ($p < 0.001$). Patients treated with tobramycin also had a reduction in the density of *P. aeruginosa* in the sputum during all three drug administration periods. Although each treatment cycle had a lesser decrease in sputum density, at week 20 the decrease in sputum *P. aeruginosa* density in the patients treated with tobramycin was still significantly greater than patients treated with placebo ($p < 0.001$). During periods without tobramycin administration, *P. aeruginosa* sputum density rebounded towards baseline values. Patients in the tobramycin group had a decrease in number of hospitalisations and days of antipseudomonal antibiotic administration compared with patients in the placebo group. Although increasing exposure to TSI did result in an increase in the recovery of resistant *P. aeruginosa* isolates compared with placebo, the authors noted that an increased MIC did not necessarily correlate with a poorer clinical outcome, as patients with MIC levels deemed resistant also responded to therapy.

At the conclusion of the randomised trials, 396 participants continued into an open-label extension phase [47]. All participants that entered the open-label phase received cyclic TSI therapy (28 days on, 28 days off) for an additional 72 weeks. A total of 242 patients completed the 96 weeks. Although a gradual decline in FEV_1 was observed over the course of the study periods, the FEV_1 in patients originally randomised to tobramycin remained 4.7% above baseline at week 92. The patients that were originally randomised to placebo and crossed over to tobramycin at the start of the open-label phase also experienced an increase in FEV_1, which persisted above the level at the start of the open-label phase. Although the crossover group experienced an increase in FEV_1 after treatment with tobramycin began, the group never reached the peak FEV_1 that the patients in the original tobramycin group attained.

Inhaled tobramycin was well tolerated in both phases of these trials [8,9,47]. In the randomised phase, voice alteration and tinnitus were reported significantly more among patients receiving tobramycin than in patients receiving placebo ($p < 0.05$) [8,9]. The incidence of voice alteration declined over the 96-week study period [47], and significant hearing loss or nephrotoxicity was not noted throughout the series [8,9,47].

The most conclusive data for the use of aerosolised antimicrobial agents lies with the use of TSI in cystic fibrosis

Table 3. Cystic fibrosis.

Ref.	Study design	N	Treatment groups	Nebuliser type	Results	Comments
Jensen *et al.* [90]	R, DB, PC	29	Aerosolised colistin 1 MU (n = 18) or placebo (n = 11) b.i.d. × 3 months	Raindrop® nebulising chamber (Puritan-Bennett Corp.)	Lung function (FEV_1) Decrease in FEV_1 from baseline No significant difference from placebo Clinical score (90 days) Colistin: Score improved Placebo: Score declined ($p < 0.01$)	A 2-week course of parenteral tobramycin plus a β-lactam antibiotic was administered prior to study entry 40 patients were initially enrolled; 29 patients completed the study and were included in the end analysis
Ramsey *et al.* [53]	R, MC, DB, PC, CO	71	Aerosolised tobramycin 600 mg × 28 days, followed by placebo for two 28-day periods (n = 36) or placebo × 28 days, followed by aerosolised tobramycin for two 28 day periods (n = 35)	Ultraneb 100/ 99® ultrasonic nebuliser (DeVilbiss)	Lung function (FEV_1 mean change, period 1) TSI: +3.72% Placebo: -5.97% ($p < 0.001$) Sputum PA density (mean change, period 1) TSI: -2.12 $\log_{10}$ cfu/g Placebo: -0.16 $\log_{10}$ cfu/g ($p < 0.001$)	No significant difference in the emergence of resistant strains between tobramycin and placebo administration ($p > 0.5$)
Ramsey *et al.* [8] Burns *et al.* [9]	R, MC, DB, PC	520	TSI 300 mg (n = 258) or placebo (n = 262) b.i.d. for 28 days on therapy followed by 28 days off therapy × three cycles	PARI LC PLUS® jet nebuliser (PARI) and a Pulmo-Aide® compressor (DeVilbiss)	Lung function (FEV_1 mean change, week 20) TSI: +10% Placebo: -2% ($p < 0.001$) Sputum PA density (mean change, week 20) TSI: -0.8 $\log_{10}$ cfu/g Placebo: +0.3 $\log_{10}$ cfu/g ($p < 0.001$) Antipseudomonal antibiotics (median day) TSI: 17 days Placebo: 26 days ($p < 0.001$)	Patients with PA with a tobramycin MIC ≥ 16 µg/ml (week 20) TSI: 26% Placebo: 17% ($p = 0.03$) Adverse effects Tinnitus TSI: 8/258 (3.1%) Placebo: 0/262 [$p = 0.003$] Voice alteration TSI: 33/258 (12.8%) Placebo: 17/262 (6.5%; $p = 0.02$)
Hodson *et al.* [10]	R	115	TSI 300 mg (n = 53) or aerosolised colistin 80 mg (1 megaunit; n = 62) b.i.d. × 4 weeks	TSI: PARI LC PLUS® jet nebuliser (PARI) and CR 50® compressor (Medic-Aid) Colistin: Ventstream® nebuliser (Medic-Aid) and CR 50® (Medic-Aid) compressor	Lung function (FEV_1 change from baseline) TSI: +6.7% Colistin: +0.37% ($p = 0.008$) Sputum PA density (mean change) TSI: -0.86 $\log_{10}$ cfu/ml Colistin: -0.60 $\log_{10}$ cfu/ml ($p = 0.007$) Improved medical condition TSI: 21/53 (39.6%) Colistin: 10/62 (16.1%) ($p = 0.006$) Self-rated improvement TSI: 13/53 (24.5%) Colistin: 8/62 (12.9%)	Resistance Patients with PA with a tobramycin MIC ≥ 4 µg/ml post-treatment TSI: 49% (38% at baseline) Colistin: 55% (55% at baseline) Patients with PA with a colistin MIC ≥ 4 µg/ml post-treatment TSI: 16% (27% at baseline) Colistin: 34% (34% at baseline) Patients with ≥ 1 treatment-emergent AE TSI: 34/53 (64.2%) Colistin: 31/62 (50%)

AE: Adverse event; CFU: Colony-forming unit; CO: Crossover; DB: Double-blind; FEV_1: Forced expiratory volume for 1 s; MC: Multi centred; MIC: Minimum inhibitory concentration; OL: Open label; PA: *Pseudomonas aeruginosa;* PC: Placebo controlled; R: Randomised; TSI: Tobramycin solution for inhalation.

patients with *P. aeruginosa*. Data regarding the use of other agents in this setting are generally either nonexistent or of poor quality. TSI when given 28 days on and 28 days off has been shown to benefit patients by decreasing the density of *P. aeruginosa* in the sputum, increasing FEV_1 from baseline and ultimately slowing the inevitable decline in lung function. Although relatively well tolerated, concerns regarding the potential consequences of resistance persist.

4.2 Bronchiectasis

Bronchiectasis, a persistent dilation of the bronchi or bronchioles, is a commonly associated consequence of cystic fibrosis disease; however, it may also result from other causes including respiratory infections in non-cystic fibrosis patients and genetic defects, such as primary ciliary dyskinesia [48]. Patients with bronchiectasis commonly suffer from chronic cough, purulent sputum production, dyspnea and recurrent or persistent respiratory tract infections. Common organisms that infect and colonise these patients include *P. aeruginosa* and *H. influenzae* [49,50]. Studies have demonstrated a reduction in quality of life and a propensity towards more severe disease in patients with bronchiectasis who become colonised with *P. aeruginosa* [51]. The successful use of TSI in cystic fibrosis patients against *P. aeruginosa* infections has led to the use of TSI for the treatment of patients with bronchiectasis stemming from causes other than cystic fibrosis.

Barker *et al.* and Couch reported results from a Phase II, randomised, double-blind, placebo-controlled study [11,12]. The study was designed to evaluate the effect of TSI on *P. aeruginosa* density in patients with non-cystic fibrosis bronchiectasis and at least 10^4 colony forming units/g *P. aeruginosa* present in the sputum. Patients were randomised to receive TSI 300 mg or placebo twice daily for 28 days followed by 14 days off therapy. A total of 74 patients received self-administered therapy using a PARI LC PLUS jet nebuliser and a Pulmo-Aide compressor. A reduction in sputum density was observed by week 2 of therapy and persisted for the remainder of the study. After the 28-days on therapy, participants were studied for an additional 2 weeks off therapy. At 2 weeks post-treatment, 13 of the 37 patients treated with TSI had eradicated *P. aeruginosa* from the sputum compared with zero patients in the placebo group. *P. aeruginosa* eradication seemed to correlate with clinical improvement as investigators noted an improvement in general medical status in 12 of 13 patients deemed eradicated. However, despite the reduction in *P. aeruginosa* density in the sputum, no significant changes in pulmonary function were noted in either group. Patients treated with TSI experienced a significantly higher incidence of dyspnea, chest pain and wheezing than patients treated with placebo. Three patients treated with TSI withdrew from the study due to adverse events. A nonstatistically significant increase in the emergence of resistant *P. aeruginosa* (defined as a MIC $\geq$ 16 µg/ml) and increases in MIC of fourfold or greater were observed in patients treated with TSI.

Two additional clinical trials evaluating the use of aerosolised tobramycin in bronchiectasis have also been reported. The first is an open-label trial that enrolled 41 subjects [13]. The trial consisted of three cycles of 14 days of TSI 300 mg therapy followed by 14 days off therapy. Treatment was self-administered twice daily using a PARI LC PLUS nebuliser and a Pulmo-Aide compressor. An additional 40-week follow up was completed by chart review. Of the patients, 31 enrolled completed all three treatment cycles; 10 patients withdrew as a result of adverse events. The two most common adverse events reported included cough and dyspnea. At the end of the three treatment cycles, 22.2% of patients who underwent microbiological evaluation had confirmed or presumed eradication of *P. aeruginosa* from the sputum. A significant improvement in mean pulmonary symptom severity scores ($p = 0.006$) and health-related quality of life questionnaire scores ($p < 0.001$) was also reported. Interestingly, this study found that improvement in these two scores was not dependent on eradication. A slight increase in *P. aeruginosa* resistance and increases in MIC values of fourfold or greater were also observed in this study.

The second trial enrolled 30 patients in a double-blind, placebo-controlled, crossover design [52]. Participants were randomised to receive either aerosolised tobramycin 300 mg or placebo twice daily for 6 months. Participants then completed a 1-month washout period and converted to the alternative treatment regimen for an additional 6 months. A jet nebuliser (System 22 Acorn®, Medic-Aid) and compressor (CR 60®, Medic-Aid) were used to administer therapy. Of the 30 patients enrolled, 20 completed the study protocol. Five patients died prior to study completion, four of which were in the tobramycin treatment period at the time of death. These patients were reported to have more severe pulmonary disease at baseline. Three additional patients receiving tobramycin withdrew due to bronchospasms. It is notable that this study used a parenteral formulation of tobramycin, which contains metasulfites, rather than the tobramycin solution approved for inhalation. Tobramycin administration resulted in a significant decrease in *P. aeruginosa* density in the sputum in the first cycle of therapy ($p = 0.038$). No difference in quality of life scores, frequency of pulmonary exacerbations, or pulmonary function test measurements was detected between treatment and placebo periods. However, the study did find that the number and days of hospitalisations were decreased during the tobramycin administration period ($p = 0.038$ and 0.047, respectively).

As summarised in Table 4, a number of studies have now been published evaluating the use of aerosolised tobramycin in patients with non-cystic fibrosis bronchiectasis. Similar to the studies in cystic fibrosis patients, these studies have generally demonstrated a decrease in *P. aeruginosa* density in the sputum in response to treatment. According to the study by Barker *et al.*, the magnitude of decrease was greater among patients with non-cystic fibrosis bronchiectasis compared with that seen in cystic fibrosis patients [8,10,11,53]. In contrast to the studies evaluating aerosolised tobramycin in cystic fibrosis patients, studies evaluating non-cystic fibrosis bronchiectasis patients failed to demonstrate an improvement in lung function as measured by FEV_1. Differences among the two patient populations and the nature of the underlying disease may have contributed to the lack of improvement in pulmonary function. The non-cystic fibrosis bronchiectasis patients as a group were greater in age and likely suffered from long-standing, severe pulmonary disease. An increase in pulmonary function may be more difficult to elicit in this study population. Moreover,

Table 4. Bronchiectasis.

Ref.	Study design	N	Treatment groups	Nebuliser type	Results	Comments
Orriols *et al.* [91]	R	15	A: Aerosolised ceftazidime 1000 mg plus tobramycin 100 mg b.i.d. (n = 7) or B: symptomatic treatment* (n = 8) × 12 months	System 22 Acorn® jet nebuliser (Medic-Aid) and CR 60® compressor (Medic-Aid)	Lung function (FEV_1) Similar decline in pulmonary function between groups Mean number of hospital admissions A: 0.6 B: 2.5 (p = 0.023) Mean days of hospital admission A: 13.1 B: 57.9 (p = 0.033)	Participants completed 2 weeks of endovenous antibiotic therapy prior to study entry 1 of 7 patients in group A was hospitalised compared with 7 of 8 patients in group B There was no significant difference in the use of oral antibiotics There was no significant difference in the emergence of antibiotic-resistant bacteria
Barker *et al.* [11] Couch *et al.* [12]	R, DB, PC, MC	74	TSI 300 mg (n = 37) or placebo (n = 37) b.i.d. × 28 days, followed by 14 days off treatment	PARI LC PLUS® jet nebuliser (PARI) and Pulmo-Aide® compressor (DeVilbiss)	Lung function (FEV_1% change at week 4) TSI: -2.2% Placebo: +1.5% (p = 0.41) Sputum PA density (week 4) TSI: -4.54 $\log_{10}$ cfu/g Placebo: + 0.02 $\log_{10}$ cfu/g (p < 0.01) PA eradication (week 6) TSI: 13/37 (35%) Placebo: 0/35 (0%) Improved medical condition (week 6) TSI: 23/37 (62%) Placebo: 14/37 (38%)	60 patients completed the study Decrease in PA sputum density was transient; some regrowth was noted after 2 weeks off therapy Eradication was associated with an improvement in general medical status Resistance (week 6 or last visit) Development of tobramycin-resistant PA (MIC ≥ 16 µg/ml) TSI: 4/36 (11%) Placebo: 1/32 (3%; p = 0.36) At least a fourfold increase in MIC TSI: 8/31 (26%) Placebo: 4/29 (14%; p = 0.25)
Scheinberg *et al.* [13]	OL	41	TSI 300 mg b.i.d. for 14 days on and 14 days off therapy × three cycles	PARI LC PLUS® jet (PARI) and Pulmo-Aide® compressor	PA eradication (presumed or confirmed) 6/27 (22.2%) Pulmonary symptom severity score Significantly improved (p = 0.006) QOL measurements Significantly improved (p < 0.001)	10 subjects (24%) withdrew from the study citing adverse effects 2 patients developed tobramycin-resistant PA (MIC ≥ 16 µg/ml) 4/21 patients had an at least fourfold increase in MIC
Drobinac *et al.* [52]	R, DB, PC, CO	30	Aerosolised tobramycin 300 mg b.i.d. or placebo administered for 6 months each with a 1-month washout period	System 22 Acorn® jet nebuliser (Medic-Aid) and CR 60®, a high-flow rate compressor (Medic-Aid)	Lung function (% change FEV_1) Tobramycin: -3.5% Placebo: -1.2% (p = 0.24) Sputum PA density (period 1) Tobramycin: Decrease in sputum PA density in period 1 (p = 0.038) QOL measurements NS difference between periods	2 weeks of intravenous ceftazidime and intravenous tobramycin were given prior to study entry An intravenous formulation of tobramycin was aerosolised in this study (Tobragobens®, Normon Labs) A total of 20 patients completed the study protocol; 3 patients receiving tobramycin withdrew due to bronchospasms NS difference in emergence of tobramycin-resistant PA between periods

*Symptomatic treatment included oxygen, bronchodilators and corticosteroids. CO: Crossover; DB: Double blind; FEV_1: Forced expiratory volume for 1 s; MC: Multi centred; MIC: Minimum inhibitory concentration; NS: Nonsignificant; OL: Open label; PA: *Pseudomonas aeruginosa;* PC: Placebo controlled; QOL: Quality of life; R: Randomised.

although administration of aerosolised tobramycin to patients with non-cystic fibrosis bronchiectasis may improve quality of life or contribute to an improvement in general medical status, results from studies have largely been inconclusive.

4.3 Ventilator-associated pneumonia

VAP, occurring at least 48 h after intubation and the start of mechanical ventilation, remains a significant concern among critically ill patients [54]. VAP affects 8 – 28% of patients

receiving mechanical ventilation [55-57]. Reported crude intensive care unit (ICU) mortality rates for patients afflicted with VAP are variable and range from 24 to 76% [57]. In addition to mortality, VAP also prolongs ICU stay, hospital stay and duration of mechanical ventilation [55,57]. These items all contribute to the significant financial burden associated with VAP [55,57]. Causative pathogens may vary somewhat and are dependent on the patient population, time to onset of VAP (early versus late onset) and underlying disease. However, common pathogens include Gram-negative bacteria such as *P. aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Acinetobacter* spp., and Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* [57]. Complicating treatment is the emergence of widespread resistance among many of these pathogens. As a result, many preventative measures have been studied in this setting to attempt to prevent VAP from occurring in this vulnerable population.

A number of trials from the 1970s evaluated the use of aerosolised or endotracheally administered antimicrobial agents for the prevention of pneumonia in ICU patients. Some of these trials caused great concern when an increase in drug-resistant organisms was observed [58-60]. Table 5 contains a summary of the results from some of the trials evaluating the use of antimicrobials administered via aerosol or endotracheal tube for the prevention of pneumonia.

Recently, Wood and colleagues evaluated the role of aerosolised ceftazidime for the prevention of VAP in a randomised, double-blind, placebo-controlled trial [61]. Patients were randomised to receive either aerosolised ceftazidime 250 mg or placebo for 7 days. A respiratory therapist administered treatment twice daily via a disposable jet nebuliser (Airlife Misty Neb®, Baxter Healthcare) connected to the ventilator tubing. A total of 59 patients were initially enrolled, of which 40 completed the study and were included in the analysis. The incidence of VAP was assessed at days 7 and 14, and for the overall ICU stay. Although no statistical difference in the incidence of VAP was detected at day 7 between groups ($p = 0.22$), a significant decrease in the incidence of VAP was observed at day 14 ($p = 0.021$) in the ceftazidime group. Throughout the ICU stay, 6 of 20 patients (30%) in the ceftazidime group compared with 13 of 20 patients (65%) in the placebo group developed VAP ($p = 0.022$). Interestingly, no significant difference in total antibiotic therapy, length of mechanical ventilation, ICU stay, or mortality was observed. The authors noted that prophylactic administration of ceftazidime did not seem to contribute to an increase in resistant organisms.

A secondary focus of the Wood *et al.* study was to evaluate the potential effect of aerosolised ceftazidime on pro-inflammatory cytokines in the sputum [61]. Cytokines are an important component of the inflammatory host response system. Previous studies have evaluated the result of increased pro-inflammatory cytokines on mortality, bacterial growth and incidence of infections [62-65]. A small number of studies have evaluated the potential ability of antimicrobial agents to attenuate the inflammatory response by decreasing pro-inflammatory cytokine concentrations [66,67]. In the Wood *et al.* study, the ceftazidime group exhibited a significant reduction from baseline in TNF-α and IL-1β concentrations compared with placebo [61]. The reduction in TNF-α and IL-1β concentrations correlated to a reduction in the development of VAP over time ($p < 0.001$ and 0.023, respectively) in the ceftazidime group. A significant decrease was also noted in IL-8 concentrations, although this reduction did not correlate as strongly with the development of VAP ($p = 0.08$).

Although the results from the Wood *et al.* study seem to be promising, too many questions remain regarding the risk–benefit profile to currently recommend the application of aerosolised antimicrobial agents for the prevention of VAP.

4.4 Antifungal prophylaxis in lung transplant patients

The development of fungal infections can result in serious and potentially lethal consequences among immunocompromised patients. Among lung transplant patients, *Aspergillus* and *Candida* spp. account for the majority of encountered fungal infections [68]. *Aspergillus* infections typically occur secondary to the inhalation of *Aspergillus* conidia from the environment into the lungs of an immunocompromised patient. The size of *Aspergillus* conidia, ~ 2.5 – 3.5 µm in diameter, allows for penetration into the small airways of the lungs where the conidia germinate and disseminate [69]. Inhalation of *Aspergillus* conidia may result in colonisation, tracheobronchitis, or invasive disease. Invasive pulmonary aspergillosis occurs in ~ 3 – 14% of patients after lung transplant and is associated with poor outcomes, including poor response to treatment and increased mortality [70-72].

Due to the severe consequences of developing and the poor outcomes associated with the treatment of invasive fungal infections in the post-transplant period, several preventative strategies have been evaluated in these high-risk patients. Systemic antifungals such as amphotericin B and intraconazole have been examined for use as prophylaxis. Unfortunately, a number of problems exist with these agents, including side effects with amphotericin B, and unreliable drug absorption and numerous drug interactions with intraconazole. The lipid formulations of amphotericin B may be an alternative; however, the high cost of therapy must be weighed against potential benefit. Aerosolising antifungal agents would provide a seemingly attractive alternative if side effects and drug interactions can be minimised while still providing reliable antifungal prophylaxis.

Reichenspurner *et al.* investigated the efficacy of aerosolised amphotericin B for the prevention of fungal infections after lung, heart-lung and heart transplants [73]. A total of 126 patients received aerosolised amphotericin B three-times daily post-transplantation. A similar cohort group who did not receive aerosolised amphotericin B was used for comparison. The use of prophylactic therapy with aerosolised amphotericin B significantly reduced the incidence of overall fungal infections and specifically *Aspergillus* infections at 3 and 12 months post-transplant compared with the control group (Table 6).

Table 5. Prophylaxis of pneumonia.

Ref.	Study design	Patient population (N)	Treatment groups	Nebuliser type	Additional results	Comments
Klastersky *et al.* [58]	R, PC	NSICU patients (85)	Gentamicin 80 mg (n = 43) or placebo (n = 42) t.i.d.	NA Endotracheal administration	At least one positive tracheal aspirate culture Gentamicin: 32/43 patients (74.4%) Placebo: 41/42 patients (97.6%; p < 0.01) Demonstrated pulmonary infections Gentamicin: 5/43 patients (11.6%) Placebo: 17/42 patients (40.5%; p < 0.01)	Increased incidence of gentamicin-resistant organisms in the patients receiving endotracheal gentamicin
Klick *et al.* [59]	PC	RSICU patients (744)	Polymixin aerosol 2.5 mg/kg/ day in six divided doses (n = 374) or placebo (n = 370) 11 alternating 2-month treatment cycles	Hand atomiser sprayed into the pharynx and tracheal tube if present	Pneumonia Polymixin: 18 patients (4.8%) Placebo: 30 patients (8.1%) *Pseudomonas aeruginosa* pneumonia Polymixin: 3 patients (0.8%) Placebo: 17 patients (4.6%; p < 0.01) *Pseudomonas aeruginosa* colonisation Polymixin: 6 patients (1.6%) Placebo: 36 patients (9.7%; p < 0.01)	Nonsignificant increase in colonisation of *Serratia*, *Proteus* and *Flavobacterium* spp. Overall mortality Polymixin: 45/374 (12.0%) Placebo: 45/370 (12.2%) *Pseudomonas aeruginosa* pneumonia-associated mortality Polymixin: 2/3 patients died Placebo: 4/17 patients died
Feeley *et al.* [60]	OL	RSICU patients (292)	Polymyxin aerosol 2.5 mg/kg/ day, given in six divided doses	Hand atomiser sprayed into the pharynx If present, 50% was also injected into the tracheal tube	Pneumonia 11 patients (3.8%) developed pneumonia 1 patients (0.3%) developed *Pseudomonas aeruginosa* pneumonia Mortality 7/11 patients (64%) with pneumonia died	Resistance Polymixin-resistance organisms caused 10/11 (91%) cases of acquired pneumonia cases
Wood *et al.* [61]	R, DB, PC	Ventilated trauma ICU patients (40)	Aerosolised ceftazidime 250 mg (n = 20) or placebo (n = 20) every 12 h for 7 days	Airlife Misty Neb® (Baxter Healthcare) jet nebuliser connected to ventilator tubing	Reduction in VAP in the ceftazidime group Day 7 (p = 0.22) Day 14 (p = 0.021) ICU stay (p = 0.022) TNF-α, IL-1β and IL-8 significantly decreased from baseline in the ceftazidime group. TNF-α and IL-1β changes significantly correlated with development of VAP (p < 0.001 and 0.023, respectively)	Overall Incidence of VAP Ceftazidime: 30% Placebo: 65% (p = 0.022) Incidence of polymicrobial VAP Ceftazidime: 1/6 patients Placebo: 8/13 patients (p = 0.14) No significant difference in mortality, ICU length of stay, duration of mechanical ventilation or total days of antibiotic use

DB: Double blind; ICU: Intensive care unit; NA: Not applicable; NSICU: Neurosurgical intensive care unit; OL: Open label; PC: Placebo controlled; R: Randomised; RSICU: Respiratory-surgical intensive care unit; VAP: Ventilator-associated pneumonia.

Aerosolised amphotericin B seemed to be relatively well tolerated. Mild nausea was the only side effect reported, occurring in ~ 8% of patients. Of patients, < 2% discontinued therapy as a result of nausea.

A second study evaluated the use of antifungal prophylaxis with systemic fluconazole plus aerosolised amphotericin B in 52 patients after lung transplant [74]. No fungal infections were reported in the post-operative period (Table 6). No toxicity was reported with therapy. In addition to nausea, other studies evaluating aerosolised amphotericin B for antifungal prophylaxis in various patient populations have reported side effects such as unpleasant taste and cough [75-77].

Table 6. Antifungal prophylaxis in transplant patients.

Ref.	Study design	Patient population (N)	Treatment groups	Nebuliser type	Results	Comments
Reichenspurner *et al.* [73]	Cohort	Lung, heart-lung or heart transplant patients (126)	Amphotericin B 5 mg t.i.d., increased up to 20 mg t.i.d. within 5 days of surgery	Not reported	Infections at 3 months (linearised rate/patient) *Aspergillus* infections Amphotericin B: 0.00 Control: 0.11 ($p < 0.005$) Fungal infections Amphotericin B: 0.08 Control: 0.20 ($p < 0.05$) Infections at 12 months (linearised rate/patient) *Aspergillus* infections Amphotericin B: 0.02 Control: 0.12 ($p < 0.005$) Fungal infections Amphotericin B: 0.04 Control: 0.07 ($p < 0.05$)	Adverse effects Mild nausea 10/126 patients (7.9%) 2/126 patients discontinued treatment due to nausea (1.6%) Control: similar cohort group of 101 patients transplanted before the initiation of aerosolised amphotericin prophylaxis
Calvo *et al.* [74]	Cohort	Lung transplant patients (52)	Systemic fluconazole 200 mg every 12 h and aerosolised amphotericin B 0.2 mg/kg every 8 h during the postoperative period	Not reported	Fungal infections in the postoperative period Fluconazole + amphotericin: 0/52 Control: 3/13 (23%)	Mean duration of antifungal prophylaxis was 42 days (range 30 – 92 days); mean follow up of 19 months (range 1 – 35 months) Control: historical control of 13 patients who received lung transplants prior to the initiation of the antifungal protocol After prophylaxis was discontinued, 7 patients developed *Aspergillus* infection or colonisation

The safety of aerosolised amphotericin B lipid complex has also been evaluated in post-lung transplant patients [76,78]. Although the formulation seems to be well tolerated, data assessing the efficacy of aerosolised lipid formulations of amphotericin B in preventing fungal infections in lung transplant patients is limited. Further controlled trials are necessary to help determine the potential role of aerosolised lipid formulations of amphotericin B for antifungal prophylaxis in lung transplant patients.

The studies evaluating aerosolised amphotericin B for antifungal prophylaxis in lung transplant patients reported a decrease in the emergence of fungal infections; however, the studies lacked randomisation and used historical controls. A number of additional studies have also examined the use of aerosolised amphotericin B for prophylaxis of invasive aspergillus infections during periods of prolonged neutropoenia due to various causes including chemotherapy and bone marrow transplant, with varying results [75,79,80].

4.5 *Pneumocystis* pneumonia prophylaxis

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia (PCP) is a serious opportunistic infection occurring in patients affected with HIV. These patients are at highest risk and require prophylaxis for PCP when their CD4 lymphocyte count falls to < 200 cells/mm^3. Trimethoprim-sulfamethoxazole is currently first-line therapy for the prevention of PCP [81-83]. Aerosolised pentamidine (NebuPent®, American Pharmaceutical Partners) has also been studied and approved for this purpose. The recommended dose is 300 mg/month administered via a Respirgard II® nebuliser (Marquest). Aerosolised pentamidine is currently being used as a potential alternative for the prevention of PCP in patients infected with HIV when trimethoprim-sulfamethoxazole cannot be tolerated [81]. In comparison to trimethoprim-sulfamethoxazole, aerosolised pentamidine is well tolerated, with cough occurring most commonly [82-84]. Other adverse effects may include dyspnea, metallic taste, dizziness or bronchospasm. Concerns regarding environmental contamination during the administration of aerosolised pentamidine have been expressed. Environmental contamination may result in adverse effects or transmission of respiratory pathogens, such as *Mycobacterium tuberculosis*, to healthcare workers unless appropriate precautions are taken to minimise these risks [85-87].

5. Advantages and disadvantages

There are many potential advantages and disadvantages associated with the aerosolised delivery of antibiotics. The major advantage is targeted delivery of the drug to the site of infection allowing for maximum concentrations to be achieved without incurring significant systemic exposure [39-41]. In addition, antibiotics that could historically only be administered intravenously are now being administered at home via nebulisers, perhaps leading to improved compliance and fewer hospitalisations.

Most of the disadvantages are a result of the drug delivery system and local effects of the drug on the lung. Delivery of drug from a nebuliser is inefficient; ~ 88% of the dose placed in the nebuliser is lost during therapy. Extrapulmonary deposition, drug loss during exhalation and drug solution trapped within the nebuliser all account for a portion of drug loss [17]. Patients and caregivers need to be taught how to properly dispose of drug that remains in the nebuliser. Microbial contamination can occur when the nebuliser is not properly maintained and cleaned [88,89]. Another disadvantage is that most sterile antibiotics solutions have not been formulated for inhalation. When these solutions are inhaled, inert ingredients may cause inflammation, bronchoconstriction and oedema. Finally, many clinicians still have concerns regarding the development of antimicrobial resistance secondary to aerosolised administration.

6. Expert opinion

Clinicians continue to search for treatment modalities that simultaneously maximise therapeutic outcomes and minimise the patient's risk for experiencing toxicity. It was out of this search that the concept of aerosolised administration of antimicrobials spawned. Despite the theoretical soundness of this approach, limited data exist to support the use of this modality outside of patients with cystic fibrosis and PCP. However, even in these populations the pharmacokinetics of aerosolised agents have been poorly studied. Until science catches up with the willingness of the clinician to use inhalation as a route of antimicrobial delivery, routine use of antimicrobial agents outside of approved indications should be discouraged.

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