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REVIEW ARTICLE

# Clinical Pharmacokinetics of Inhaled Antimicrobials

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**Abstract** Administration of inhaled antimicrobials affords the ability to achieve targeted drug delivery into the respiratory tract, rapid entry into the systemic circulation, high bioavailability and minimal metabolism. These unique pharmacokinetic characteristics make inhaled antimicrobial delivery attractive for the treatment of many pulmonary diseases. This review examines recent pharmacokinetic trials with inhaled antibacterials, antivirals and antifungals, with an emphasis on the clinical implications of these studies. The majority of these studies revealed evidence of high antimicrobial concentrations in the airway with limited systemic exposure, thereby reducing the risk of toxicity. Sputum pharmacokinetics varied widely, which makes it challenging to interpret the result of sputum pharmacokinetic studies. Many novel inhaled antimicrobial therapies are currently under investigation that will require detailed pharmacokinetic studies, including combination inhaled antimicrobial therapies, inhaled nanoparticle formulations of several antibacterials, inhaled non-antimicrobial adjuvants, inhaled antiviral recombinant protein therapies and semi-synthetic inhaled antifungal agents. Additionally, the development of new inhaled delivery devices, particularly for mechanically ventilated patients, will result in a pressing need for additional pharmacokinetic studies to identify optimal dosing regimens.

**Key Points**

The clinical pharmacokinetics of inhaled antimicrobials are characterized by high pulmonary exposure, low systemic exposure and rapid absorption from the respiratory tract.

Many noncompartmental pharmacokinetic studies have been performed with inhaled antimicrobial agents, although relatively few population pharmacokinetic studies have been performed. These studies identified high variation in sputum pharmacokinetics, which makes it challenging to interpret the results of sputum pharmacokinetic studies.

Emerging inhaled antimicrobial technologies, including combination therapies, novel delivery devices and lipid nanoparticle formulations, are currently in various stages of preclinical development and early-phase clinical trials. In the next 5–10 years, pharmacokinetic studies will be needed to define appropriate dosing regimens for these new inhaled antimicrobials.

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## 1 Introduction

In comparison with other non-invasive routes of xenobiotic administration, inhalation provides several advantages, including rapid systemic delivery, high bioavailability and minimal metabolism [1]. Consequently, inhaled medications are attractive for the treatment of pulmonary diseases and for situations in which it is desirable to have the drug rapidly enter the systemic circulation [2]. In both circumstances, the anatomy of the airway, the physical conditions that the drug will encounter in the airway (e.g. humidity), the clearance mechanisms of the lung (e.g. mucociliary clearance and alveolar macrophages) and the pathophysiological effects of acute and chronic diseases (e.g. pulmonary tissue scarring in chronic obstructive pulmonary disease [COPD]) must be considered when an inhaled medication is being developed [3].

The human airway comprises a series of narrowing branches, including the trachea, bronchi, bronchioles and alveoli [2]. The optimal location for drug deposition following inhalation varies, depending on the indication for therapy and the physicochemical properties of the drug [4]. Many lower respiratory tract infections feature both purulent tracheobronchitis and alveolar disease, which require deposition of the inhaled antimicrobial throughout the lungs [4]. In contrast, infections such as *Pneumocystis carinii* pneumonia, which are confined to the alveolar regions of the lungs, are likely to benefit from peripheral deposition [5]. Several factors affect the pattern of drug deposition in the lungs. Aerosol particles with a mass median aerodynamic diameter (MMAD) of 1–2 μm can be deposited in the lung with up to 90 % efficiency if inhaled slowly and deeply [6]. Larger particles, particularly when inhaled too quickly, are primarily deposited in the mouth, throat and upper airway [7]. However, forceful inhalation from a pressurized metered-dose inhaler (MDI) can increase lung penetration for larger aerosolized particles that would typically be deposited in the oropharynx [7].

As the drug is inhaled, it travels down the airway through the bronchi. The bronchi feature a thick absorptive epithelial layer comprising several different cell types, including ciliated cells, which expel unwanted lung particulates from the respiratory tract; brush cells, which metabolize xenobiotic compounds; goblet cells, which secrete the liquid mucus that lines the airways; and basal cells, which are progenitor cells for the epithelium (Fig. 1) [8]. As the drug proceeds further down the respiratory tract, the primary bronchi branch into smaller bronchioles. After approximately 16–17 bifurcations, the alveoli are reached, which feature an epithelial thickness of <0.1 μm [7, 8]. Small hydrophobic molecules rapidly diffuse across the alveolar surface within seconds, whereas small hydrophilic molecules are absorbed via specific transporters or tight junctions [8]. Because of the rapidity with which small molecules are absorbed within alveolar cells, plasma drug concentrations can be difficult to measure following inhalation [9]. This distinguishes pharmacokinetic investigations of inhaled antimicrobials from traditional pharmacokinetic studies, as a very sensitive assay is needed and repeated sampling over a short period of time is often required to quantify the absorption rate [10].

The physicochemical properties of the formulation (e.g. its surface tension and viscosity) can also affect the pharmacokinetics of an inhaled drug [11]. Following deposition, absorption of the inhaled drug from a solution on the airway surface can be described quantitatively with the following equation:

$$\text{Absorption rate} = \text{Membrane permeability} \cdot \text{Surface area} \cdot \text{Concentration in mucosal fluids} \quad (1)$$

In this 'irreversible transfer relationship', it is assumed that the systemic concentration of the drug of interest is negligible [12]. Additionally, the membrane permeability of the drug can be regarded as being directly proportional to the partition coefficient of the drug and as being inversely proportional to the thickness of the epithelial membrane [7]. Although ultra-rapid absorption is often desirable, drugs may be absorbed from the lungs and cleared from the systemic circulation too quickly, which can result in a brief duration of action and can lead to frequent dosing requirements. For such situations, it may be necessary to modify the drug to delay its absorption from the lungs. Poorly soluble drugs, such as the antifungal agent amphotericin B, can persist in the lungs for several days [13]. Similarly, positively charged, moderately lipophilic drugs, such as the antibacterials pentamidine and tobramycin, preferentially bind to lung tissue, thereby increasing their pulmonary half-life [14, 15].

The physicochemical properties of the inhaled drug formulation can also be modified through the use of alternative delivery devices [9]. Improvements in aerosolization methods have made it possible to deliver larger doses and finer particles into the lungs [16]. It is now increasingly recognized that the development of a safe and effective inhaled antimicrobial requires consideration of optimization of the whole system, including the drug, the formulation and the aerosol delivery device [2, 16]. For this reason, this article critically reviews the clinical pharmacokinetics of several widely used and emerging inhaled antimicrobials and their delivery devices.

To identify recent and historical articles describing the clinical pharmacokinetics of inhaled antimicrobials, PubMed was searched with the following key terms:

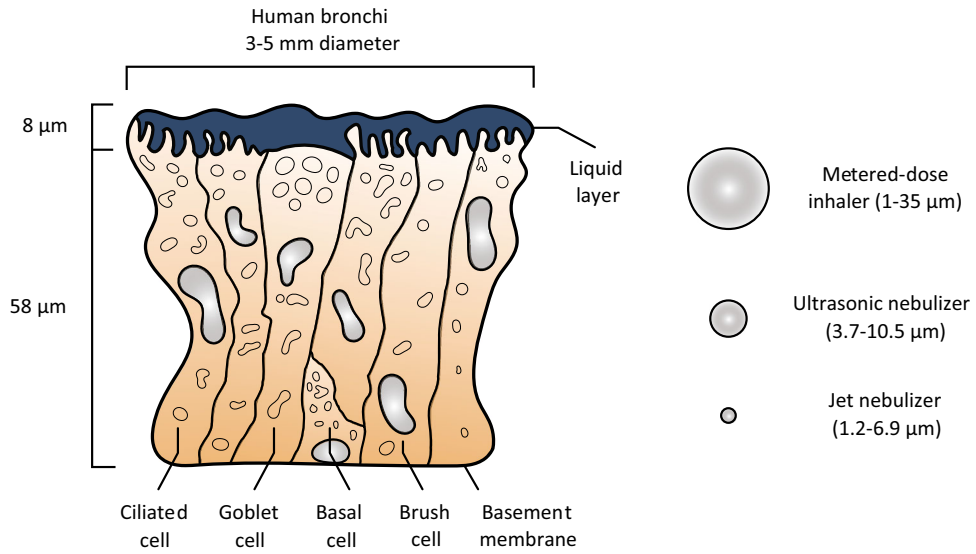


**Fig. 1** Cross-sectional schematic of the human upper respiratory tract epithelium. Typical mass median aerodynamic diameters (MMADs) of aerosolized particles for several aerosolization methods are presented to scale. As these aerosolized particles descend deeper into the airway, the absorptive epithelial layer becomes thinner until reaching the alveoli, which feature an epithelial thickness of <0.1 µm. The surfaces of the epithelial layer in the human bronchi are covered in a thin liquid layer. The bronchi comprise several different cell types, including ciliated cells, which move the liquid layer and aid in expelling foreign substances; brush cells, which are involved in the metabolism of xenobiotic compounds; goblet cells, which secrete the liquid needed to form the liquid layer; and basal cells, which are the progenitor cells for the epithelium. The basement membrane is an extracellular biopolymer matrix, which provides structural support for the epithelial cells. Reprinted by permission from Macmillan Publishers Ltd: [Nat Rev Drug Discov] (Patton and Byron [7], copyright 2007)

'aerosolized antimicrobial', 'aerosolized antibiotic', 'aerosolized antibacterial', 'aerosolized antiviral', 'aerosolized antifungal', 'nebulized antimicrobial', 'nebulized antibiotic', 'nebulized antibacterial', 'nebulized antiviral', 'nebulized antifungal' and 'pharmacokinetic' or 'pharmacodynamic'. Both American and British spellings (e.g. aerosolized/aerosolised) were employed in the literature search. Additionally, the reference list of each article identified using the search terms featured above was reviewed. No articles were excluded from the search on the basis of their publication date or geographic region.

## 2 Antibacterials

### 2.1 Tobramycin

Aminoglycosides, including tobramycin, display concentration-dependent bactericidal activity [17]. Aminoglycosides also feature low protein binding and high water solubility, which impede their ability to cross cellular membranes and limit their effectiveness in treating pulmonary infections when they are administered intravenously or orally [18–20]. Tobramycin solution for inhalation (TSI) was developed in an effort to overcome these limitations and was licensed for the treatment of pulmonary *Pseudomonas aeruginosa* infections in patients with cystic fibrosis in the USA in 1998 [21, 22]. In clinical pharmacokinetic studies, it was demonstrated that aerosolization of 300 mg of tobramycin yielded sustained improvements in pulmonary function [23, 24]. Additional trials reported that patients receiving inhaled tobramycin had fewer acute pulmonary exacerbations of cystic fibrosis and lower hospitalization rates [23, 25].

The fraction of the aerosolized tobramycin dose that is systemically absorbed is assumed to be eliminated primarily via glomerular filtration, on the basis of pharmacokinetic studies conducted with intravenous tobramycin [26]. The remaining fraction of the tobramycin dose that is not absorbed and is retained within the endobronchial space is likely eliminated in expectorated sputum [26]. The primary disadvantage associated with the use of aerosolized aminoglycosides in patients with cystic fibrosis is sputum antagonism, which occurs when mucin in the sputum binds to the drug, thereby inhibiting its antimicrobial activity. To achieve bactericidal activity, sputum antagonism can lead to dose requirements in excess of 20 times the minimum inhibitory concentration (MIC) [27].

In two confirmatory phase III trials, 258 patients ≥6 years of age with cystic fibrosis received aerosolized TSI, using the PARI LC Plus® nebulizer [23]. A population pharmacokinetic analysis was conducted using the data from these trials, and it was determined that a two-compartment model adequately described the pharmacokinetic profile of inhaled tobramycin [28]. Systemic clearance was estimated as 5.79 L/h, the apparent

clearance was estimated as 49.6 L/h and the estimated bioavailability was 11.7 % [28]. In subgroup analyses, no significant effects on sputum or serum tobramycin concentrations were identified with respect to age, gender or baseline disease severity. In a phase I study of an inhaled fosfomycin and tobramycin combination, a limited noncompartmental pharmacokinetic analysis presented at the 2008 Annual North American Cystic Fibrosis Conference identified a target dose of fosfomycin 160 mg and tobramycin 40 mg in a 4 mL volume, which was advanced into phase II trials; however, more detailed results have yet to be published [29]. The phase II trial was completed in December of 2013, although the results of that trial have not yet been released (ClinicalTrials.gov study identifier NCT00794586). Detailed results of several additional inhaled tobramycin noncompartmental pharmacokinetic studies are summarized in Supplemental Table 1 in the Electronic Supplementary Material [28, 30–39]. These studies commonly used doses of 150 and 300 mg, which achieved peak concentrations below the potentially toxic threshold of 2 μg/mL and were generally well tolerated.

Although systemic concentrations rarely reach levels associated with toxicity, a recent case report found that therapeutic drug monitoring and/or dosing adjustments may be needed in the setting of renal failure, despite aerosolized administration of tobramycin [40]. Additionally, it has been reported that nebulization of tobramycin results in generation of an aerosol cloud, which is sufficient to contaminate the skin and can lead to erroneously high plasma concentrations in fingerprick blood samples [41].

### 2.2 Amikacin

An inhaled liposomal nanoparticle formulation of amikacin has been developed and evaluated in phase I, II and III clinical trials for the treatment of *P. aeruginosa* infections in patients with cystic fibrosis [42, 43]. This liposomal formulation has been shown to effectively penetrate into recalcitrant pseudomonal biofilms, feature potent bactericidal activity, achieve high lung concentrations and feature a favourable safety profile [42, 44]. Two parallel, randomized, placebo-controlled, phase II trials were conducted to evaluate the pharmacokinetics, safety and efficacy of once daily inhaled liposomal amikacin for the treatment of *P. aeruginosa* infections in patients ≥6 years of age with cystic fibrosis [42]. Serum samples were collected on days 1, 14 and 28, which revealed a slight increase from a mean peak concentration of 1.3 (±0.8) μg/mL on day 1 to 2.4 (±1.6) μg/mL on day 28 in patients who were randomized to the highest (560 mg) dosing regimen [42]. Pharmacodynamic analyses demonstrated a moderate association between the administered dose and lung function parameters on days 7, 14, 21 and 28 [42].

More recently, the results of a large, multicentre, phase III trial (CLEAR-108) were presented at the 2013 Annual North American Cystic Fibrosis Conference [43]. The authors found that liposomal amikacin administered once daily was non-inferior to TSI administered twice daily with respect to the primary outcome, the change from baseline in the forced expiratory volume in 1 s (a measure of pulmonary function) [43]. The lower bound of the 95 % confidence interval was −4.95 %, which was only slightly above the −5 % threshold needed to declare non-inferiority; however, it should be noted that the primary outcome was evaluated only in the population of patients who were treated according to the study protocol, whereas all of the secondary outcomes were evaluated using the more robust modified intention-to-treat population [43]. The extent to which this may affect interpretation of the results of the trial can be answered only through a more detailed review of the data; however, the results of the trial have not yet been published.

Inhaled liposomal amikacin is currently being evaluated in phase II trials for the treatment of nontuberculous mycobacterial infections [45]. The results of an interim analysis were promising, which prompted the data safety monitoring board to recommend continuing the randomized, double-blind, placebo-controlled trial [45].

Inhaled amikacin is also being investigated for the treatment of ventilator-associated pneumonia caused by Gram-negative bacteria [27, 46]. Recently, the results of a randomized, double-blind, placebo-controlled, phase I study of an inhaled amikacin/fosfomycin combination were published [47]. The authors evaluated nine mechanically ventilated patients who received escalating doses of an amikacin/fosfomycin combination, which was administered with an investigational eFlow® inline nebulizer positioned in the inspiratory limb tubing of the ventilator [47]. Pharmacokinetic analyses revealed that amikacin was rapidly cleared from the airway. Additionally, plasma concentrations were considerably lower with aerosolized administration than with intravenous dosing (peak amikacin concentration 1.4 μg/mL and peak fosfomycin concentration 0.8 μg/mL). No adverse respiratory effects were recorded during the study. A detailed summary of several other inhaled amikacin pharmacokinetic studies can be found in Supplemental Table 2 [27, 42, 46–49]. These studies demonstrated that nebulization of amikacin at doses up to 60 mg/kg resulted in lower systemic concentrations than were observed following administration of a 15 mg/kg intravenous dose in healthy volunteers. Amikacin was also shown to be effectively cleared from the serum by haemodialysis. For mechanically ventilated patients with Gram-negative pneumonia, the pharmacokinetic/pharmacodynamic target associated with efficacy was achieved in 50 % of patients on the first day of therapy with a dosing regimen of 400 mg administered twice daily.

### 2.3 Aztreonam

Aztreonam is a synthetic monobactam antibacterial, which inhibits cell wall synthesis in many Gram-negative aerobic organisms [50]. Maximal microbiological efficacy is achieved when the penicillin binding proteins are completely occupied, which occurs at 3–4 times the MIC when concentrations exceed the MIC for ≥50 % of the dosing interval [51, 52]. In vitro and in vivo studies have demonstrated synergy between aztreonam and aminoglycosides used against *P. aeruginosa* [53, 54]. Aztreonam arginine is formulated for parenteral administration but is unsuitable for inhalation as it causes widespread airway inflammation [55]. However, aztreonam lysine is safe for inhalation and has been investigated as a therapy for patients with acute pulmonary exacerbations of cystic fibrosis caused by *P. aeruginosa* and for patients with bacterial pneumonia caused by other Gram-negative organisms [55–57].

Several clinical pharmacokinetic studies have been conducted with inhaled aztreonam lysine in patients with cystic fibrosis, including a phase Ib dose-escalation trial, a phase II trial and two phase III trials [55, 58–60]. Pooled pharmacokinetic data from these trials are available in the USA and the European Union prescribing information documents [50, 61, 62]. In each of these trials, aztreonam lysine was aerosolized using the Altera® nebulizer system (previously known as the eFlow® electronic nebulizer) [63]. All of the trials conducted to date reported high between-subject variability [55, 58–60]. In the phase Ib trial, sputum aztreonam concentrations ranged from 31 to 2170 μg/g following a single 75 mg dose of inhaled aztreonam lysine [58]. Additionally, across all dosages, the median sputum concentrations were consistently lower in adolescents than in adults (Fig. 2). The authors hypothesized that this may have been attributable to less severe pulmonary disease in the adult participants, which may have led to reduced central airway deposition and increased lung clearance [58]. Plasma concentrations were reported only in adults who received the 75 mg dose (see Supplemental Table 3); however, plasma concentrations were low, which suggests that systemic toxicity is unlikely to occur with this dosing regimen in patients without evidence of renal impairment [58]. On the basis of these findings, the 75 mg dose of aztreonam lysinate was advanced into phase II clinical trials. A pooled analysis including data from 195 patients with cystic fibrosis who received 75 mg of aztreonam lysine three times daily for 28 days found that aztreonam lysine did not accumulate in the sputum or the plasma [50]. The elimination of aerosolized aztreonam lysine has not been well studied, although it may be speculated that the fraction of the aztreonam dose that is not absorbed from the lungs is eliminated via sputum expectoration [61]. Following intravenous dosing, aztreonam is primarily excreted via the kidneys, with approximately 68 % of the administered dose being excreted unchanged in the urine; however, because of the relatively low bioavailability of inhaled aztreonam lysine, approximately 10 % of the inhaled dose is excreted in the urine [50, 64].

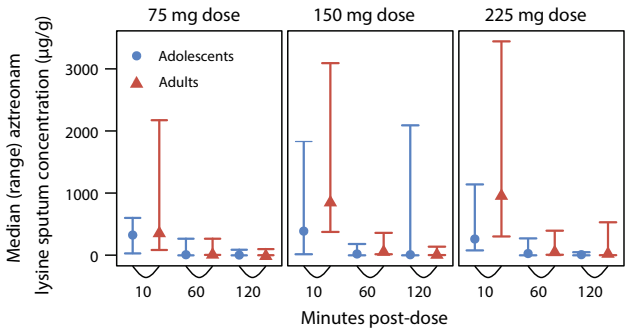


**Fig. 2** Sputum aztreonam lysine concentrations in adolescents and adults who received a single 75, 150 or 225 mg dose of aztreonam lysinate for inhalation. The median sputum concentrations were consistently lower in adolescents than in adults for all dosages at all tested time points. The data are adapted from Gibson et al. [58]

### 2.4 Colistin

Colistin, or polymyxin E, is a cationic polypeptide, which has been used clinically in the USA since the 1950s [65]. Colistin is the bioactive constituent, which is formed following hydrolysis from its precursor, colistimethate [66]. Colistin features concentration-dependent bactericidal activity, which continues for more than an hour following sub-MICs (a 'post-antibiotic effect') [65]. Colistin has bactericidal activity against many Gram-negative aerobic bacilli, including *P. aeruginosa, Acinetobacter* species, *Klebsiella* species and *Escherichia coli* [67]. Nephrotoxicity has been noted to occur when colistimethate is administered intravenously, which has led to the development of an inhaled formulation resulting in lower systemic concentrations [68].

A population pharmacokinetic study by Kechagia et al. [69] evaluated 20 mechanically ventilated adults with Gram-negative infections caused by polymyxin-sensitive bacterial pathogens, who were treated with 80 mg of colistimethate sodium aerosolized and injected into the inspiratory limb of their ventilators. Serial sampling from the blood and the epithelial lining fluid was performed to assess colistin concentrations systemically and at the site of action [69]. A one-compartment model with a Weibull absorption model was used to fit the data. Because of high peak concentrations, the authors suspected that premixing of colistimethate prior to administration may have resulted in hydrolysis, thereby increasing the concentrations of

colistin in solution [69]. The biological rationale for this is based on an alert from the US Food and Drug Administration (FDA) in 2007, which featured a case report describing a patient with cystic fibrosis who received premixed colistimethate and died because of pulmonary toxicity attributed to increased colistin concentrations following an extended period of hydrolysis [69–71]. To compensate for the abnormally high peak concentrations that the authors observed, a 'systematic bias' term was introduced into the residual error model for all concentrations measured within 4 h of administration [69]. Inclusion of this term improved the model fit and yielded pharmacokinetic parameters that were consistent with those derived from previous noncompartmental analyses conducted in patients with ventilator-associated pneumonia and cystic fibrosis (see Table 1, Supplemental Table 4) [66, 71]. Results from a noncompartmental pharmacokinetic analysis involving mechanically ventilated adults with ventilator-associated Gram-negative tracheobronchitis suggested that a single dose of 80 mg of colistimethate sodium (1 million international units of colistimethate sodium) was insufficient to treat multidrug-resistant Gram-negative ventilator-associated pneumonia. However, in individuals with cystic fibrosis, a dose of 2 million international units of colistimethate sodium was associated with an improvement in lung function parameters, with high peak serum concentrations.

### 2.5 Ciprofloxacin

Fluoroquinolones, including ciprofloxacin, feature impressive tissue penetration, which makes them ideal for inhaled administration [72, 73]. The most well studied inhaled ciprofloxacin formulation is available in a dry powder inhaler (DPI) formulation, which is prepared using an emulsion-based, spray-drying process, creating uniform particles with an MMAD <5 μm [32, 74, 75]. A phase I pharmacokinetic study conducted using this DPI formulation of ciprofloxacin was performed in six healthy male adult volunteers [76]. Following aerosolized administration of 50 and 100 mg of the DPI ciprofloxacin, the peak sputum concentrations were similar, with peak serum concentrations of 0.08 and 0.3 μg/mL, respectively [76]. The authors also reported a plasma half-life of 9.5 h (additional pharmacokinetic parameters are reported in Supplemental Table 5) [76]. In a follow-up, single-dose, dose-escalation, phase I study conducted in adults with cystic fibrosis, low systemic exposure and high, variable sputum exposure were observed [77, 78]. The same group of investigators also evaluated the pharmacokinetics of this DPI formulation of ciprofloxacin in patients with moderate to severe COPD in a double-blind, cross-over study involving a single dose of 32.5 or 48.75 mg of ciprofloxacin separated by a 7- to 14-day washout period [79]. Systemic exposure was slightly higher with the 48.75 mg dose; however, the peak sputum concentrations and area under the concentration–time curve (AUC) values were similar with the two doses, which led the authors to recommend advancing the lower dose into later-phase trials. The same DPI formulation of ciprofloxacin is also being evaluated in patients with non-cystic fibrosis bronchiectasis [80, 81]. Limited pharmacokinetic data have been published; however, preliminary efficacy studies have demonstrated that a dose of 32.5 mg twice daily for 28 days was well tolerated and reduced the sputum bacterial load in comparison with placebo-treated subjects [81]. Phase III studies in this population are currently recruiting participants (ClinicalTrials.gov study identifiers NCT01764841 and NCT02106832).

A dual-release formulation of ciprofloxacin has also been developed for inhalation, which includes both an immediate effective dose (free ciprofloxacin) and a mechanism for providing sustained release over a period of 24 h through encapsulation of ciprofloxacin within a liposome [82]. Preclinical studies have demonstrated a pulmonary half-life of approximately 12 h following inhalation in animal models, as compared with approximately 1 h for free ciprofloxacin alone [82]. Additional preclinical studies have found that inhalation of liposomal ciprofloxacin was associated with improved efficacy in a murine model of lethal pulmonary tularaemia [83]. Human studies have also established a systemic half-life of approximately 10 h and observed that sputum concentrations persisted above 20 μg/g for up to 22 h following inhalation [84, 85]. Pharmacokinetic data for this inhaled liposomal ciprofloxacin hydrochloride formulation have been presented in abstract form for a pooled phase I and phase II analysis with a single dose of 3, 6, 9 or 50 mg/L administered via nebulization to patients with cystic fibrosis [84]. The authors reported observing an absorption-limited half-life of approximately 10.5 h following administration of single and multiple doses. High concentrations of ciprofloxacin were detected in the sputum, which were associated with a reduction in the sputum density of *P. aeruginosa* and a 7 % improvement in pulmonary function at the end of a 14-day treatment period [86]. As with the DPI ciprofloxacin formulation, the inhaled liposomal formulation is also being studied in patients with non-cystic fibrosis bronchiectasis [87]. Limited pharmacokinetic data have been published, although the efficacy of this formulation has been studied in a phase II trial in 42 adult subjects with bronchiectasis [87]. Serisier et al. [87] observed a 4.2 $\log_{10}$ decrease in the sputum *P. aeruginosa* bacterial load in comparison with placebo, and an increase in the time to the next pulmonary exacerbation from 58 to 134 days. On the basis of these promising findings, two phase III trials are currently

**Table 1** Population pharmacokinetic studies with inhaled antibacterials

| Study | Class | Antibacterial | Population | Formulation and regimen | Aerosolization device | Model structure | Pharmacokinetic parameters | Influential covariates | Clinical implications |
|---|---|---|---|---|---|---|---|---|---|
| Touw et al. [31] | Aminoglycoside | Tobramycin | Adults with cystic fibrosis ($n = 6$) | 600 mg of tobramycin dissolved in 10 mL of water, with pH adjusted to 6–7 and tonicity of 270 mosmol/kg | Ultrasonic nebulizer (Wisto Senior®) | 1-Compartment model with first-order absorption and first-order elimination | CL/$F$: 7.0 ± 2.9 L/h<br>$V_{ss}/F$: 1.7 ± 1.0 L/kg<br>$k_a$: 2.0 ± 1.4 $h^{-1}$<br>F: 17.5 ± 8.8 % | None tested | Bioavailability reflects pulmonary deposition of tobramycin, which suggests that future studies in patients with cystic fibrosis should have a concentration-controlled design |
| Ting et al. [39] | Aminoglycoside | Tobramycin | Children and adults with cystic fibrosis ($n = 139$) | Tobramycin powder for inhalation<br>Single dose of 28, 56, 84 or 112 mg<br>Multiple doses of 112 mg administered twice daily | T-326 DPI | 2-Compartment model with first-order absorption and first-order elimination | CL/$F$: 14.5 L/h (SE 5.0 %)<br>$V_1/F$: 85.1 L (SE 3.6 %)<br>$k_a$: 2.4 $h^{-1}$ (SE 4.8 %)<br>$Q/F$: 6.4 L/h (SE 12.9 %)<br>$V_2/F$: 210.0 L (SE 29.9 %) | BMI and pulmonary function (statistically significant but not clinically significant) | No dosing adjustments are needed to accommodate differences in BMI or baseline pulmonary function |
| Okusanya et al. [48] | Aminoglycoside | Amikacin | Children and adults with cystic fibrosis ($n = 24$) | 500 mg of liposomal amikacin administered once daily for 14 days | PARI LC® Star nebulizer with a DeVilbiss compressor | 2-Compartment model with zero-order absorption into the lungs, first-order absorption from the lungs into the central compartment and first-order elimination | *Day 1:*<br>CL/$F$: 68.4 L/h (SE 10.3 %)<br>$V_d/F$: 286.0 L (SE 12.3 %)<br>$k_a$: 3.3 $h^{-1}$ (SE 32.5 %)<br>$CL_R$: 45.2 L/h (SE 15.4 %)<br>*Day 14:*<br>CL/$F$: 45.2 L/h (SE 8.0 %)<br>$V_d/F$: 250.0 L (SE 8.5 %) | None tested | A significant association was observed with higher serum AUC/MIC ratios and reductions in *P. aeruginosa* density; additionally, reductions in *P. aeruginosa* density were associated with improvements in pulmonary function parameters |

**Table 1** continued

| Study | Class | Antibacterial | Population | Formulation and regimen | Aerosolization device | Model structure | Pharmacokinetic parameters | Influential covariates | Clinical implications |
|---|---|---|---|---|---|---|---|---|---|
| Kechagia et al. [69] | Polymyxin | Colistin | Mechanically ventilated adults with ventilator-associated tracheobronchitis caused by a Gram-negative bacterium ($n = 20$) | 80 mg of colistin methanesulfonate | Aeroneb® Pro vibrating mesh nebulizer | 1-Compartment model with a Weibull absorption process | CL/*F*: 6.79 L/h (SE 6.4 %)<br>$V_d/F$: 37.2 L (SE 5.0 %)<br>Weibull scale (a): 1.4 h (SE 1.5 %)<br>Weibull shape (b): 2.1 (SE 2.9 %)<br>Standardized bias: 0.5 (SE 6.1 %) | $CL_{CR}$ | A single dose of inhaled colistimethate sodium resulted in sustained high concentrations in the epithelial lining fluid at 1 and 4 h; despite this, a dose of 80 mg of colistin methanesulfonate appears to have been insufficient for treatment of multidrug-resistant Gram-negative ventilator-associated pneumonia |
| Stass et al. [76] | Fluoroquinolone | Ciprofloxacin | Healthy male adults ($n = 6$) | 32.5 mg of ciprofloxacin dry powder | T-326 DPI | Physiologically based pharmacokinetic model | $AUC_\infty$: 354.4 µg·h/L (CV 30.3 %)<br>$C_{max}$: 56.4 µg/L (CV 32.2 %)<br>CL/*F*: 91.7 L/h (CV 30.3 %)<br>$V_2/F$: 1262 L (CV 33.2 %) | None tested | This DPI formulation of ciprofloxacin was well tolerated in healthy volunteers, resulted in minimal systemic exposure and achieved high ciprofloxacin concentrations in the lungs |

*AUC* area under the concentration–time curve, $AUC_\infty$ AUC from time zero to infinity, *BMI* body mass index, *CL/F* apparent total clearance, $CL_R$ renal clearance, $C_{max}$ maximum concentration, *CV* coefficient of variation, *DPI* dry powder inhaler, *F* bioavailability, $k_a$ absorption rate constant, *MIC* minimal inhibitory concentration, *Q/F* apparent intercompartmental clearance, *SE* standard error, $V_1/F$ apparent central volume of distribution, $V_2/F$ apparent peripheral volume of distribution, $V_d/F$ apparent volume of distribution, $V_{ss}/F$ apparent steady-state volume of distribution

enrolling participants (ClinicalTrials.gov study identifiers NCT01515007 and NCT02104245).

### 2.6 Levofloxacin

Levofloxacin is a third-generation member of the fluoroquinolone family [88]. Levofloxacin features a broad spectrum of activity against Gram-positive and Gram-negative bacteria; however, unlike other fluoroquinolones, levofloxacin has improved activity against *Enterococcus faecalis* and *Streptococcus pneumoniae* [89]. Like ciprofloxacin, levofloxacin exerts its antibacterial effects by inhibiting bacterial DNA replication through targeting of DNA gyrase and topoisomerase IV, which are vital enzymes needed to stabilize DNA replication machinery [90, 91].

Levofloxacin features concentration-dependent bactericidal activity, with a strong association between higher rates of bacterial killing and higher levofloxacin concentrations at the site of the infection [92]. Because of this pharmacokinetic/pharmacodynamic property, the large proportion of an inhaled dose that reaches the lower respiratory tract greatly improves the efficacy of levofloxacin for the treatment of acute and chronic pulmonary infections alike [93].

An aerosolized formulation of levofloxacin (MP-376) has been developed for the treatment of chronic pulmonary infections caused by *P. aeruginosa* in patients with cystic fibrosis [94]. Griffith et al. [95] conducted a single-ascending-dose, phase I pharmacokinetic trial in eight patients with cystic fibrosis. The lowest dose of aerosolized levofloxacin achieved a peak sputum concentration more than 8-fold higher than those observed following oral levofloxacin administration [95]. Moreover, serum levofloxacin concentrations were more than 10-fold lower. Subsequently, the authors conducted a single-blind, crossover, phase I pharmacokinetic trial with patients ≥16 years of age with cystic fibrosis [94]. The serum AUC from 0 to 24 h ($AUC_{24}$) values were 9.1 and 14.8 μg·h/mL for the 180 and 240 mg doses, respectively, which were calculated to be 12–19 % of the serum AUC values observed following administration of a 750 mg oral dose of levofloxacin in an earlier study [94, 96]. Systemic absorption occurred rapidly, with a peak serum concentration observed within 20 min of dosing [94]. These positive findings led the authors to conduct a phase II clinical trial to evaluate the efficacy and tolerability of the 240 mg dose of inhaled levofloxacin solution [97]. A total of 151 patients with cystic fibrosis were recruited, and aerosolized levofloxacin was administered twice daily for a period of 28 days. The primary outcome was the change from baseline in the sputum *P. aeruginosa* density. At the end of the 28-day treatment period, placebo-treated patients experienced a 0.2 $\log_{10}$ decrease in the sputum *P. aeruginosa* density, as compared with a 0.7 $\log_{10}$ decrease in patients who received aerosolized levofloxacin [97]. However, after 28 days off treatment, the sputum *P. aeruginosa* density returned to baseline levels in all groups [97]. More recently, two pivotal phase III clinical trials were conducted to evaluate the safety and efficacy of inhaled levofloxacin solution (ClinicalTrials.gov study identifiers NCT01270347 and NCT01180634). The results of these trials have not yet been published. Although it is beyond the scope of this review, interested readers are referred to more detailed examinations of the pharmacodynamics, clinical efficacy and tolerability of inhaled levofloxacin solution [98, 99].

## 3 Antivirals

### 3.1 Zanamivir

Zanamivir is a neuraminidase inhibitor, which was approved by the FDA in 1999 for the treatment of influenza virus infection in patients ≥7 years of age and for influenza prophylaxis in patients ≥5 years of age [100–106]. Several clinical studies have demonstrated that the use of zanamivir is associated with a decrease in the duration of symptoms of approximately 1–2.5 days [100–105]. Because of its high polarity, zanamivir does not readily cross cell membranes and therefore features relatively poor oral bioavailability [107]. However, influenza virus replicates in the airway epithelium, which is readily accessible following inhalation of zanamivir [108, 109].

A clinical pharmacokinetic study involving healthy adult volunteers evaluated four zanamivir dosing regimens, including inhalation via a nebulizer and a DPI [110]. Both methods of administration yielded low systemic exposure (approximately 10–20 % bioavailability) with linear, dose-dependent kinetics [110]. In a separate study, the deposition of zanamivir was examined using radiolabelled technetium, which revealed that 13 % of the inhaled dose was deposited in the bronchi and lungs, with the majority (78 %) being deposited in the oropharynx [111]. Peng et al. [112] examined sputum zanamivir concentrations and found that they consistently exceeded the 0.9 ng/mL concentration needed to inhibit viral replication by 50 % ($IC_{50}$).

A single population pharmacokinetic study was performed by Peng et al. [113], which pooled data from two phase II trials involving the DPI formulation of zanamivir. Healthy adult volunteers who received zanamivir as a prophylactic agent and patients with influenza-like illness (fever and headache, myalgia, cough or sore throat) were studied [113]. A one-compartment model was used to fit the data, and the resulting pharmacokinetic parameters are

featured in Table 2. After accounting for the formulation and route of administration, no significant covariates were identified, which suggests that zanamivir pharmacokinetics are similar in healthy volunteers and influenza-infected individuals [113]. Recently, a clinical trial of inhaled zanamivir in pregnant women was completed, although the results of that trial have not yet been published (ClinicalTrials.gov study identifier NCT01462487).

A single inhaled dose of zanamivir was administered to children 3 months to 12 years of age with symptoms of an acute respiratory tract infection [114]. In a noncompartmental analysis, no significant differences in zanamivir pharmacokinetics were identified with respect to age [114]. For children ≥5 years of age, the manufacturer recommends that the standard adult dose of 10 mg be administered twice daily with the Rotadisk®/Diskhaler®; however, not all children are capable of efficiently using the Rotadisk®/Diskhaler®, because of age or physical restrictions [115]. Consequently, a nebulized formulation of zanamivir may be clinically useful. However, recently, a woman using a nebulized formulation of zanamivir outside the USA died following obstruction of the nebulizer. This suggests that further work is needed to optimize the nebulized delivery of zanamivir. As an alternative option, an intravenous formulation of zanamivir is currently being evaluated in clinical trials, which may be suitable for patients who are not able to use the DPI zanamivir formulation with the Rotadisk®/Diskhaler® (ClinicalTrials.gov study identifiers NCT01231620 and NCT01014988).

### 3.2 Laninamivir

Laninamivir is a long-acting neuraminidase inhibitor, which is delivered via inhalation as the prodrug laninamivir octanoate [116]. Laninamivir octanoate has been approved for the treatment and prevention of influenza infection in Japan and is currently in phase II clinical trials in the USA (ClinicalTrials.gov study identifier NCT01793883) [117, 118]. Preclinical studies have demonstrated prolonged retention of laninamivir in the respiratory tract, which suggests that a single dose may be suitable for treatment [119]. Moreover, a weekly prophylactic dosing regimen is expected to yield sufficient exposure to prevent influenza infection [120]. In vitro experiments have demonstrated activity against influenza A and B viruses, including subtypes N1–N9, oseltamivir-resistant viruses, H5N1 and the pandemic 2009 H1N1 virus [121].

In phase I clinical pharmacokinetic studies, laninamivir octanoate was administered to healthy male adult volunteers in (1) a series of single ascending doses; (2) a single high dose; and (3) a series of multiple ascending doses [122]. The doses administered ranged from 5 to 120 mg, with a proportional increase in the half-life ranging from 6 to 81 h. In further studies, it was observed that patients with impaired renal function had increased AUCs following administration of inhaled laninamivir octanoate [123]. Surprisingly, the half-life was not significantly prolonged, which the authors attributed to the relatively slow release of laninamivir from retaining tissues into the plasma, which would not be expected to be affected by renal impairment (a phenomenon known as 'flip-flop pharmacokinetics') [123]. On the basis of these findings, the authors suggested that because laninamivir octanoate is administered as a single dose for therapeutic purposes, accumulation is unlikely to occur in patients with renal insufficiency [123]. More recently, an alternative delivery device was used in healthy adults, which led to increases in the peak plasma concentration and the AUC of approximately 2- to 3-fold in comparison with the results of the earlier phase I trial [124]. These findings suggest that newer inhalers may yield higher systemic exposure, for which additional study is necessary to determine whether dosing adjustments are warranted for patients with end-stage renal disease.

To examine the intrapulmonary pharmacokinetics of laninamivir and its prodrug, laninamivir octanoate, Ishizuka et al. [125] recruited healthy adult volunteers who received a single inhaled dose of laninamivir octanoate and had serial bronchoalveolar lavages performed. The authors found that laninamivir concentrations exceeded the $IC_{50}$ for viral neuraminidases for up to 240 h following inhalation, supporting the long-lasting effect of laninamivir following a single administration [125].

The only published population pharmacokinetic analysis of laninamivir used data derived from seven clinical trials, including six phase I studies and one phase II study [126]. Overall, 113 healthy volunteers and 30 children with influenza infection were studied. A metabolite model was developed in which laninamivir octanoate was modelled using two compartments, and formation of the active metabolite laninamivir was modelled with a third compartment [126]. The pharmacokinetic parameters identified from this analysis are featured in Table 2. Of note, in covariate analyses, creatinine clearance had a strong influence on laninamivir clearance, and weight influenced the volume of distribution [126]. Additionally, it was reported that approximately 12 % of the inhaled dose is deposited in the airway as laninamivir, and a further 3 % of the laninamivir octanoate dose is metabolized into laninamivir in the systemic circulation [126]. As with earlier noncompartmental analyses, the half-life of laninamivir in the respiratory tract was estimated as 58 h, which likely occurs as a consequence of local hydrolysis, uptake of laninamivir octanoate by airway epithelial cells and trapping of laninamivir in airway cells, due to its hydrophilicity and poor membrane permeability [122, 127].

**Table 2** Population pharmacokinetic studies with inhaled antivirals

| Study | Class | Antiviral | Population | Formulation and regimen | Aerosolization device | Model structure | Pharmacokinetic parameters | Influential covariates | Clinical implications |
|---|---|---|---|---|---|---|---|---|---|
| Peng et al. [113] | Neuraminidase inhibitor | Zanamivir | Healthy adults and patients with influenza ($n = 173$) | 10 mg of zanamivir dry powder administered twice daily | Commercial DPI | 1-Compartment model | CL/F: 34.4 L/h (95 % CI 29.1–39.7)<br>$V_d$/F: 121 L (95 % CI 92–150)<br>$k_a$: 2.10 $h^{-1}$ (95 % CI 1.52–2.68) | None tested | Zanamivir pharmacokinetics are similar in healthy individuals and influenza-infected individuals, which suggests that pathophysiological changes in the airway associated with influenza infection do not substantially alter the pharmacokinetics of zanamivir |
| Yoshihara et al. [126] | Neuraminidase inhibitor | Laninamivir octanoate | Healthy adults ($n = 113$) and children with influenza ($n = 30$) | Laninamivir octanoate (dry powder)<br>Single dose of 5, 10, 20, 40, 80 or 120 mg<br>Multiple doses of 20 or 40 mg administered twice daily, or 20 mg administered four times daily | Prototype or commercial DPI | *Laninamivir octanoate:*<br>2-Compartment model with instantaneous bolus input and first-order elimination<br>*Laninamivir:*<br>1-Compartment model with linear elimination | *Laninamivir octanoate:*<br>CL/*F*: 64.8 L/h (SE 4.6 %)<br>$CL_R$: 1.95 L/h (SE 2.6 %)<br>$V_1/F$: 215 L (SE 4.8 %)<br>$V_2/F$: 303 L (SE 11.9 %)<br>*Laninamivir:*<br>$CL_R$: 5.2 L/h (SE 1.7 %)<br>$V_d/F$: 21.3 L (SE 2.6 %) | $CL_{CR}$ on CL/*F* and $CL_R$ of laninamivir octanoate and laninamivir; body weight on laninamivir octanoate $V_1/F$ and laninamivir $V_d/F$ | $CL_{CR}$ was a significant covariate on clearance, which affected laninamivir systemic exposure |

*CI* confidence interval, $CL_{CR}$ creatinine clearance, *CL/F* apparent total clearance, $CL_R$ renal clearance, *DPI* dry powder inhaler, $k_a$ absorption rate constant, *SE* standard error, $V_1/F$ apparent central volume of distribution, $V_2/F$ apparent peripheral volume of distribution, $V_d/F$ apparent volume of distribution

### 3.3 Ribavirin

An aerosolized formulation of ribavirin received FDA approval in 1986 for the treatment of respiratory syncytial virus (RSV) bronchiolitis in infants and young children [128]. Ribavirin is a synthetic nucleoside analogue, which features moderate antiviral activity against RSV [129]. Aerosolized ribavirin has also been shown to be effective in the treatment of influenza infection in adults [130–133]. Ribavirin is administered by dissolving the drug in distilled water, which is then placed into a collision nebulizer [134].

Although ribavirin has been used clinically for approximately 30 years, few pharmacokinetic studies exist in the scientific literature. Early reports suggested that pulmonary deposition of ribavirin (scaled per kilogram of body weight) was higher in infants than in adults following inhalation of an aerosol containing ribavirin 200 μg/L [135]. Additionally, females had lower respiratory tract deposition than males, and patients who were febrile experienced higher pulmonary deposition [135]. A separate noncompartmental pharmacokinetic study was performed, in which nine children 6 weeks to 7 years of age with signs and symptoms consistent with RSV infection received inhaled ribavirin three times daily for 2 h from a reservoir containing ribavirin 60 mg/mL of distilled water (flow volume 7–8 mL/min) [136]. The authors found that ribavirin was rapidly cleared, with a mean half-life of 1.9 ± 0.8 h. Placebo-controlled clinical trials have failed to demonstrate a consistent improvement in clinical outcomes with the use of inhaled ribavirin, which, because of its high cost and uncertain clinical utility, has led the American Academy of Pediatrics to recommend against the use of aerosolized ribavirin for routine treatment of RSV bronchiolitis [137]. However, aerosolized ribavirin continues to be used clinically and studied in immunocompromised patients, including stem cell transplant recipients (ClinicalTrials.gov study identifier NCT01502072).

## 4 Antifungals

### 4.1 Amphotericin

Amphotericin B is a macrolide polyene antifungal agent, which was first produced in 1955 through a fermentative process involving the soil actinomycete *Streptomyces nodosus* [138]. Amphotericin B was approved for clinical use in 1959 [139]. For many years, amphotericin B was the only parenterally available antifungal agent with a broad spectrum of activity. Amphotericin B is a first-line agent for the treatment of life-threatening fungal infections, including those caused by *Candida albicans* and *Aspergillus fumigatus* [140]. The mechanism of action of amphotericin B stems from its preferential binding to ergosterol, which is the principal component of fungal cell membranes. Amphotericin B was initially marketed as a mixture with deoxycholate to improve its solubility [141]. However, the clinical utility of amphotericin B deoxycholate has been limited because of its pronounced dose-related nephrotoxicity [142]. This has spurred efforts to develop lipid-based formulations, which have now largely superseded the use of amphotericin B deoxycholate [143]. These formulations involve the use of a lipid-carrier and yield low serum concentrations of free amphotericin B, while maintaining high concentrations in target areas of fungal infection—thereby decreasing the incidence of systemic adverse effects [144].

Patients with poor lung function and those who are immunosuppressed as a consequence of solid-organ or haematopoietic stem cell transplantation, leukaemia or chemotherapy are at high risk of fungal infection by invasive species such as *Aspergillus* [145]. Literature estimates report that approximately 20–25 % of lung and bone marrow transplant recipients develop invasive aspergillosis [145]. Consequently, aerosolized delivery of antifungal agents is an attractive therapeutic option. Inhaled formulations of amphotericin B are typically aerosolized using jet and ultrasonic nebulizers [146–149].

Monforte et al. [147] conducted a pharmacokinetic study in which 39 patients received inhaled amphotericin B deoxycholate aerosolized with a jet nebulizer at a concentration of 1 mg/mL, with a total solution volume of 50 mL. At 24 h, the concentrations of amphotericin B were 0.37 μg/mL in bronchial aspirate secretions and 11.02 μg/mL in bronchoalveolar lavage specimens [147]. Five subjects (13 %) had undetectable serum concentrations (Table 3). On the basis of in vitro results, the authors concluded that the concentrations of amphotericin B in the distal airway were sufficient to prevent *Aspergillus* infection [147].

The pharmacokinetics of Abelcet® (a lipid-based formulation of amphotericin B) were examined in 35 lung transplant recipients [150]. These patients received aerosolized Abelcet® 1 mg/kg every 24 h for 4 days. In all evaluated subjects, the median amphotericin B concentrations were higher in the epithelial lining fluid than in the plasma [150]. Additionally, the median epithelial lining fluid concentration of amphotericin B remained above the *Aspergillus* MIC at 7 days post-administration. In contrast, serum concentrations remained below 0.08 μg/mL at all sampled time points, suggesting that systemic absorption of amphotericin B from the respiratory tract was minimal [150].

**Table 3** Physicochemical properties, aerosolization methods and noncompartmental pharmacokinetics of inhaled antifungals

| Property | Amphotericin B | | | Pentamidine |
|---|---|---|---|---|
| | Abelcet® | AmBisome® | Fungizone® | Nebupent® |
| Formulation properties | | | | |
| Class | Lipid complex | Liposomes | Colloidal system | Solution |
| Particle diameter (nm) | 1600–6000 | 60–80 | 80–100 | NA |
| Structure | Ribbon-like | SUVs | Mixed micelles | NA |
| Aerosol properties | | | | |
| MMAD (μm) | 3.7 | 3.0 | 2.5 | NA |
| Aerosolization device | AeroEclipse® | Venstream® | System 22 Acorn® | Ultravent® |
| Pharmacokinetics | | | | |
| Dose | 1.0 mg/kg | 50 mg vial | 50 mg vial | 4 mg/kg |
| $C_{max}$ in ELF or BAL (μg/mL) | 8.3 (3.9–82.7)[a] | 11.1 (16.5–5.7)[b] | 15.8 (10.9–20.6)[b] | 0.003 ± 0.0055[c] |
| $C_{max}$ in plasma (μg/mL) | 0.05 (0.03–0.06)[a] | Undetected | Undetected | 0.023 ± 0.0024[c] |

Data from Monforte et al. [147], Husain et al. [148], Monforte et al. [151] and Conte et al. [159]

*BAL* bronchoalveolar lavage, $C_{max}$ maximum concentration, *ELF* epithelial lining fluid, *MMAD* mass median aerodynamic diameter, *NA* not applicable or not reported, *SUV* small unilamellar vesicle

[a] Median (interquartile range)

[b] Mean (95 % confidence interval)

[c] Mean (±standard deviation)

The pharmacokinetics of a colloidal dispersion of amphotericin B (AmBisome®) were investigated in 27 patients who received 50 mg of AmBisome® three times per week [151]. Concentrations of amphotericin B in bronchoalveolar lavage specimens remained high enough to inhibit the growth of most *Aspergillus* species over a 14-day treatment period [151]. Similar to findings from studies involving amphotericin B deoxycholate and Abelcet®, serum concentrations of amphotericin B following aerosolized administration of AmBisome® were undetectable in all but one patient, and that patient's concentration was 0.1 μg/mL (slightly above the lower limit of quantitation) [151]. Overall, these results demonstrate the superior pharmacokinetic profile of aerosolized amphotericin B formulations as compared with parenterally administered amphotericin B for the treatment of pulmonary fungal infections.

### 4.2 Pentamidine

Pentamidine isethionate is an aromatic diamidine, which has been known to feature significant anti-protozoal activity against African trypanosomiasis from studies conducted as early as 1938 [152]. More recently, pentamidine has been found to feature activity against *P. carinii* pneumonia [153–155]. The mechanism of action of pentamidine is not fully understood; however, in vitro studies have indicated that pentamidine inhibits nucleic acid, phospholipid, protein and polyamine synthesis, all of which interfere with nuclear metabolism [156]. Pentamidine has also been shown to kill non-replicating cells, which suggests that inhibition of DNA synthesis is not solely responsible for its antimicrobial activity [157].

During the acquired immunodeficiency syndrome (AIDS) epidemic of the late 1980s and early 1990s, it was discovered that more than 80 % of individuals became infected with *P. carinii* pneumonia [153]. With the widespread recognition of the clinical utility of pentamidine for the treatment of *P. carinii* pneumonia, efforts were made to develop aerosolized formulations of pentamidine isethionate [158, 159]. In a landmark community prophylaxis trial, aerosolized pentamidine was administered to 408 subjects at 12 treatment centres in San Francisco (CA, USA) [160]. Patients randomized to the high-dose (300 mg) arm of the trial had eight confirmed episodes of *P. carinii* pneumonia at 18 months post-randomization, as compared with 22 events in patients randomized to the low-dose (30 mg) treatment group [160].

Limited pharmacokinetic data exist for aerosolized formulations of pentamidine; however, a study by O'Doherty et al. [161] assessed the tissue distribution of radiolabelled, nebulized pentamidine in seven patients with human immunodeficiency virus (HIV) infection. The authors found that total pulmonary deposition amounted to approximately 5 % of the initial nebulized dose. Relatively small amounts were detected in the thyroid at 4 and 24 h (0.1 and 0.4 %, respectively). Similar proportions were identified in the gut (0.2 and 0.1 % at 4 and 24 h, respectively) and in the bladder (0.4 and 0.7 %, respectively).

## 5 Aerosolized Delivery Devices

Significant progress has been made in refining aerosolized delivery devices over the last 60 years [162]. For most inhaled antimicrobials, liquid formulations have been favoured, which have historically been administered using ultrasonic and jet nebulizers. Ultrasonic nebulizers use a piezoelectric crystal that vibrates at a high frequency (typically 1–3 MHz) to generate a fountain of liquid in the nebulization chamber [163]. Ultrasonic nebulizers can nebulize solutions more quickly than jet nebulizers; however, they are relatively ineffective in aerosolizing suspensions or high-viscosity liquids. In contrast, the Bernoulli principle governs the function of jet nebulizers, in which a compressed gas is passed through a narrow opening, which creates an area of low pressure at the outlet of the nearby liquid-filled tube. The drug solution is then pulled up from the fluid reservoir and shattered into droplets in the stream of compressed gas. These nebulization methods require very little patient coordination or skill, although pulmonary deposition is limited to approximately 10 % of the total dose [164]. Recently, vibrating mesh nebulizers have attracted attention, as they feature several advantages over traditional jet nebulizers. Vibrating mesh nebulizers are silent, do not require compressed air, are portable and can be powered with alternating current or batteries. These devices have also been customized for use in mechanically ventilated patients, and, when paired with a valved spacer, have been reported to result in up to 70 % of the inhaled dose being deposited in the lungs [165].

MDIs are convenient, portable, aerosolized delivery devices, which employ a chemical propellant to aerosolize and expel the medication through a nozzle at high velocity (>30 m/s) [166]. Because of the high velocity and large particle size of the drug aerosol, only 10–20 % of the emitted dose is deposited in the lungs. Hand–mouth coordination when actuating the MDI device is also challenging. Crompton [167] reported that 24 % of patients stopped inspiring when the aerosol was projected into their mouth, and 12 % accidentally inspired through their nose. It has also been clearly demonstrated that the pattern of pulmonary deposition with an MDI depends on the patient's breathing pattern and inspiratory flow rate [168]. When using an MDI, the optimal conditions include an initial volume equal to the patient's functional residual capacity, actuation of the MDI at the start of inspiration, an inspiratory flow rate of <60 L/min and a period of 10 s in which the breath must be held at the end of inspiration [169].

DPIs were developed in an effort to eliminate the patient coordination difficulties associated with the use of MDIs. These systems use a dry powder formulation of the drug, which is produced by milling. The patient's inspiratory force disaggregates the dry powder, thereby creating the aerosol. Approximately 10–40 % of the emitted dose is deposited in the lungs, with 20–25 % of the drug being retained within the device [170, 171]. In contrast to use of MDIs, for use of DPIs, pulmonary deposition is enhanced by inhaling rapidly. Borgstrom et al. [172] demonstrated that an increase in the inspiratory flow rate from 35 to 60 L/min using the Turbuhaler® increased pulmonary terbutaline deposition from 15 to 28 %. Until recently, only a limited number of medications could be administered with a DPI, because of the requirement that they be formulated as a dry powder; however, new spray-drying emulsions have broadened the spectrum of medications that can now be administered using a DPI [9, 173]. This technology has been successfully used for inhaled tobramycin, in which the use of a DPI achieved more than 3-fold higher pulmonary deposition than a jet nebulizer [33].

## 6 Conclusions and Future Directions

The clinical pharmacokinetics of many inhaled antimicrobials have been rigorously studied using noncompartmental methods. The majority of these studies have demonstrated that inhaled delivery results in high antimicrobial concentrations in the airway, with relatively limited systemic exposure, thereby reducing the risk of toxicity. Sputum pharmacokinetics are marked by high variability for many inhaled antimicrobials, which makes it challenging to interpret the results of sputum pharmacokinetic studies. Several factors can influence sputum antimicrobial concentrations, including the rate of respiration, the inspiratory flow rate, the tidal volume, and the degree and location of airway obstruction [173]. Additionally, sputum concentrations can reflect local deposition in the upper airway and may not adequately represent concentrations at the site of the infection in the lower respiratory tract. Despite these challenges, clinical pharmacokinetic studies of inhaled antimicrobials have informed the development of safe and therapeutic dosing regimens, led to the creation of novel aerosolized formulations and aided in designing next-generation aerosolization devices.

Over the course of the next 5–10 years, many vitally important clinical pharmacokinetic studies will be needed to evaluate novel inhaled nanoparticle formulations of several antibacterials, including amikacin, ciprofloxacin, tobramycin and vancomycin [174–177]. Additionally, several combination formulations of inhaled antibacterials are currently being investigated in preclinical models, including a co-spray dried combination of ciprofloxacin and doxycycline, a ciprofloxacin and gatifloxacin combination, a tobramycin and fosfomycin combination, a tobramycin and ceftazidime combination, and a colistin

and rifampicin combination, among many others [178–180]. Emerging non-antibacterial adjuvants will also deserve study, including the use of metal-ion chelators, which sequester metallic cations (e.g. iron, calcium and magnesium) necessary for bacterial growth; osmotic agents (e.g. mannitol), which increase the influx of water into the thick dehydrated mucus found in the airways of patients with cystic fibrosis; and nitric oxide donors and D-amino acids, both of which have been reported to exhibit biofilm-dispersal effects in vitro [16].

The pipeline of new inhaled antiviral agents is dominated by the development of new anti-influenza agents (e.g. high-dose ribavirin and recombinant human catalase) [181, 182]. However, a recombinant protein with sialidase activity (DAS181) has been used to treat human parainfluenza virus 3 infection in several small case reports [183–185]. Additionally, inhaled cidofovir has been shown to protect against rabbitpox (a member of the same viral family as smallpox) infection in rabbits [186].

Several inhaled antifungal agents are also being investigated in early preclinical models, including voriconazole, itraconazole, caspofungin and the semi-synthetic analogues of the echinocandins, known as pneumocandins [187–194]. In a rat model of pulmonary aspergillosis, 80 % of the rats that received a 10 mg/kg dose of the aerosolized pneumocandin L-693,989 survived for 7 days, in comparison with 20 % of the control group [193].

As we look to the future, there are a number of inhaled antimicrobials currently under investigation for which clinical pharmacokinetic studies will be needed to establish evidence of safety and efficacy. Development of aerosolization devices will further enhance the number of research questions deserving study, particularly with respect to breath-actuated aerosolization devices, new spacers and valved-holding chambers, and novel dry powder delivery systems for mechanically ventilated patients [195]. Moreover, many currently used inhaled antimicrobials warrant further investigation using population pharmacokinetic methods to ensure that variability in pharmacokinetic parameters can be reduced to the greatest extent possible and to ensure that optimal dosing regimens are identified.

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