Inhaled Anti-infective Agents: Emphasis on Colistin

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Abstract
The administration of antibiotics by the inhaled route is a widely recognized treatment in patients with cystic fibrosis (CF) and bronchiectasis. Tobramycin solution for inhalation (TOBI) has been available for many years and is licensed in the USA and Europe. While strong data support the use of aerosolized antibiotics for the treatment of respiratory infections in patients with CF or bronchiectasis, only a few clinical studies have examined the role of aerosolized antibiotics in the treatment of pneumonia, including ventilator-associated pneumonia (VAP) in these patients. During the last decade increasing interest has been directed towards alternative treatments to the systemic administration of antimicrobial agents for the treatment of patients with hospital-acquired pneumonia or VAP due to multidrug-resistant (MDR) Gram-negative bacteria. Recent publications demonstrate the clinical benefits from administering inhaled aminoglycosides or polymyxins in patients with hospital-acquired pneumonia or VAP. In addition to antibiotics, antifungals, and antivirals have been administered by inhalation to specific groups of critically ill patients. However, randomized controlled trials dealing with the administration of anti-infective agents via the respiratory tract are necessary in order to validate the efficacy, safety, advantages, and disadvantages of this therapeutic approach for the treatment of nosocomial pneumonia.

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Introduction

The first report in the medical literature on the administration of antibiotics by inhalation is dated 1950 and refers to aerosolized penicillin and streptomycin [1]. Since then, inhaled antibiotics have been used largely in patients with cystic fibrosis (CF). During the last decade, anti-infective agents have been administered via the respiratory tract to patients with hospital-acquired or ventilator-associated pneumonia (VAP), invasive pulmonary aspergillosis, and *Pneumocystis carinii* pneumonia (PCP).

This review presents an update of the current status and knowledge regarding the aerosolized administration of anti-infective agents. The first part of the article reports on three classes of antibiotics (aminoglycosides, polymyxins, aztreonam), as well as amphotericin and pentamidine, all administered via the respiratory tract for the management of pneumonia. Special emphasis is given to inhaled colistin. This is followed by a detailed report of all of advantages and side effects related to this route of administration as well as practical considerations and pharmacokinetic, and pharmacodynamic characteristics.

Inhaled Anti-infective Agents

Aminoglycosides

Tobramycin

Many studies have investigated the efficacy and safety of inhaled tobramycin (TOBI) for eradicating *Pseudomonas aeruginosa* in patients with CF (Table 1). The majority of these patients showed improvement of lung function, expressed by an increase of the predicted percentage FEV_1 (predicted forced expiratory volume in 1 s), decrease in the density of *Ps. aeruginosa* in patients' sputum, and reduced need for administration of iv anti-pseudomonal antibiotics and for hospitalization due to respiratory tract infections [2–9].

Inhaled TOBI was also administered in patients with VAP. Better clinical results have been reported with TOBI than with iv tobramycin. However, the number of patients enrolled in that study was very small, not allowing any definitive conclusion to be drawn [10].

Gentamicin

In one study, inhaled gentamicin (120 mg b.i.d.) was administered in 12 patients with CF for a minimum of 3 years in order to prevent colonization and respiratory

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Table 1
Inhaled antibiotics administered in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*.

Reference number	Year of publication	Study design	Subjects (n)	Controls	Agent	Dosage
[2]	1989		14	0	Tobramycin	80 mg b.i.d.
[3]	1989	RCT	15	12	Tobramycin placebo	80 mg t.i.d.
[4]	1998	RCT	11	11	Tobramycin placebo	80 mg b.i.d.
[5]	1999	RCT	258	262	Tobramycin placebo	300 mg b.i.d.
[6]	2001		15	0	Tobramycin	300 mg bid
[7]	2002	RCT	61	67	Tobramycin placebo	300 mg b.i.d.
[8]	2002	RCT	53	62	Tobramycin colistin	300 mg b.i.d. 80 mg b.i.d.
[9]	2003	RCT	8	13	Tobramycin placebo	300 mg b.i.d.

Reference number	Key observations
[2]	Subjects: Decreased frequency of hospital admissions. The best long-term results were obtained in moderately ill children. No evidence of ototoxicity or nephrotoxicity. Acquisition of bacterial resistance (5/14). IV antibiotics were administered if necessary Controls: No
[3]	Subjects: No change in PFTs and clinical status. No significant nephrotoxicity or ototoxicity. Acquisition of resistant *Pa* (9/15) Controls: Significant decline in pulmonary function tests and clinical status of the control group (11/12)
[4]	Subjects: Two patients stopped inhalation before the 12-month treatment period. Shorter time of eradication. Unchanged PFTs and markers of inflammation Controls: Six patients stopped inhalation before the 12 month treatment period
[5]	Subjects: Receiving aerosolized tobramycin in three cycles, with each cycle consisting of 28 days with drug and 28 days with no drug. 88% compliance. 10% increase in FEV_1 and decrease of density of *Pa* in sputum at week 20 as compared with week 0. Reduced need for iv anti-pseudomonal antibiotics and for hospitalization. No ototoxic or nephrotoxic effects. 7% increase of resistance of tobramycin in *Pa* isolates Controls: 93% compliance. 2% decline in FEV_1 at week 20 as compared with week 0. Increase of density of *Pa* in sputum in week 20 compared with week 0.3% decrease of resistance at week 24 compared to week 0
[6]	Subjects: Eradication of *Pa* in 14/15 patients with cystic fibrosis. Duration of inhalation: 12 months. No other drug with known activity against *Pa* was given during treatment or follow-up. After 2 years of follow-up, nine patients had negative serum antibody titers against *Pa*. Tobramycin-resistant bacteria were not seen during the treatment period Controls: No
[7]	Subjects: 14.3% increase of predicted FEV_1% and decrease of density of *Pa* in sputum at week 96 as compared with week 0. Reduced need for iv anti-pseudomonal antibiotics (32%) and for hospitalization (19%) compared to those observed during placebo exposure. No ototoxic or nephrotoxic effects. Significant increase of resistance of tobramycin in the *Pa* isolates Controls: No significant increase (1.8%) in predicted FEV_1% at week 96 as compared with week 0. No significant reduction in *Pa* cfu density
[8]	Subjects: 6.7% increase in FEV_1% predicted and a decrease in sputum *Pa* density in chronically infected patients from baseline to week 4 Controls: A decrease in sputum *Pa* density in chronically infected patients but no significant increase in FEV_1% predicted from baseline to week 4
[9]	Subjects: Significant difference between treatment groups in the reduction in *Pa* density; no *Pa* was detected in BAL on day 28 in any of the patients. No differences between treatment groups for clinical indices, markers of inflammation, or incidence of adverse events. No complications (increase of serum creatinine, no episodes of significant bronchospasm) Controls: *Pa* was detected on day 28 in 1/13 patients

RCT: Randomized controlled trial; FEV_1%: predicted forced expiratory volume in 1 s; Pa: *Ps. aeruginosa*; PFTs: pulmonary function tests; BAL: bronchoalveolar lavage

tract infection. None of the patients became chronically infected with *Ps. aeruginosa.* In contrast, seven of 16 patients who discontinued inhaled gentamicin for a variety of reasons became chronically infected with *Ps. aeruginosa*. Lung function and chest X-ray scores were significantly worse in the latter group than in those of the subjects receiving inhaled gentamicin for the whole period [11]. In another study, inhaled gentamicin was also administered to 17 patients with CF for targeting the eradication of initial *Ps. aeruginosa* colonization. The subjects received

inhaled and/or systemic anti-pseudomonal treatments. Initial *Ps. aeruginosa* colonization was successfully eradicated in 15/17 patients for at least 2 years [12].

Some years later, *Palmer* et al. published the results of their double-blind, randomized, placebo-controlled study performed in critically ill adult intubated patients with tracheobronchitis. Patients were randomized to receive aerosolized antibiotic or saline for 14 days or until extubation. The patients received aerosolized gentamicin (80 mg in 2 ml normal saline, every 8 h) for Gram-negative bacteria and aerosolized vancomycin (120 mg in 2 ml normal saline, every 8 h) for Gram-positive cocci. The administration of aerosolized antibiotics decreased VAP, facilitated weaning, and reduced bacterial resistance and the use of systemic antibiotics [13]. In addition, *Ghannam* et al. administered inhaled aminoglycosides in critically ill cancer patients with VAP due to Gram-negative bacteria. The patients tolerated inhaled aminoglycosides without any serious toxicity. Patients treated with inhaled antibiotics were more likely to have complete resolution of the clinical infection (81% vs 31% in the iv antibiotic group) and microbiologic eradication (77% vs 8% in the iv antibiotic group) [14].

Polymyxins

Polymyxins, a group of polypeptide antibiotics that consists of five chemically different compounds (polymyxins A–E), were discovered in 1947 [15]. Only polymyxin B and polymyxin E (colistin) have been used in clinical practice.

Polymyxin E (Colistin)

Colistin, a cationic cyclic decapeptide linked to a fatty acid through an α-amide linkage (Figure 1a) [16], has a molecular weight of 1,750 Da. The amino acid components in the colistin molecule are D-leucine, L-threonine, and L-α-γ-diaminobutyric acid. The latter is linked to the fatty acid residue, which has been identified as 6-methyl-octan-oic acid (colistin A) or 6-methyl-eptanoic acid (colistin B) [15]. Colistin is a multi-component antibiotic comprising a mixture of at least 13 decapeptides. Polymyxin E1 is the main component of colistin and it is used for the quantification.

Two forms of colistin are commercially available, colistin sulfate and colistimethate sodium (also called colistin sulphomethate or methanesulfate, pentasodium colistimethanesulfate, and colistin sulfonyl methate). While both formulations of colistin have been used for aerosol treatment, colistimethate sodium is less potent and less toxic than colistin methate [15] and is associated with fewer adverse effects, such as bronchospasm, chest tightness, throat irritation, and cough. Colistin sulphomethate is the drug of choice for aerosolized administration of colistin and can be prescribed by nebulization. However, it should be noted that any consideration of the relative merits of colistimethate sodium vs colistin (unmodified) is greatly complicated by the fact that colistimethate sodium actually appears to be inactive and that all of its activity relates to its *in vivo* conversion to colistin. Unfortunately, the vast majority of publications use bioanalytic systems that are unable to distinguish the two forms; indeed, it may not be possible to extract blood without at least partial *ex vivo* conversion. The chemical structure of colistimethate sodium is shown in figure 1B [17]. It is produced by a sulfomethylation reaction of colistin in which the primary amine groups of L-α-γ-diaminobutyric acid are reached with formaldehyde followed by sodium bisulfate [18–20]. The term "colistin" in this article refers to colistimethate sodium.

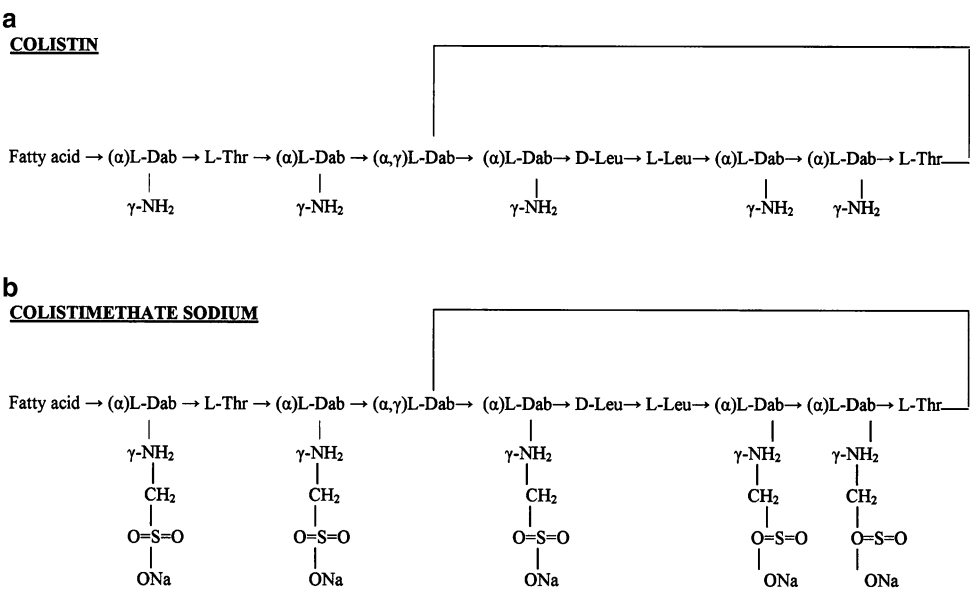

Figure 1. a. Colistin. b. Colistimethate sodium

The antimicrobial activity of colistin is targeted to the bacterial cell membrane. Interaction between the drug and the anionic lipopolysaccharide (LPS) molecules of the outer membrane of Gram-negative bacteria leads to derangement of the cell membrane, resulting in increased permeability of the cell envelope, leakage of cell contents and, ultimately, cell death [21]. Colistin has bactericidal activity against most Gram-negative aerobic bacilli, such as *Acinetobacter* species, *Ps. aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Escherichia coli*, *Haemophilus influenzae*, *Citrobacter* species, *Salmonella* species, *Morganella morganii*, *Shigella* species, and *Yersinia pseudotuberculosis* [19, 22]. It has also notable activity against *Stenotrophomonas maltophilia*, with 83–88% of the isolated strains being susceptible to colistin [23].

The recommended dose of colistin when given by inhalation is 40 mg (500,000 IU) every 12 h for patients with a body weight < 40 kg, and 80 mg (1,000,000 IU) every 12 h for patients who weigh > 40 kg [24]. For recurrent or severe pulmonary infections, the dose can be doubled to 160 mg (2,000,000 IU) administered every 8 h. The recommended dose for spontaneously breathing patients is 80 mg (1,000,000 IU). The colistin is added to 4 ml of normal saline or sterile water, and the solution is nebulized with 8 l/min oxygen flow and inhaled via a face mask [15]. Nevertheless, the exact optimal dosing remains unclear, as the precise pharmacokinetics and pharmacodynamics of the drug have not yet been clarified. Colistin is not approved by the FDA (Food and Drug Administration) to be inhaled via a nebulizer.

Despite the lack of data on the efficacy and safety of inhaled colistin from randomized controlled clinical trials, inhaled colistin has been recommended as a therapeutic option, supplementary to conventional iv antibiotics, for the treatment of multidrug-resistant (MDR) Gram-negative nosocomial and VAP. Most of the clinical experience that has been published on the use of colistin for the treatment of pneumonia has involved parenteral administration. Only limited data exist on the use of colistin by nebulization. In 1963, *Pino* et al. used aerosolized colistin in patients with pulmonary suppurations [25].

In a later study, 14 patients with CF received inhaled colistin plus oral ciprofloxacin for 3 weeks to prevent *Ps. aeruginosa* colonization and infection. Twelve patients who did not receive anti-pseudomonal chemotherapy during the same period served as controls. During the 27-month period of the trial, infection with *Ps. aeruginosa* became chronic in 2/14 (14%) patients of the first group vs 7/12 (58%) control patients. Fewer *Ps. aeruginosa* strains were isolated in routine sputum cultures from 49/214 (23%) of patients receiving chemotherapy vs 64/158 (41%) of controls [26].

During the last 15 years, nebulized colistin has been administered for the eradication of pathogens from the respiratory tract in CF patients in combination with ciprofloxacin administered orally for at least 3 weeks or, even better, for 3 months or by means of inhaled tobramycin as monotherapy for 4 weeks or longer. The therapeutic results of this preventive strategy have been successful [27].

The most recent data in critically ill patients receiving colistin by nebulization for the management of VAP due to MDR Gram-negative bacteria show beneficial results. *Michalopoulos* et al. conducted a study in eight patients who received aerosolized colistin concomitant to iv colistin or other antibiotics. Seven patients responded to treatment, four were cured, and three improved and moved from the intensive care unit to the ward [28]. *Kwa* et al. studied 21 patients with MDR *Ps. aeruginosa* and *Acinetobacter baumannii* pneumonia who were treated with aerosolized colistin. The clinical and microbiological response rates were 57.1% and 85.7%, respectively [29]. A study carried out in 2005 examined the efficacy of colistin (71 courses of nebulized colistin, 12 courses of iv or intramuscular, and two courses of intrathecal colistin) in 80 patients infected by MDR *Ps. aeruginosa* and *Acinetobacter baumannii*. The causative organisms were cleared in 92% of the patients from whom post-treatment repeat specimens were obtained [30].

In another study, *Michalopoulos* et al. administered aerosolized colistin to 60 critically ill patients with a mean APACHE II score of 16.7 for the treatment of VAP due to MDR pathogens (*Acinetobacter baumannii* [37/60 cases], *Ps. aeruginosa* [12/60 cases], and *Klebsiella pneumoniae* strains [11/60 cases]). Half of the isolated pathogens were susceptible only to colistin. The mean (± SD) daily dosage of aerosolized colistin was 2.2 (± 0.7) million international units (IU). All patients received 2,946 inhalations of colistin, and the mean duration of administration was 16.4 days. 57 patients received concomitant iv treatment with colistin or other antimicrobial agents. The bacteriological and clinical response of VAP was observed in 50/60 (83.3%) patients, and no adverse effects related to inhaled colistin were recorded. All-cause hospital mortality was 25%, while mortality attributable to VAP was 16.7%. Aerosolized colistin may be considered as adjunctive to iv antimicrobial treatment in critically ill patients with VAP due to MDR Gram-negative bacteria susceptible to colistin [31].

In conclusion, although only small numbers of patients have been studied in uncontrolled studies, aerosolized colistin appears to be effective for the treatment of respiratory tract infections. High drug concentrations are usually achieved in sputum and bronchial secretions, and these are maintained for 8–12 h in the majority of patients. Systemic colistin concentrations are low [32]. Colistin is generally well tolerated, with a good activity against a wide range of nosocomial pathogens. Its role in the treatment of MDR Gram-negative pneumonia needs further evaluation.

Polymyxin B

Marschke and *Sarauw* reported two cases of pneumonia due to *Ps. aeruginosa* in patients with underlying bron-

chiectasis in which polymyxin B was prescribed by inhalation [33]. In a study carried out much later, *Pereira* et al. administered inhaled polymyxin B at the dose of 500,000 IU twice a day following the administration of an aerosolized beta (2)-agonist to 19 patients with pneumonia or tracheobronchitis due to MDR Gram-negative bacteria, mainly *Ps. aeruginosa* and *Klebsiella pneumoniae*. There was a 53% cure rate, and 42% of the patients showed improvement [34].

Aztreonam

Aztreonam lysinate is another antibiotic that has been investigated for inhaled administration in a double blind placebo controlled trial that tested for pharmacokinetics and tolerability in patients with CF. The drug is a novel monobactam formulation with anti-pseudomonal activity. The antibiotic concentrations in sputum were above MIC_{50} for at least 4 h post-dose. Systemic exposure was low. These data support the continued development of aztreonam inhalation for the treatment of *Ps. aeruginosa* pulmonary infections in CF patients [35].

Inhaled Amphotericin

Aerosolized amphotericin B as both deoxycholate and lipid formulations has been administered in high-risk patients for prophylaxis and treatment of fungal infections. In a recent randomized, placebo-controlled, study it has been shown that the prophylactic inhalation of liposomal amphotericin B significantly reduced the incidence of invasive pulmonary aspergillosis in high-risk patients with hematologic disease and expected chemotherapy-induced prolonged neutropenia. A total of 271 patients were studied during 407 neutropenic episodes. Coughing was the most frequently reported adverse effects [36]. It has been showed that nebulized amphotericin B administered as prophylaxis against *Aspergillus* infection in lung-transplant recipients resulted in high concentrations in BAL and bronchial secretions, with distribution of the drug being uniform in patients without bronchiolitis obliterans [37].

However, the available data remain inconclusive regarding the clinical efficacy of this therapeutic approach, mainly due to lack of standardization of administration methods and doses. In high-risk patients, prophylactic inhalation of liposomal amphotericin B significantly reduced the incidence of invasive pulmonary aspergillosis. Owing to uncertain clinical benefit and concern for pulmonary toxicities, the use of aerosolized amphotericin B should be limited to clinical investigations at this time [38].

Inhaled Pentamidin

Pneumocystis carinii pneumonia remains the leading AIDS illness and the leading cause of death due to an AIDS-related complication. In patients not receiving antiretroviral therapy, the annual risk of acquiring PCP without prophylaxis is 60–70% in patients with prior PCP and 40–50% in those with a CD4 cell count > 100 cell/μl. Prophylaxis reduces the mortality rate due to PCP among patients with AIDS. Aerosolized pentamidine is an alternative prophylactic treatment in those patients. It has the advantages of minor side effects and results in a decreased incidence of PCP at 1 year compared to placebo (9% vs 27%) [39]. Aerosolized pentamidine is less effective in patients with a CD4 count < 100 cell/μl [40].

Marras et al. administered aerosolized pentamidine prophylaxis for PCP in patients undergoing allogeneic marrow transplantation and reported that it is an effective and well-tolerated second-line agent in preventing PCP post-transplantation. However, they suggest that it should be administered using a well-studied protocol – and only when trimethoprim/sulfamethoxazole (TMP-SMX) is not tolerated [41].

The recommended dose of aerosolized pentamidine is 300 mg monthly via a Respirgard II nebulizer at 6-ml diluents delivered at 6 l/min until the reservoir is dry (usually about 45 min). Frequent treatments, every 15 days, are tried in patients with recurrent episodes of PCP. Aerosolized pentamidine is only locally effective, and the upper lobes of the lungs appear to be more difficult to protect with aerosolized pentamidine. The major side effect of aerosolized pentamidine is bronchoconstriction and cough, but these can be controlled with the use of β_2-agonists prior to treatment. Another side effect is the risk of pneumothorax development [42]. Also of great concern is the transmission of tuberculosis (TB) to healthcare workers and other patients through a pentamidine-induced cough, which is why screening for active TB should be performed in patients at risk who would normally receive aerosolized pentamidine [43]. Many authorities recommend that even with negative screens for active TB, aerosolized treatments in HIV-infected patients should be performed in negative pressure containment rooms.

Advantages of Inhaled Anti-infective Agents

The major advantages regarding the inhaled administration of antibiotics, is the reduction of adverse effects associated with the systemic administration of the drugs and the ability to achieve high drug concentrations to the site of infection. For example, inhaled administration of antibiotics in patients with CF requires delivery of the agents to the lung airway to concentrations sufficient to overcome the physical and chemical barriers of the lung. Mucus plugs and destruction of lung parenchyma in the CF patients are added to biological barriers of the lung, resulting in reduction of the antibiotics to the site of infection [44]. This is a main problem in oral or intravenous drug administration because high concentrations are needed to reach the lumen [45].

Side Effects of Inhaled Anti-infective Agents

Hoarseness (for example, by inhaled tobramycin), bacterial transmission (due to contaminated devices), and

bronchial hyperactivity (due to a specific drug formulation, e.g., piperacillin solution) are topical side effects of inhaled antibiotic administration [45]. Aerosol osmolarity, composition of the aerosol, and the pH of the solution can cause side effects to the airway (mucosal irritation). Changes in drug formulations and aerosol generators result in a different exposure to the drug and are likely to have rare adverse effects in the airways that may not yet have been observed. For this reason, there is a need for large clinical studies. It should be noted that some aerosolized solutions have high osmolality and/or pH levels, implying that it is reasonable to expect a greater risk of bronchospasm.

The side effects of nebulized colistin include bronchoconstriction (caused by histamine release), cough, chest tightness, and apnea (due to neuromuscular blockade) [28]. Treatment with β_2-agonists before the inhalation of colistin would prevent bronchoconstriction and cough. In general, aerosolized colistin is well tolerated in the majority of patients as demonstrated by a lack of change in the FEV_1 performed before and after the inhalation. Renal toxicity and neurotoxicity appear to be minimal with inhaled colistin. Another significant concern regarding the use of aerosolized colistin is the dissemination of MDR bacteria through nebulized devices, which can be eliminated by the appropriate use of infection control guidelines by medical and nursing staff [46, 47].

Nevertheless, inhaled antibiotics can be used in much higher concentrations than oral and parenteral administration. At tenfold the tobramycin MIC, inhaled tobramycin inhibits the growth of *Ps. aeruginosa*, and at 25-fold, it has a bactericidal effect. Consequently, more effective concentrations can be achieved by inhaled antibiotics, thereby preventing disease progression without substantial systemic side effects (renal toxicity, ototoxicity, or vestibular toxicity) [48].

Practical Considerations

Practical aspects that should be considered in any evaluation of inhaled antibiotics include device-related factors and biochemical factors. The former include the type of devices (nebulizers, dry powder inhalers, metered-dose inhalers), size of droplets, drug output rate, and distribution of the medication to the lungs [49]. The device has to be appropriate for the drug solution being used in order to ensure maximum clinical response. Different nebulizers can substantially alter the drug concentration in the sputum [6, 50]. Devices that produce particles with an aerodynamic diameter of 3–4 mm deposit the drug into the lower airways, resulting in the maximum therapeutic effect and minimum toxicity. In hospitalized patients, antibiotics are usually aerosolized by nebulizing a solution of the drug, either by use of an air jet or by ultrasonic sound waves. There are two main devices for delivering the drug by aerosol: metered-dose inhalers (wet aerosol) and dry powder inhalers [51, 52]. The main distinction between dry powders and wet aerosols is that in the dry powder inhalers the particle size distribution is manufactured in the formulation rather than created by the device. It has been reported that tobramycin inhalation powder has a more efficient and rapid delivery than the TOBI with similar pharmacokinetic and pharmacodynamic characteristics [51]. *Labiris* et al. also reported the superiority of dry powder nebulizers over small-volume nebulizers, with the former resulting in a significant lowering of gentamicin dosage [53]. However, the position of dry powder inhalation of antibiotics is still in the pilot study stage [49]. Conventional jet nebulizers are the mainstay of inhalation therapy, although a more efficient and a more patient-friendly new generation of wet aerosol devices are being developed (e.g., e-flow electronic nebulizer for aztreonam administration).

Pharmacokinetic and Pharmacodynamics Characteristics

Biochemical factors having practical significance for an inhaled antibiotic include the microbial spectrum, pharmacokinetics, and pharmacodynamics. The pharmacokinetics of the inhaled antibiotic includes the stability of the drug in the aerosol, the rate of deposition, bioavailability, metabolism, and elimination of the aerosolized antibiotic [54]. Bioavailability is the amount of the drug available for action at the site of infection. It is generally accepted that inhaled therapies are safer than systemic administration because the inhaled antibiotics are bio-available in the lumen. Drug deposition is much higher by inhaled administration than by systemic formulation, although the amount of drug that is deposited in the lungs is less than that loaded in the device. Distribution (localization) of the inhaled drug is dependent on the size of the particles, the ability of the patient to inhale the aerosol, and the degree of bronchi obstruction [45]. The deposit of the aerosolized drug in the airway is determined by two mechanisms: impaction for the larger articles (> 8 μm) and sedimentation for the particles 1–5 μm in diameter. The larger particles stay in the upper airway and the smaller one, due to gravity, reach the bronchioles and the alveoli [55].

The pharmacodynamics of a drug refers to the relation between the concentration of the drug and its biochemical and physiologic effects (peak amount of the antibiotic at the infection site). The killing ability of an antibiotic is concentration-dependant or time-dependant. An antibiotic that exhibits concentration-dependant killing is optimal for inhaled formulation because it can be administered intermittently to the site of the infection at high concentrations, thereby achieving the maximum effect [56]. Another main pharmacodynamic consideration after exposure of the bacteria to the antibiotic is the development of acquired resistance. However, in a study with inhaled tobramycin, the pattern of resistance after repeated antibiotic courses was not investigated [57].

Conclusions

In conclusion, the role of aerosolized antibiotics, which achieve high drug concentrations in the target organ, seems to be clear for the eradication of *Ps. aeruginosa* and for the treatment of Gram-negative respiratory infections in patients with CF or bronchiectasis. In addition, inhaled antibiotics could play a beneficial role in the management of nosocomial acquired pneumonia, mainly VAP due to MDR Gram-negative bacteria. Inhaled pentamidine has been administered for PCP prophylaxis post transplantation, and amphotericin has been used as prophylaxis against *Aspergillus* infection in lung-transplant recipients or patients with hematologic disease and expected chemotherapy-induced prolonged neutropenia. However, to date, limited evidence is available showing a clear benefit from the administration of antimicrobial agents via the respiratory tract for the treatment of nosocomial pneumonia or VAP [58]. In addition, there is limited data on the doses of anti-infective agents for inhaled administration. With the exception of TOBI, the majority of the available anti-infective agents have not yet been approved for inhaled administration and, consequently, they are used largely ''off-label''. At the present time, very few, if any, of the effects of inhaled antibiotics have been demonstrated and confirmed in two, independent, adequately sized, and controlled trials, and such data from these trials are the standard criteria for ''evidence'' in clinical medicine.

Conflict of interest statement. None.

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