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THERAPY IN PRACTICE

Inhaled Antimicrobials for Ventilator-Associated Pneumonia: Practical Aspects

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Abstract Positive experience with inhaled antibiotics in pulmonary infections of patients with cystic fibrosis has paved the way for their utilization in mechanically ventilated, critically ill patients with lower respiratory tract infections. A successful antibiotic delivery depends upon the size of the generated particle and the elimination of drug impaction in the large airways and the ventilator circuit. Generated droplet size is mainly affected by the type of the nebulizer employed. Currently, jet, ultrasonic, and vibrating mesh nebulizers are marketed; the latter can deliver optimal antibiotic particle size. Promising novel drug-device combinations are able to release drug concentrations of 25- to 300-fold the minimum inhibitory concentration of the targeted pathogens into the pulmonary alveoli. The most important practical steps of nebulization include pre-assessment and preparation of the patient (suctioning, sedation, possible bronchodilation, adjustment of necessary ventilator settings); adherence to the procedure (drug preparation, avoidance of unnecessary tubing connections, interruption of heated humidification, removal of heat-moisture exchanger); inspection of the procedure (check for residual in drug chamber, change of expiratory filter, return sedation, and ventilator settings to previous status); and surveillance of the patient for adverse events (close monitoring of the patient and particularly of peak airway pressure and bronchoconstriction). Practical aspects of nebulization are very important to ensure optimal drug delivery and safe procedure for the patient. Therefore, the development of an operational checklist is a priority for every department adopting this modality.

Key Points

Delivery of inhaled antibiotics in mechanically ventilated patients is a modality with increasing interest and utilization among intensivists, without well-recognized standard procedures.

The type of nebulizer used is the major determinant of all practical issues.

The most important practical steps of nebulization include pre-assessment and preparation of the patient; adherence to the procedure (drug preparation, ventilator settings, and circuit adjustments); and monitoring of the procedure for completeness and safety.

1 Introduction

Inhaled antibiotics were introduced in the treatment of acute and chronic bacterial infections of the airways in the 1940s, with the first attempts of aerosolized neomycin, polymyxin, and penicillin G [1, 2]. However, they failed to gain acceptance owing to reports of superinfections with

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resistant strains to polymyxin B in 1975, probably attributable to inadequate delivery systems [3, 4]. In the late 1990s, the interest for inhaled antibiotics and particularly tobramycin in the management of patients with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* colonization was rekindled [5]. Experience in this particular group of patients was followed by an impressive evolution of drug-delivery devices [6]. Recently, the emergence of the ESKAPE group of multidrug-resistant (MDR) pathogens (*Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa*, and *Enterobacter* spp.) has significantly challenged the treatment of patients in intensive care units with ventilator-associated pneumonia (VAP) and other respiratory infections [7, 8].

As a consequence, similar epidemiological features with patients with CF have prompted the use of inhaled antibiotics in mechanically ventilated (MV) patients, despite scarce clinical evidence [9]. Nebulized antibiotics have been administered in a wide array of indications in MV patients, mainly in the treatment of VAP and ventilator-associated tracheobronchitis [10, 11]. The clinical benefit is yet to be evaluated because studies are mostly observational and heterogeneous, employing either an intravenous (i.v.) plus inhaled form of the same antibiotic, or an inhaled approach adjunctive to other i.v. antibiotics, and even an inhaled-only approach [12–14]. Two recent surveys have explored the real-life use of inhaled antibiotics by intensive care physicians [11, 15, 16]. No standardized technique, dosage, and delivery system was employed, and indications and antibiotics used were variable. Both surveys elucidated prescribers' uncertainty about practical aspects of nebulization and the need for the development of guidance on the use of inhaled antibiotics for MV patients. The aim of this review is to summarize published evidence relating to the practical aspects of nebulization and help to optimize the use of this new modality of antibiotic delivery in MV patients. Assessment of the clinical efficacy of inhaled antibiotics in MV patients is beyond the scope of the article and is detailed in other recent reviews [10, 17, 18] and systematic reviews [12–14]. The term 'inhaled antibiotics' was adopted in this article to describe using antibiotics via a nebulizer; statements made should not be extrapolated to other types of delivery devices or to inhaled antibiotics in general.

2 Rationale and Description of the Technique

The bronchial mucosa, epithelial lining fluid (i.e., interstitial/extracellular space), and alveolar macrophages (i.e., intracellular space) offer interfaces to evaluate drug disposition into the various compartments of the lung. The lung is a difficult organ; many systemically administered antibiotics achieve lower concentrations at the target site for conventional extracellular pathogens (i.e., interstitial space) compared with the blood concentrations [19]. This may be attributed to their inability to cross the alveolar-capillary barrier (vancomycin, colistin, aminoglycosides), or achieve predictable concentrations in inflamed and consolidated lung areas [17, 19, 20]. Furthermore, in MV patients, altered antibiotic pharmacokinetics has been recently recognized as an important factor compromising optimal drug penetration [21, 22].

Moreover, the inability to achieve concentrations above the minimum inhibitory concentration (MIC) of the targeted pathogen predisposes to an increased probability of clinical failure; overcoming mutant prevention concentration might prove to be even more challenging [23–25]. In addition to this, the presence of the endotracheal tube, being responsible for biofilm formation, makes eradication of bacteria extremely difficult [26]. The ESKAPE pathogens, usually exhibiting a MDR or even pan-drug-resistant profile, impose an additional challenge in the treatment of respiratory infections in MV patients. Importantly, as MDR and pan-drug resistant pathogens have been associated with worse clinical outcomes compared with susceptible counterparts, epidemiological data underline the need for early appropriate treatment to ensure reduction in mortality [7, 27, 28].

In this epidemiologic milieu, porcine experimental studies have demonstrated that inhaled antibiotics achieved 30- to 200-fold higher lung tissue antibiotic concentrations and higher bactericidal activity when compared with similar amounts of intravenously administered antibiotics [6]. Other experimental studies showed that aminoglycosides, despite poor penetration in the lung parenchyma after i.v. administration, when given in an inhaled form, diffuse in the systemic circulation through inflamed lung tissues but maintain non-toxic serum levels even when administered in high doses [29–34]. In contrast, colistin is almost undetectable in lung tissues after i.v. administration and poorly absorbed in the systemic circulation when given by inhalation, even in the presence of lung inflammation [35].

Based on the above-mentioned challenges, increased interest in the use of inhaled antibiotics in MV patients is an attempt to: (1) overcome the generally reduced penetration of antimicrobials into the interstitial space of the lung; (2) treat pulmonary infections by pathogens resistant according to the established breakpoints based on serum pharmacokinetics; (3) prevent the emergence of resistant pathogens; (4) avoid systemic toxicity caused by i.v. administration of boosted doses; and ultimately (5) impact positively on patients' outcomes [10, 17].

An efficient delivery of antibiotics in the lung parenchyma requires an optimal aerosol generator (the

nebulizer), a carefully selected and properly prepared antibiotic solution, and finally a wisely selected patient, who has to be properly prepared along with all the ventilator and circuit adjustments [10]. Efficacy of the procedure depends largely on the size of the generated aerosol particle, the synchronization of the patient with the nebulizer, and the avoidance of turbulences and extra-pulmonary drug losses [33]. Supervision of the whole procedure is important for an uncomplicated and successful performance to ensure optimal and safe antibiotic nebulization in MV patients.

3 Selection of Nebulizer, Adjustment of Ventilator Settings, and Management of Circuit Parameters

One of the most important aspects of antibiotic nebulization in MV patients is the selection of the aerosol generator. Optimal drug concentration at the site of infection is clearly associated with aerosol particles of 1–5 μm in diameter (measured as mass median aerodynamic diameter or volumetric median diameter). This is the particle size that ensures maximal antibiotic delivery in the alveoli, satisfactory delivery in the distal bronchi, and minimal extra-pulmonary drug loss in the trachea and the ventilator circuit [6, 36–38]. The deposition of the drug is influenced also by the humidity in the ventilator circuit that may increase droplet size in the endotracheal tube and the presence of rough inner surfaces or sharp angles promoting droplet impaction in the circuit [39, 40].

3.1 Types of Generators

As a general principle, nebulizers are connected to the ventilator's circuit and deliver a specific fraction of the drug that was inserted in their drug chamber (nominal drug dose), following aerosolization of the drug solution. Drug losses ensue in the chamber and in the ventilator's circuit, whereas fractions of the delivered dose (the actual dose that escapes the device) is retained in the trachea and the bronchi or exhaled. Finally, only a fraction of the nominal drug dose reaches the pulmonary tissue, which represents the net capacity of the drug delivery of the device [6, 18, 41]. Currently, the available devices for inhalation of antibiotics include jet, ultrasonic, and vibrating mesh nebulizers (Table 1).

Jet nebulizers are the most commonly used because of their easiness in use, low cost, and single-use convenience without the need of disinfection between patients [6, 36–39]. They can operate with an external gas source or as ventilator-integrated systems. As external gas source may interfere with the ventilator's gas flow causing drug turbulences, ventilator-integrated systems are preferred [6, 36]. The generated aerosol particle size is suboptimal and non-homogenous, resulting in a net capacity of drug delivery approximately 15% of the nominal drug dose [39, 40, 42].

Ultrasonic nebulizers, using a piezo-electric vibrating source, produce variable droplet sizes depending on the amplitude and frequency of the vibration. Heat generated in the drug chamber during the procedure may have unpredictable effects on its physicochemical and pharmacological properties [43]. Furthermore, ultrasonic nebulizers are characterized by a high acquisition cost and a large bedside size, large residual drug volume, inability to aerosolize viscous solutions, and the need of disinfection between patients because they are multiple-use devices [6, 36, 44]. They have a rapid delivery capacity reaching 30–40% of the nominal drug dose. As with jet nebulizers, non-homogeneous droplet size explains drug losses, with medium-sized particles (>3 μm) being deposited in the tracheal tree and proximal bronchi and larger particles (>5 μm) being impacted in the ventilator circuit or the endotracheal tube, particularly in the presence of humidification and sharp angles [39, 45].

Currently, vibrating mesh nebulizers provide the best-available nebulization performance because they produce homogenous and optimal-size drug particles, thus ensuring rapid and maximal deposition in the alveoli [6, 10, 37]. Novel vibrating mesh nebulizers are single use, not requiring disinfection between patients. However, cleaning of the device from congregating particles around the vibrating element's apertures may prove copious. Probably, with a drug-delivery capacity in the range of 40–60% of the drug's nominal dose, the only disadvantage of vibrating mesh nebulizers remains the high acquisition cost [6, 37, 46, 47].

The evolution of vibrating mesh nebulizers, in the form of drug-device combinations such as the 'pulmonary drug-delivery system' (PDDS NKTR-061 BAYER® Inhale Program) and the 'eFlow Rapid Nebuliser System®' (PARI GmbH, Starnberg, Germany) is of great interest. NKTR-061 is a disposable device designed to integrate a new formulation of Amikacin Inhalation Solution (BAY41-6551 Inhale Program) into the lungs [48]. The PDDS senses the patient's breaths and synchronizes nebulization without interfering with humidification. It is characterized by antibiotic delivery reaching 60% of the nominal drug dose and minimal lung irritation and risk of bronchospasm, and the possibility to be used after extubation as a hand-held configuration [6, 10, 44, 47, 49] (Fig. 1).

The PARI system is a single-patient multiple-use device developed to deliver a combination of fosfomycin and amikacin (five to two ratio). PARI is placed in the inspiratory arm of the circuit while a stainless steel vibrating

Table 1 Types of nebulizers for aerosolization of antibiotics in mechanically ventilated patients

Device	Mode of function	Settings	Advantages	Disadvantages
Jet nebulizers	High-pressure air or oxygen/air-blast atomization is delivered into the circuit with the antibiotic directly connected to an external gas source or ventilator-integrated system	Usually placed in the inspiratory limb Operates continuously when connected to an external gas source or intermittently when connected to a ventilator-integrated system Heat humidification should be removed before use Expiratory filter should be changed after each nebulization	Low cost Small dimension Disposable Breath synchronized	Delivery of antibiotic varies depending on the gas source and does not exceed 15% of the initial dose Great variability of droplet size Potential increase of tidal volume owing to external gas flow, which may require changes in ventilator's settings Long duration of nebulization
Ultrasonic nebulizers	Aerosol is generated through high-frequency vibration by a piezoelectric quartz crystal underneath the reservoir Size of the particle is inversely proportional to the vibration's frequency	Placed 10–15 cm from the Y-piece in the inspiratory limb It operates continuously Advisable practices Heat humidification should be removed before use Expiratory filter should be changed after each nebulization	Delivery of antibiotic varies from 30 to 40% of the initial dose No interference with the flow delivered by the ventilator Rapid drug delivery Ease of use	Variability of droplet size Heat production in the antibiotic chamber High cost Non-disposable Large dimension
Vibrating mesh nebulizers	Ceramic vibrational element placed above a tapered holes plate exerts a pump-like rapid movement to the antibiotic in the chamber creating the aerosol whose aerosol particle size depends on the diameter of the holes	Placed 10–15 cm from the Y-piece in the inspiratory limb Operates continuously Advisable practices Heat humidification should be removed before use; expiratory filter should be changed after each nebulization	Delivery of antibiotic varies from 40 to 60% of the initial dose No variability of droplet size No temperature increase of the delivered drug Ventilator synchronized Low residual drug volume Ease of use Small dimension Disposable Rapid drug delivery: 7–10 min with 3 mL of albuterol (Aeroneb®)	High cost Inadequate nebulization of solution with increased viscosity Variable delivery time according to the administered antibiotic
PARI EFlow®	Drug-device combination delivered through perforated oscillating membrane Vibrating mesh principles	Placed in the inspiratory limb Heat humidification does not need to be removed before use	Delivery of antibiotic varies from 31 to 44% of the initial dose Breath enhanced Multiple-use, single-patient device	Variable delivery time according to the administered antibiotic May only be used for the administration of the amikacin/fosfomycin combination, which is stored separately and mixed in the chamber Unknown cost Results of RCT showing the combination to be ineffective in improving clinical outcomes

Table 1 continued

Device	Mode of function	Settings	Advantages	Disadvantages
Bayer Amikacin Inhale	Pulmonary drug delivery system Vibrating mesh principles	Placed before the Y-piece proximal to the patient Heat humidification and moisture exchanger device should be removed before use	Delivery of antibiotic varies from 35 to 58% of the initial dose on-vent and from 35 to 64% hand-held Aerosolization of the antibiotic is synchronized with the first 3/4 of the inspiratory flow Breath synchronized when on-vent and continuously when hand-held Delivered dose of amikacin is not affected by humidification Treatment does not require the patient to be intubated No need for ventilator setting or dose adjustment	Variable delivery time according to patient and flow parameters varying from 45 to 60 min on ventilator or 10–20 min Hand-held, fixed drug-device combination Cost

RCT randomized controlled trial

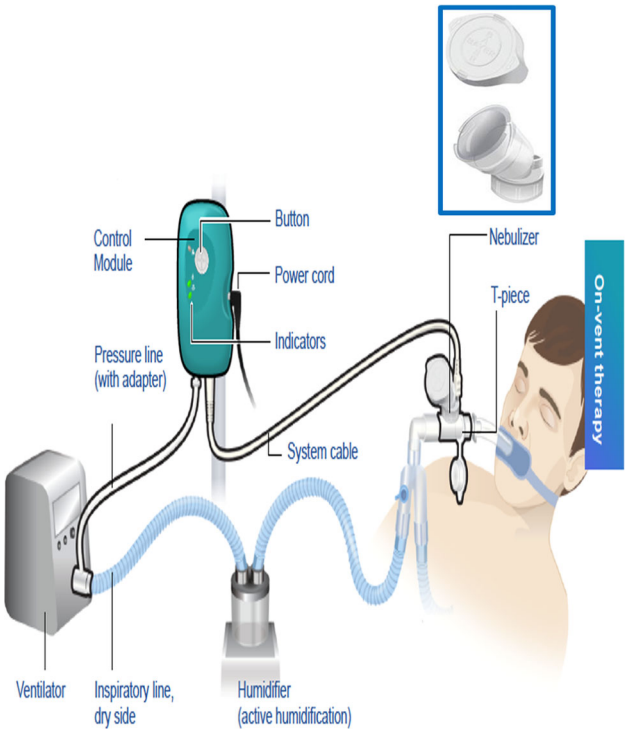

Fig. 1 Specially formulated Amikacin Inhalation Solution—Pulmonary Drug Delivery System. Figure reproduced with permission from Bayer™

ejector is placed at the same axis with the air flow and operates continuously [50]. Particle diameter increases from 2.8 to 3.2 mm, when exposed to circuit humidification; however, it remains adequately small for efficient delivery. Nebulization with the PARI releases efficiently approximately 90% of the charge dose; including drug solutions with high viscosity [51] (Fig. 2). PARI was used in a phase I trial including patients with VAP in whom a combination of amikacin hydrochloride with fosfomycin was administered, achieving an efficient pulmonary delivery in a short time frame of 12 min without any adverse events [52].

3.2 Connection of Nebulizer and Ventilator Settings

The principal purpose of connection and ventilator adjustments is to ensure perfect synchronization of the patient with the nebulizing device and the elimination of drug impaction in the tubing and large airways. A thorough review of the published literature has shown that the following settings have been associated with optimal drug deposition: volume-controlled mode, constant inspiratory flow, tidal volume of 8 mL/kg, and inspiratory to expiratory ratio $\leq$50%. In addition, the deposition of particles in the lung is facilitated by an end-inspiratory pause of 20% of the duty cycle [6, 31, 32, 42, 53]. Particular ventilator

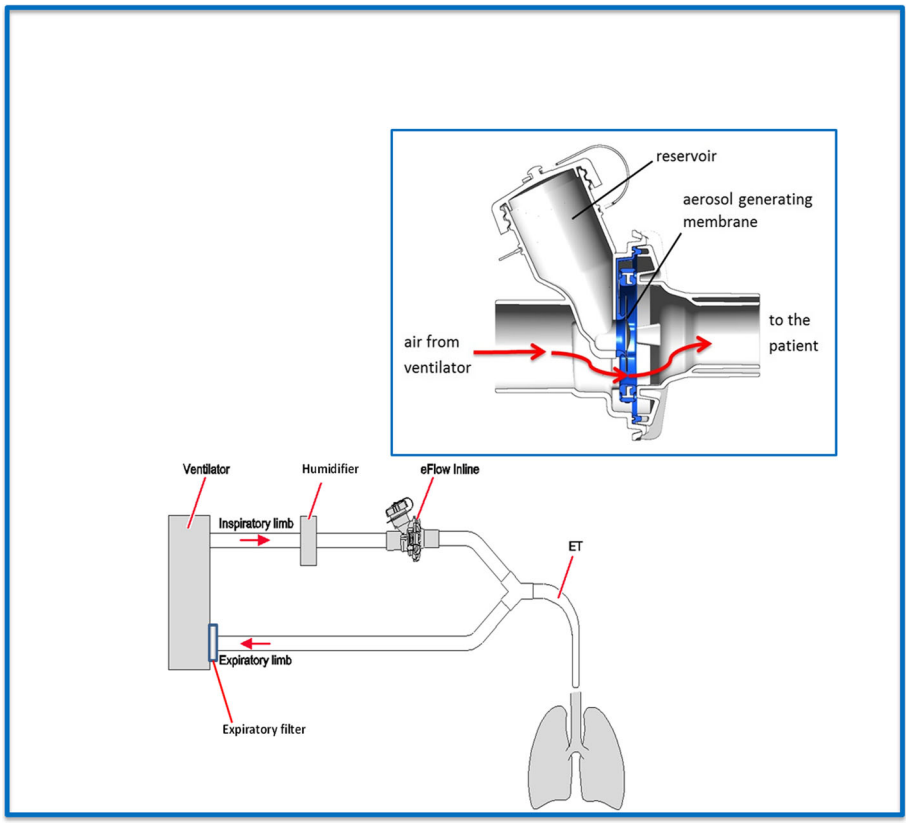

Fig. 2 eFlow inline nebuliser (PARI®). Figure reproduced with permission from Cardeas Pharma™. *ET* endotracheal tube

settings and connections for each type of nebulizer are presented in Table 1. An advancement with the new drug-delivery devices is the ability to maintain humidifiers during nebulization. However, the heat and moisture exchanger filter should be removed from the system during every nebulization because it affects hygroscopic features of the drug particles promoting extra-pulmonary droplet loss. It is important to mention that the expiratory bacterial/viral filter has to be changed after each nebulization irrespective of the device used. Occlusion of this filter by inevitable congregation of particles in the expiratory limb can be the cause of life-threatening complications [47].

4 Drug and Dose Selection

The selection of the inhaled antimicrobial should encompass several properties and characteristics to achieve maximum effectiveness including (1) activity against the causative pathogen; (2) physical properties to ensure maximal pulmonary delivery and minimal extra-pulmonary loss; and (3) the achievement of adequate concentrations in the lung well above the pathogen's MIC, taking into account the need for the prevention of resistance and the presence of biofilm [10, 17].

Among multiple antimicrobials that have been used through nebulization, only colistin, tobramycin, and aztreonam possess formulations approved for aerosolized use and particularly in patients with CF [6, 10, 17]. The ideal inhaled antibiotic should be preservative free, non-hyperosmotic, and pyrogen free; possess a pH ranging from 4.0 to 8.0, an osmolarity ranging from 150 to 1200 mOsm/L, and contain at least 30 mEq of permeant anions [54]. The latter is important to prevent bronchospasm, cough, or occlusion of the expiratory filter, as in the case of ceftazidime [55]. In contrast to optimal properties for gastrointestinal absorption, moderately lipophilic and positively charged small molecules (such as tobramycin) are preferable for inhaled use [56, 57]. Viscosity should be taken into consideration as it may be incompatible with ultrasonic nebulizers and some first-generation vibrating mesh nebulizers [51]. Ideally, the volume of the diluted drug should not exceed the device's chamber capacity, to ensure a reasonable and convenient administration time. If this is not the case, multiple consecutive nebulizations will be required [6, 10]. The evolution of continuous nebulization systems could also assist with high-volume nebulizations.

The appropriate dosage of inhaled antibiotics remains a matter of controversy, and pharmacokinetic/pharmacodynamic properties differ greatly among antibiotics. The most well-studied antibiotics are colistin and aminoglycosides. Early studies of these antibiotics intended for i.v. use were performed with the formulation intended for i.v. use

administered in empirical doses via inhalation [35, 58–74]. As data from clinical trials accumulate, we will be able to gain further insight into the correct dose selection. Trials assessing various dosages of the aforementioned antibiotics are summarized in Table 2 [35, 58–74].

Colistin dosed at less than 2 million IU of colistimethate sodium using a vibrating mesh nebulizer achieved inadequate drug concentrations in the epithelial lining fluid [75]. In two recent studies, the administration of 4 million IU of inhaled colistin as monotherapy and 5 million IU every 8 days as monotherapy or in combination with intravenous aminoglycosides yielded similar results as compared to intravenous colistin and other conventional treatment, respectively, without increased nephrotoxicity [35, 58].

When administered systemically, aminoglycosides need to be administered in high doses to achieve concentrations well above the MIC owing to their reduced penetration into the interstitial space [76]. Although their efficacy in combination with other intravenous antibiotics is well known, studies assessing their administration via inhalation against MDR Gram-negative pathogens are lacking. The advent of a proprietary drug device for amikacin (PDDS) will facilitate dose selection to a standardized manner. PDDS achieved concentrations of amikacin over 6400 μg/mL in tracheal aspirates, which is equal to greater than 25 times the maximum MIC for amikacin, in half of the patients [63].

Fosfomycin is never administered as monotherapy because of the rapid emergence of resistance [77–79]. The relevant proprietary drug device combination (PARI eflow®) achieved high concentrations for amikacin and fosfomycin of $12{,}390 \pm 3986$ and 6174 ± 2548 μg/g, respectively [80–82]. Pharmacokinetic/pharmacodynamic data obtained with the novel drug-device combinations are heralding a new era in the microbiology of respiratory infections in MV patients. Based on the local antibiotic concentrations after nebulization and experience in CF, conventional in-vitro susceptibility testing may no longer predict the clinical efficacy of inhaled antibiotics, probably necessitating the implementation of "lung infection specific breakpoints" [83].

Inhaled ceftazidime and amikacin combined with intravenous antibiotics was not found to be superior to intravenous treatment in patients with VAP due to *P. aeruginosa* [68]. A trial assessing inhaled doripenem was interrupted in phase II as a result of pneumonitis and other allergic reactions [84]. Studies assessing inhaled vancomycin are very scarce. Two randomized placebo-controlled trials from a single center employing 120 mg of vancomycin delivered every 8 h through a vibrating mesh device, showed superior bacterial eradication and reduced acquired resistance in MV patients with ventilator-associated tracheobronchitis and VAP compared with the counterparts treated with conventional i.v. regimens [85, 86]. A considerable portion of patients were also receiving inhaled aminoglycosides based on a sputum Gram stain.

Finally, the integration of pharmacokinetic/pharmacodynamic data into daily practice may place inhaled antibiotics in the context of different therapeutic strategies. Although inhaled aminoglycosides cross inflamed lung tissues, they are not systemically accumulated [30, 87]. However, i.v. co-administration mandates the monitoring of serum levels to avoid systemic toxicity. Probably, the most suitable strategy for inhaled aminoglycosides is as adjunctive treatment to a different agent administered intravenously. However, colistin does not cross lung membranes either when administered intravenously, or when given as an inhaled form in an inflamed lung [6]. As an adjunctive treatment of i.v. administered colistin it will cause fewer considerations for incremental toxicity. However, with accumulating evidence, inhaled colistin may also represent a candidate for adjunctive treatment to another systemic antibiotic, avoiding systemic colistin administration. An absolute inhaled-only therapeutic approach (without systemically administered antibiotics) remains the ultimate challenge for inhaled antibiotics. Encouraging data have been reported only from single-center studies, although jeopardized by the well-recognized lack of a reliable definition for VAP; further large-scale randomized trials are needed [6, 35, 85, 86].

5 Patient Selection and Preparation

Optimal deposition of the drug requires perfect synchronization of the patient with the ventilator. Quite often, a patient on spontaneous breathing should step back to sedation, whereas a difficult-to-sedate patient may require to be almost paralyzed to achieve synchrony with the ventilator. This may prolong days on mechanical ventilation by delaying the weaning procedure [6, 10, 68]. Patient characteristics that may significantly impede efficient nebulization include severe bronchoconstriction, abundant viscous secretions, and spontaneous respiratory pattern or the presence of intrinsic positive end-expiratory pressure [6, 88]. Patients with asthma or acute respiratory distress syndrome (ARDS) may be less suitable for nebulization, owing to the difficulty in adjusting the necessary ventilator settings and tendency to develop complications with increased inspiratory time or tidal volume required for an efficacious nebulization [6, 37, 46, 89, 90]. In this clinical scenario, the decision to use nebulization should be made on an individual patient basis and carefully supervised [91].

Table 2 Drug dosage in studies administering inhaled antibiotics in patients with ventilator-associated pneumonia [35, 58–74]

Antibiotic tested by inhalation	Author, year (references)	No. of patients (test + control)	Pathogens	Drug dosage	Type of nebulizer
Polymyxins	Michalopoulos et al. [70]	8	AB, PA	Daily dose of colistin ranged from 1.5 to 6 million IU (divided into three or four doses), and the mean duration of administration was 10.5 days	NS
	Pereira et al. [72]	19	KP, PA, *Alcaligenes* spp., *Burkholderia* spp.	Polymyxin B 0.5 million IU q12 h after an aerosolized β_2-agonist	Conventional inhalator
	Michalopoulos et al. [69]	60	MDR AB, PA, KP	Mean (±SD) daily dosage of colistin was 2.2 (±0.7) million IU	By means of the ventilator
	Falagas et al. [60]	5	AB, PA, KP	Colistin 1 million IU q8 h or 0.5 million IU q6 h	NS
	Rattanaumpawan et al. [73]	100 (51 + 49)	AB, PA	Colistin 75 mg CBA in 4 mL of normal saline q12 h vs. normal saline	Jet or ultrasonic nebulizer
	Lin et al. [67]	45	AB	Mean daily dosage of colistin was 4.29 ± 0.82 million IU	NS
	Kofteridis et al. [63]	86 (43 + 43)	AB, PA, KP	Colistin 2 million IU divided into 2 doses	Vibrating mesh nebulizer
	Korbila et al. [65]	21(87 + 43)	AB, PA, KP	Average daily dosage of colistin was 2.1 ± 0.9 million IU	For ventilated patients by means of the ventilator
	Lu et al. [35]	165 (43 + 122)	PA, AB	Colistin 5 million IU q8 h either in monotherapy ($n = 28$) or combined with 3-day i.v. aminoglycosides	Vibrating plate nebulizer
	Kuo et al. [66]	39 + 39	AB	Colistin 2 million IU q12 h	T-bird AVS ventilator
	Kalin et al. [62]	45	AB	Colistin 150 mg CBA given in two divided doses in 4 mL of normal saline; the solution was nebulized with an oxygen flow of 8 L/min	Solution was nebulized with an oxygen flow of 8 L/min
	Zah Bogovic et al. [74]	31 (8 + 23)	AB, KP, PA	Colistin 4 million IU q12 h	NS
	Abdellatif et al. [58]	149 (73 + 76)	MDR AB, PA, KP	Colistin 4 million IU by nebulization three times per 24 h	Vibrating mesh nebulizer
Amikacin	Niederman et al. [71]	69 (21 + 26 + 22)	PA, *Escherichia coli*, KP, AB	Amikacin 400 mg q12 h or qd (plus standard systemic therapy)	Investigational drug-device through PDDS clinical device
Colistin and aminoglycosides	Ghannam et al. [61]	32 (16 + 16)	PA, KP	Tobramycin 300 mg q12 h, colistin 100 mg q8 h, gentamicin 100 mg q8 h, and amikacin 100 mg q8 h or 300 mg q12 h	Jet nebulizer
	Arnold et al. [59]	93 (19 + 74)	AB, PA	Colistin 150 mg q12 h, in 5 mL of normal saline, or tobramycin 300 mg in 5 mL of normal saline q12 h	Nebulizers generating droplet sizes 1–5 μm
Ceftazidime and amikacin	Lu et al. [68]	40 (20 + 20)	PA	Ceftazidime 15 mg/kg/3 h and amikacin 25 mg/kg/day	NS

Table 2 continued

Antibiotic tested by inhalation	Author, year (references)	No. of patients (test + control)	Pathogens	Drug dosage	Type of nebulizer
Amikacin/fosfomycin fixed combination	Kollef et al. [64]	143 (71 + 72)	Gram-negative bacteria	Amikacin 300 mg/fosfomycin 120 mg or placebo (saline) q12 h for 10 days (or to extubation if <10 days)	eFlow inline system

AB Acinetobacter baumannii, *AVS*, *CBA* colistin base activity, *i.v. intravenous, KP Klebsiella pneumoniae, MDR* multidrug resistant, *NS* not specified, *PA Pseudomonas aeruginosa, PDDS* pulmonary drug-delivery system device, *qd* once daily, *q6 h* every 6 h, *q8 h* every 8 h, *q12 h* every 12 h, *SD* standard deviation

Suctioning of secretions is an important step before initiating nebulization, otherwise, abundant secretions may entrap antibiotics, occlude the expiratory filter, or delay drug delivery. Interruption of the procedure for suctioning is not advisable [6, 10, 37, 46]. Severe hypoxia before nebulization may predispose to episodes of de-recruitment during nebulization, particularly in patients with a PaO_2/FiO_2 ratio <200 [68]. In severely hypoxic patients, prior recruitment maneuvers can be considered on an individual patient basis for exclusion from nebulization [53]. Premedication with β_2-agonists to avoid bronchoconstriction is generally adopted in some studies [61, 69, 82] without being evaluated in randomized controlled trials (RCTs). This practice is advisable however in patients with a history of pre-existing bronchial hyperreactivity [asthma or chronic obstructive pulmonary disease (COPD)] [91] and in those who developed bronchoconstriction with prior antibiotic nebulization and responded effectively to bronchodilators [75].

As mentioned above, the heat-moisture exchange filter should always be removed from the tubing, as it may segregate antibiotic during nebulization, whereas heated humidification should be set to 'off' mode, depending on the type of nebulizer. Circuit surfaces should be as smooth as possible to avoid turbulences and all unnecessary connections should be removed. A bacterial/viral filter in the expiratory limb is advisable, but should be replaced after antibiotic nebulization [6, 10, 47, 53].

A checklist would be extremely useful for every department, ensuring that all the necessary equipment is in place before onset of the procedure. Finally, the implicated personnel should be flexible to adjust procedures according to the manufacturer of the available devices and consumables. An example of a checklist for the pre-assessment of the patient and supervision throughout the procedure is presented in Fig. 3.

6 Procedure Monitoring and Safety

Adverse reactions may arise from the nebulization procedure and local or systemic actions of the administered drug.

6.1 Procedure-Related Adverse Events

An amount of droplet impaction is anticipated in the expiratory limb, entailing a risk of occlusion of the flow meter or the expiratory filter. In one study, three patients developed this complication, two of them being censored by increased peak airway pressure, whereas the third patient developed fatal cardiac arrest [68]. In a second study, a sudden expiratory valve malfunction was reported [92]. Therefore, potential blockage of the expiratory filter should be checked for during nebulization by monitoring the peak airway pressure. Replacement of the expiratory bacterial filter is advisable after each nebulization procedure [68]. Suctioning and connecting procedures before nebulization were associated with severe de-recruitment in patients with pre-nebulization severe hypoxia; therefore, patients with a PaO2/FiO2 ratio <200 and/or ARDS, pre-existing COPD, or asthma should be carefully monitored for this complication [68, 89, 90]. Patients with asthma and COPD may also deteriorate with increased inspiratory time and patients with ARDS with the increased tidal volume that is required for effective nebulization [68, 89, 90]. Sedation-related consequences should also be taken into account, and caution is required so as to terminate nebulization without delay and return the patient rapidly to previous sedation levels if required [6, 68].

6.2 Local Antibiotic-Related Adverse Reactions

Bronchial reactivity to the inhaled antibiotic expressed as bronchospasm, cough, and chest tightness is the most common drug-related adverse event with nebulization. In patients with CF, it affected 39–45% of those receiving either tobramycin or colistin in an RCT, whereas higher rates were encountered with colistin dry powder [92–98]. Patients with a history of preexisting bronchial hyperreactivity (asthma or COPD) require close monitoring and premedication with inhaled β_2-agonists [99]. In the most recent RCT, 2.7% of inhaled colistin-treated patients developed bronchospasm. In all cases, β_2-agonists were used without recurrence [58]. Two cautionary reports of direct lung toxicity with colistin are of concern. In the first,

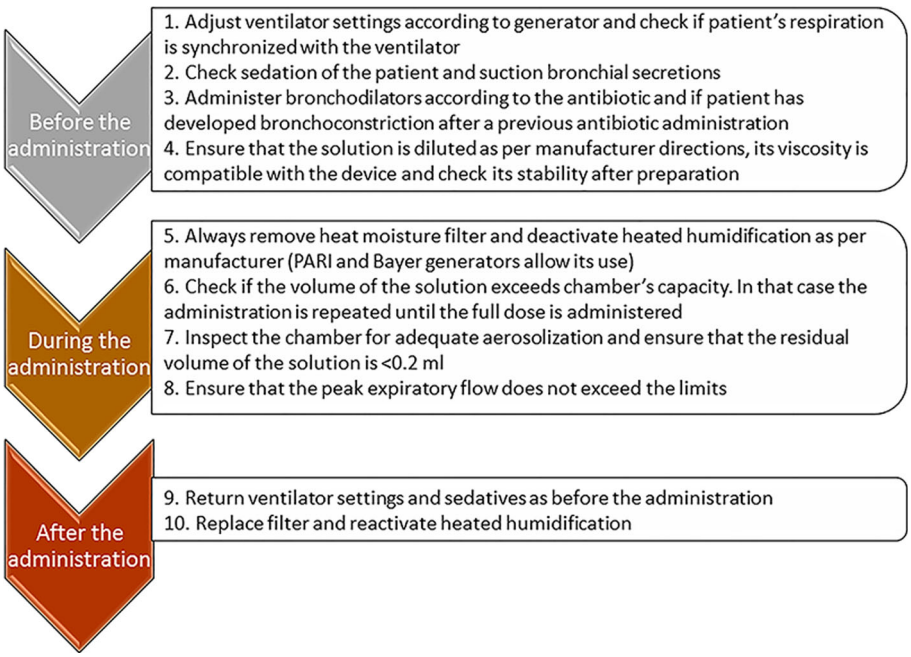

Fig. 3 Proposed checklist for assessment of the patient and supervision of the procedure, for mechanically ventilated patients in whom inhaled antibiotics will be administered

a 5-week-old pharmacy-compounded colistin solution was responsible for the development of ARDS, attributed to the conversion of colistimethate sodium to the active and toxic form of colistin. A US Food and Drug Administration warning calls for freshly prepared solutions of colistin when using non-commercial compounds for inhalation [100, 101]. In the second, hypersensitivity pneumonia emerged after 12 days of high-dose inhaled colistin in another patient [102]. Finally, β-lactams were associated with allergic reactions from the lung and a trial of doripenem was halted because of severe bronchoconstriction [12, 84]. Clinicians should be cautious with the use of parenteral formulations of antibiotics and administer, when possible, formulations designed for inhaled use; the optimized physicochemical properties of the latter ensure better pulmonary delivery, better compatibility with aerosol generators, and less risk for toxicity.

6.3 Systemic Toxicity Due to Antibiotic Absorption

When administering high-dose inhaled aminoglycosides, serum levels should be monitored to avoid possible nephrotoxicity due to systemic accumulation, given the fact that aminoglycosides are theoretically able to cross the alveolar-capillary barrier in inflamed lungs [31, 32]. The risk is almost negligible with inhaled colistin even in the presence of infection due to its anionic molecule, which is unable to cross the alveolar-capillary barrier [68, 99]. Although detectable serum levels were reported with an inhaled dose of 5 MIU twice daily, no systemic or incremental toxicity was recorded in previous studies and in meta-analyses with inhaled colistin in MV patients [12, 14, 35, 99, 103]. A proposed checklist for assessment of the patient for the safety and supervision of the procedure is presented in Fig. 3.

7 Conclusions

Antibiotic nebulization in MV patients is a modality with increasing interest and utilization among intensivists. However, published clinical experience in this field is still limited and very heterogeneous in terms of devices, antibiotics, doses, and indications. Evidently, extrapolation of results from patients with CF and animal models to human infections and especially MV patients is not straightforward. Clearly, more clinical data with inhaled antibiotics in critically ill MV patients are required and particularly RCTs employing the evolving drug-device combinations. The accumulated evidence so far has helped us to better understand the physiology, pharmacokinetics, and practical aspects of nebulization, which are important for an efficacious and safe antibiotic delivery in critically ill MV patients. Selection of the correct nebulizer, adherence to manufacturer's technical details, correct preparation of the procedure and the patient, continuous surveillance of the session, and early recognition of an adverse event are the most important steps for clinicians using this modality. Familiarization of personnel with the technique and type of nebulizer can ensure an optimal drug deposition in lung parenchyma and avoidance of significant drug losses in the large airways and the ventilator circuit. In addition, a checklist guarantees correct and prompt preparation of the procedure, while a strictly defined

monitoring predisposes to efficacious drug delivery and safety for the patient. It is of paramount importance that intensive care unit departments employing inhaled antibiotics develop local protocols to avoid misuse with possible adverse consequences.

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Compliance with ethical standards

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