Aerosolized antibiotics to treat ventilator-associated pneumonia

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Introduction
Aerosol antibiotic administration offers the theoretical advantages of achieving high drug concentrations at the infection site and low systemic absorption, thereby avoiding toxicity, particularly the renal toxicity of aminoglycosides. Antibiotic aerosolization has good results in children with cystic fibrosis [1,2], but data are scarce for patients on mechanical ventilation. The poor development of this potentially advantageous technique is partly due to the fact that, during mechanical ventilation, high amounts of the particles dispersed by conventional nebulizers remain in the ventilatory circuits and the tracheobronchial tree, therefore, not reaching the distal lung, and hence, less drug is available in the alveolar compartment. With the development of new generations of nebulizers that use a vibrating mesh or plate with multiple apertures to produce an aerosol [3,4,5,6,7], antibiotic aerosolization in patients with ventilator-associated pneumonia (VAP) has renewed potential. Herein, we review the recent literature on this subject.

Why use nebulized antibiotics?
The rate of VAP caused by multidrug-resistant strains has increased in recent years [8]. For these strains, particularly for Gram-negative multidrug-resistant bacilli, minimum inhibitory concentrations (MIC) of still active antibiotics, mainly aminoglycosides, are high. By increasing the antibiotic dose given intravenously to remain effective on multidrug-resistant strains with a given antibiotic, the patient is exposed to toxicity. Moreover, when infused intravenously, lung penetration of antibiotics, especially aminoglycosides, is poor. For example, lung penetration of tobramycin or gentamicin is between 10 and 30% after a single intravenous infusion [9–11]. The objective of direct antibiotic delivery to the lower airways is to achieve a high drug concentration at the parenchymal level although the blood level is low, thereby avoiding or limiting toxicity. Tracheal instillation is one way to deliver antibiotic to the lower airways; it results in high antibiotic concentration in the tracheal secretions [12], but the amount of drug distributed to the alveoli is not known, making this technique not completely reliable. Nebulization offers the theoretical advantage of more uniform and homogenous distribution along the Airways than tracheal instillation. The results obtained from animal studies showed that nebulization efficacy was good with high amikacin levels in the lung tissue, even in the more peripheral airways and alveoli [13,14].
Which type of nebulizer to use?
There are three kinds of nebulizers: jet, ultrasonic and vibrating-mesh or plate nebulizers [3**,6**,15].

Jet nebulizers use air or oxygen under high pressure to generate the aerosol. During mechanical ventilation, they are connected to the inspiratory limb of the circuit. They can operate continuously or only during inspiration, in which case the inspiratory flow from the ventilator generates the aerosol. With this type of nebulizer, the aerosol flow and the size of the generated particles vary from one device to another [6**].

With ultrasonic nebulizers, the aerosol is produced by the vibration of a piezo-electric crystal. Drug output and droplet size are determined by the vibration amplitude and frequency, respectively. Generally speaking, ultrasonic nebulizers have a higher output rate than jet nebulizers, but the particles generated are larger [6**].

Vibrating-mesh nebulizers use a mesh or plate with multiple apertures to generate the aerosol [5*]. These devices can be operated with either a battery pack or an electrical source, making them portable, and they are quieter than conventional jet nebulizers. Moreover, these devices have higher drug output because their residual volume is negligible [5*,6**]. A recent study in piglets showed that vibrating-mesh nebulizers were comparable with ultrasonic nebulizers for ceftazidime aerosolization [16]. The Pulmonary Drug Delivery System (PDDS) Clinical was specifically designed for patients requiring mechanical ventilation: the device is synchronized on the inspiratory limb via a pressure transducer, and it delivers the aerosol only during a specific portion of inspiration. This nebulizer has very high efficiency, delivering 50–70% of the dose to the lung [5*,6**]. However, the PDDS Clinical is still under investigation and is not commercially available at present.

Antibiotic aerosolization to treat ventilator-associated pneumonia
For children with cystic fibrosis, aminoglycosides and polymyxins are the most commonly used antibiotics [1]. For patients receiving mechanical ventilation, aminoglycosides are the most frequently used, mainly because they are still active against multidrug-resistant Gram-negative bacilli. However, polymyxins and vancomycin have also been evaluated [17–19].

Aminoglycosides
In animal models of VAP, the amikacin deposition in infected lung parenchyma and its bactericidal efficacy were better after nebulization than intravenous administration [13]. In humans, Le Conte et al. [20] found that a single tobramycin aerosol in patients with healthy lungs led to high lung concentrations, evaluated by scintigraphy, with low systemic absorption. In a preliminary study, the same authors randomized 38 patients with VAP, treated with intravenous β-lactam and tobramycin, to receive aerosolized tobramycin (6 mg/kg/day, n = 21) or placebo (n = 17). Their findings showed that aerosols were well tolerated and they did not observe any adverse event or toxicity, but because of the study design (all patients received intravenous tobramycin), they could not draw any definitive conclusions [21]. In an observational study conducted 10 years ago, Palmer et al. [22] treated six patients, colonized with multidrug-resistant bacteria, with aerosolized gentamicin or amikacin. They reported that this antibiotic delivery route led to smaller tracheal secretion volumes and lower bacterial burdens in tracheal aspirates. In their study, tracheal aminoglycoside concentrations were very high without high systemic absorption in patients with normal renal function. More recently, the same team used aerosolized gentamicin to treat patients with purulent tracheobronchitis and Gram-negative microorganisms identified by Gram staining. They showed that, compared with aerosolized placebo, gentamicin nebulization combined with intravenous antibiotics led to a lower VAP rate, less bacterial resistance and use of fewer systemic antibiotics and might have accelerated weaning from mechanical ventilation [23**].

The newer generations of nebulizers, which use a vibrating mesh, are still under investigation. In a recent study using one of these devices, the PDDS Clinical, Niederman et al. [24] randomized 69 mechanically ventilated patients with Gram-negative VAP to receive, in conjunction to intravenous antimicrobials, 7–14 days of aerosolized amikacin 400 mg b.i.d. (n = 21), amikacin 400 mg once daily and placebo 12 h later (n = 26) or placebo b.i.d. (n = 22). The authors found that the nebulized drug was well distributed in the lung parenchyma with high tracheal and alveolar levels, but low serum concentration below the renal toxicity threshold [25–27]. Moreover, aerosolized amikacin was well tolerated without any severe adverse event, and patients who received amikacin twice daily required significantly less systemic antibiotics than patients given placebo b.i.d. [24]. However, those data were obtained for a small number of patients and require confirmation on a larger scale.

Polymyxins
Polymyxins are a group of polypeptide antibiotics. Polymyxin E (colistin) and polymyxin B are the main products used in humans. Their activity spectrum includes only Gram-negative aerobic bacilli, particularly nonfermenting Gram-negative bacilli (Pseudomonas aeruginosa and Acinetobacter baumannii), and strains resistant to almost all commercially available antibiotics are still susceptible to polymyxins [17]. However, one of the main limitations
for their intravenous use is their nephrotoxicity, making
direct delivery to the lower respiratory tract, particularly
nebulization, attractive for ICU patients with VAP.

Nebulized colistin has been evaluated with encouraging
results in patients with pneumonia due to multidrug-
resistant Gram-negative bacilli [28]. In 21 patients with
VAP due to multidrug-resistant  P. aeruginosa  (n = 4) or A.
baumannii  (n = 17) who received nebulized colistin, Kwa
et al. [29] showed that 18 (85.7%) patients had confirmed
or probable pathogen eradication and a mortality rate of
46.7%. All these patients received intravenous antibiotics
that were not active against the pathogens responsible for
VAP [29]. In another study on 80 patients with multidrug-
resistant infections due to  P. aeruginosa  or A. baumannii
who received nebulized  (n = 71), intravenous  (n = 12) or
intrathecal  (n = 2) colistin, Berlana et al. [30] demon-
strated that 92% of them had confirmed or probable pathogen eradication with an in-hospital mortality rate of
18%. More recently, Michalopoulos et al. [31] adminis-
tered nebulized colistin to 60 patients with VAP due to
multidrug-resistant Gram-negative bacteria. Although
half of the isolated pathogens were susceptible only to
colistin, good clinical and bacteriological responses of
VAP were obtained in 50/60 (83.3%) patients with a
mortality rate of 20%. None of those studies reported
the emergence of colistin-resistant pathogens or renal
toxicity due to colistin nebulization [17,29–32].

Vancomycin

Data on the impact of antibiotic aerosolization active
against Gram-positive bacteria are scarce. In a recent
placebo-controlled trial, Palmer et al. [23] randomized
43 patients with purulent tracheobronchitis and Gram-
stain identified microorganisms to receive aerosolized antibiotics  (n = 19) or placebo  (n = 24). The antibiotic
was chosen according to tracheal aspirate Gram-staining
results (vancomycin for Gram positive and gentamicin for
Gram negative). Most of their patients had clinical signs
of VAP and were on systemic antibiotics at the time of
randomization. Their data showed that antibiotic aerosolization led to faster resolution of clinical signs of pneumonia than placebo, fewer subsequent VAP episo-
des, less bacterial resistance and use of systemic antibi-
otics and perhaps accelerated weaning from mechanical
ventilation.

The same team recently showed that for patients
on mechanical ventilation receiving vancomycin for
methicillin-resistant  Staphylococcus aureus  pneumonia,
the vancomycin concentrations in their tracheal aspirates
were very low and sometimes below the therapeutic
range. When patients were given aerosolized vancomycin
in conjunction to intravenous vancomycin, tracheal-
aspirate antibiotic concentrations rose, and they were
always above the therapeutic range [19]. However, those
data were obtained in a small number of patients and
need to be confirmed in larger trials.

Antibiotic aerosolization to prevent
ventilator-associated pneumonia

Bacterial colonization of the lower respiratory tract is the
first step on the way to lung infection. Prophylactic aeroso-
lization (or tracheal instillation) of antibiotics is one of the
strategies developed for VAP prevention. A recent meta-
analysis, including available trials on this topic, concluded
that the limited evidence available supports that prophy-
lactic administration of antibiotics via the respiratory tract was associated with fewer cases of occurrence of ICU-acquired VAP. However, evidence
from noncomparative studies suggested that this preventive
strategy might lead to enhanced emergence of resistant
bacteria [33]. Thus, the Centers for Disease Control
and the Canadian Critical Care Society do not recom-
end the use of nebulized antibiotics for VAP prevention
[33].

Aerosolization drawbacks

Although antibiotic nebulization appears attractive, it has
several drawbacks, and some questions have not yet
been resolved.

Adverse effects of antibiotic inhalation

In addition to the effects of the systemically absorbed
antibiotic (i.e. renal toxicity for aminoglycosides and
polymyxins), most adverse events result from the direct
toxicity on airways and lung parenchyma (mucosal irri-
tation). The most frequently described events are cough
and a disagreeable taste [2], which are minor and
transient. Bronchospasm is a more severe, possibly
life-threatening, but less common side effect that has
been described in patients receiving nebulized antibi-
tic, especially when the intravenous formulation
was used. Bronchospasm during aerosolization imposes
the immediate withdrawal of the aerosol and β-agonist
nebulization [2]. Reintroduction of the same drug by the
same route should be avoided.

Parenchymal lung penetration

Antibiotic penetration into the lung parenchyma is one of
the key problems of aerosolization. In healthy humans,
antibiotic penetration into lung tissues is good [34].
However, in patients with alveolar consolidations, it is
more uncertain. Most studies evaluating aerosolized antibi-
tics in patients with VAP found high antibiotic levels
in the tracheal aspirates [2,22], but high sputum antibiotic
levels does not necessarily mean high levels at the
infection site, that is, in the lung parenchyma. In piglets
with experimental pneumonia, Goldstein et al. [13] found
that amikacin penetration into the lung, even in poorly
aerated areas, was good. In humans, Luyt et al. [26,35] found that administering aerosolized amikacin to patients with Gram-negative VAP achieved very high aminoglycoside concentrations in epithelial lining fluids (ELF) and VAP-affected lung zones, although maintaining well tolerated serum drug concentrations. The ELF concentrations always exceeded the antibiotic’s MIC for Gram-negative microorganisms usually responsible for VAP. The parenchymal lung penetration seems to be better with new-generation devices, that is, vibrating-mesh nebulizers [5*,26,34*,35].

Antibiotic inactivation by inhibitors in sputum
Tracheal secretions contain inhibitors that can prevent antibiotic activity. The authors of two studies reported that the aminoglycoside MICs in tracheal aspirates increased to 10–25-fold higher than those observed in vitro [2,36,37]. Moreover, antibiotic nebulization might be responsible for changes in the molecule’s activity. These potentially noxious effects must be addressed in future studies evaluating this antibiotic delivery route.

Emergence of resistant strains
The prolonged use of broad-spectrum antibiotics is known to lead to emergence of multiresistant strains, and nebulization is not an exception to the rule [38]. Thus, as for every antibiotic strategy, aerosolization must be managed prudently, particularly concerning treatment duration, which should be kept as short as possible [39].

Cost
Most of the devices, especially those of newest generation (vibrating-mesh nebulizer), are expensive. Moreover, to be nebulized, a special antibiotic formulation must be prepared that can also be costly. Lastly, most companies have developed antibiotic formulations to be administered via a specific device, thereby, further increasing the cost of delivery by nebulization [2].

Legal concerns
Antibiotics have been approved for intravenous use, but not for direct delivery to the lungs. Although many studies evaluated antibiotic formulations in the United States, to date, the Food and Drug Administration has not approved the use of colistin and tobramycin (for which a specific formulation, TOBI, exists) to treat VAP [2].

Conclusion
Although promising, antibiotic aerosolization to treat VAP has not yet entered the armamentarium for daily practice. The results of recent investigations emphasized its potential contribution as a good adjunctive therapy to intravenous antibiotics, but the clinical impact of such a strategy has not yet been definitively established. Moreover, at present, treating patients with VAP using aerosolized antibiotics alone is premature [28**]. Indeed, at present, antibiotic aerosolization can only be recommended to treat patients with multidrug-resistant VAP, for which colistin and aminoglycosides are the drugs of choice, further narrowing its indication to Gram-negative pneumonia.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 206).

5 Dhand R, Sohal H. Pulmonary Drug Delivery System for inhalation therapy in mechanically ventilated patients. Expert Rev Med Devices 2008; 5:9–18. This study summarizes the characteristics and advantages of one of the new-generation nebulizers, that is the vibrating-mesh nebulizer, especially designed for aerosolization during mechanical ventilation.
Respiratory infections


The author randomized 43 patients with purulent tracheobronchitis and Gram stain-identified microorganisms to receive aerosolized antibiotics (vancomycin for Gram positive and gentamicin for Gram negative) or placebo. Their data showed that antibiotic aerosolization led to faster resolution of clinical signs of pneumonia than placebo, fewer subsequent VAP episodes, less bacterial resistance and use of systemic antibiotics and perhaps accelerated weaning from mechanical ventilation.


A well performed review on aerosolized antimicrobial monotherapy for pneumonia. The authors concluded that this strategy might be considered when systemic access is not available, refused by the patients or when concerns exist regarding bioavailability to the lungs or systemic toxicity.


A well performed pharmacokinetic study on nebulized amikacin in healthy volunteers, which showed that this way of delivery is well tolerated and is associated with lower serum levels than intravenous infusion.


