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Nebulized antibiotics for ventilator-associated pneumonia: methodological framework for future multicenter randomized controlled trials

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Network for Nebulized Antibiotics in Ventilator-associated Pneumonia
(ENAVAP)*

Purpose of review

Although experimental evidence supports the use of nebulized antibiotics in ventilator-associated pneumonia (VAP), two recent multicenter randomized controlled trials (RCTs) have failed to demonstrate any benefit in VAP caused by Gram-negative bacteria (GNB). This review examines the methodological requirements concerning future RCTs.

Recent findings

High doses of nebulized antibiotics are required to reach the infected lung parenchyma. Breath-synchronized nebulizers do not allow delivery of high doses. Mesh nebulizers perform better than jet nebulizers. Epithelial lining fluid concentrations do not reflect interstitial lung concentrations in patients receiving nebulized antibiotics. Specific ventilator settings for optimizing lung deposition require sedation to avoid patient's asynchrony with the ventilator.

Summary

Future RCTs should compare a 3–5 day nebulization of amikacin or colistimethate sodium (CMS) to a 7-day intravenous administration of a new cephalosporine/ β -lactamase inhibitor. Inclusion criteria should be a VAP or ventilator-associated tracheobronchitis caused by documented extensive-drug or pandrug resistant GNB. If the GNB remains susceptible to aminoglycosides, nebulized amikacin should be administered at a dose of 40 mg/kg/day. If resistant to aminoglycosides, nebulized CMS should be administered at a dose of 15 millions international units (IU)/day. In VAP caused by pandrug-resistant GNB, 15 millions IU/day nebulized CMS (substitution therapy) should be compared with a 9 millions IU/day intravenous CMS.

Keywords

breath-synchronized nebulization, epithelial lining fluid concentrations, nebulized amikacin, nebulized colistimethate sodium, nebulizers

INTRODUCTION

Animal experiments demonstrate that nebulized aminoglycosides and polymyxins produce high

lung tissue concentrations and provide rapid and efficient bacterial killing in the lung parenchyma infected by Gram-negative bacteria (GNB) [1]. These

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KEY POINTS

- To optimize lung deposition of nebulized antibiotic in VAP, specific ventilator settings should be used during nebulization to reduce inspiratory flow velocity; humidification and warming of inspired gas should be interrupted to avoid a rainout effect in the circuits and airways, and sedation administered to avoid dyssynchrony with the ventilator.
- In ventilated patients treated by nebulized antibiotics, epithelial lining fluid antibiotic concentrations markedly overestimate lung interstitial space fluid concentrations due to the bronchial contamination of the fluid lavage.
- Future multicentre RCTs on nebulized amikacin and colistimethate sodium should include patients with VAP and ventilator-associated tracheobronchitis caused by extensive-drug and pandrug resistant gram-negative bacteria.
- Nebulization of amikacin or colistimethate sodium alone should be compared with a 7-day intravenous administration of new cephalosporine/ β -lactamase inhibitors (monotherapy) or colistimethate sodium.
- High doses amikacin (40 mg/kg/day) and colistimethate sodium (15 millions IU/day) should be administered using continuous rather inspiration-synchronized nebulization for 3–5 days.
- Expected benefits from nebulized antibiotics are a shorter time to clinical cure, a decrease in colistimethate sodium-induced renal toxicity, a shorter duration of antibiotic administration and a reduction of mechanical ventilation duration.

benefits were demonstrated using postmortem lung tissue homogenates [2,3] and in-vivo microdialysis [4[■]]. Despite experimental evidence of efficacy, clinical studies in ventilator-associated pneumonia (VAP) have failed to provide convincing results. Multicentre randomized controlled trials (RCTs) are sparse, have used nonoptimized techniques of nebulization, have enrolled heterogeneous populations of patients with hospital-acquired pneumonia or VAP and failed to demonstrate superiority for the nebulization route [5,6[■],7]. As a consequence, American and European academic societies do not recommend the routine use of nebulized antibiotics to treat VAP [8–12]. In 2016, American guidelines suggested that VAP due to GNB that are susceptible to only aminoglycosides or polymyxins could be treated with both nebulized and intravenous agents (adjunctive therapy) [8]. In 2017, the French guidelines suggested the use of nebulized colistimethate sodium (CMS) and/or aminoglycosides in VAP caused by GNB sensitive only to CMS and/or aminoglycosides [11]. In this opinion article, reflecting the

view of the European Investigators Network for Nebulized Antibiotics in Ventilator-associated Pneumonia [13[■]], we analyse potential underlying reasons that led multicenter RCTs to fail, and we propose various insights to improve methods of future RCTs on nebulized amikacin and CMS in patients with VAP caused by GNB.

PATIENTS WITH VENTILATOR-ASSOCIATED PNEUMONIA WHO MAY BENEFIT FROM NEBULIZED AMIKACIN AND COLISTIMETHATE SODIUM

In theory, VAP caused by microorganisms susceptible only to antibiotics with limited pulmonary penetration, could benefit from the nebulization route. Lung tissue penetration is excellent for quinolones, variable for β -lactams and weak for glycopeptides, aminoglycosides and polymyxins [14]. As a consequence, aminoglycosides and CMS are the main antibiotics whose nebulization could provide clinical benefit. Recently experimental data suggest that such benefit could also be obtained by nebulized vancomycin [15[■]].

Treatment of VAP by mono or dual combination therapy is a key methodological issue for future RCTs. Adding intravenous aminoglycosides or fluoroquinolones to β -lactams is not more efficient than intravenous β -lactams alone to treat sepsis and VAP [16,17]. For the initial empirical therapy, European and American guidelines recommend an intravenous bitherapy in patients at risk of VAP caused by multidrug resistant GNB [8,10,11]. American guidelines suggested to continue bitherapy in patients with septic shock [18] and documented multidrug resistant GNB [8]. European guidelines suggested to continue bitherapy only in patients with documented extensive-drug resistant (XDR) GNB [10]. French recommendations suggested to use monotherapy after the identification of the causative microorganism, considering the lack of evidence supporting the benefit of bitherapy [11].

Referring to the stratification of GNB resistance (Fig. 1) [19], patients with VAP caused by XDR GNB susceptible to aminoglycosides, could benefit from nebulized amikacin whereas patients with VAP caused by XDR GNB resistant to aminoglycosides could benefit from nebulized CMS. Compared with the intravenous administration of a new cephalosporine/ β -lactamase inhibitor, the nebulization of amikacin and CMS may have several advantages: reduction of bacterial resistance in the ICU [20], more efficient treatment of ventilator-associated tracheobronchitis (VAT) due to the very high tracheobronchial antibiotic concentrations [21], and shorter duration of treatment allowing to reduce antibiotic pressure in the ICU.

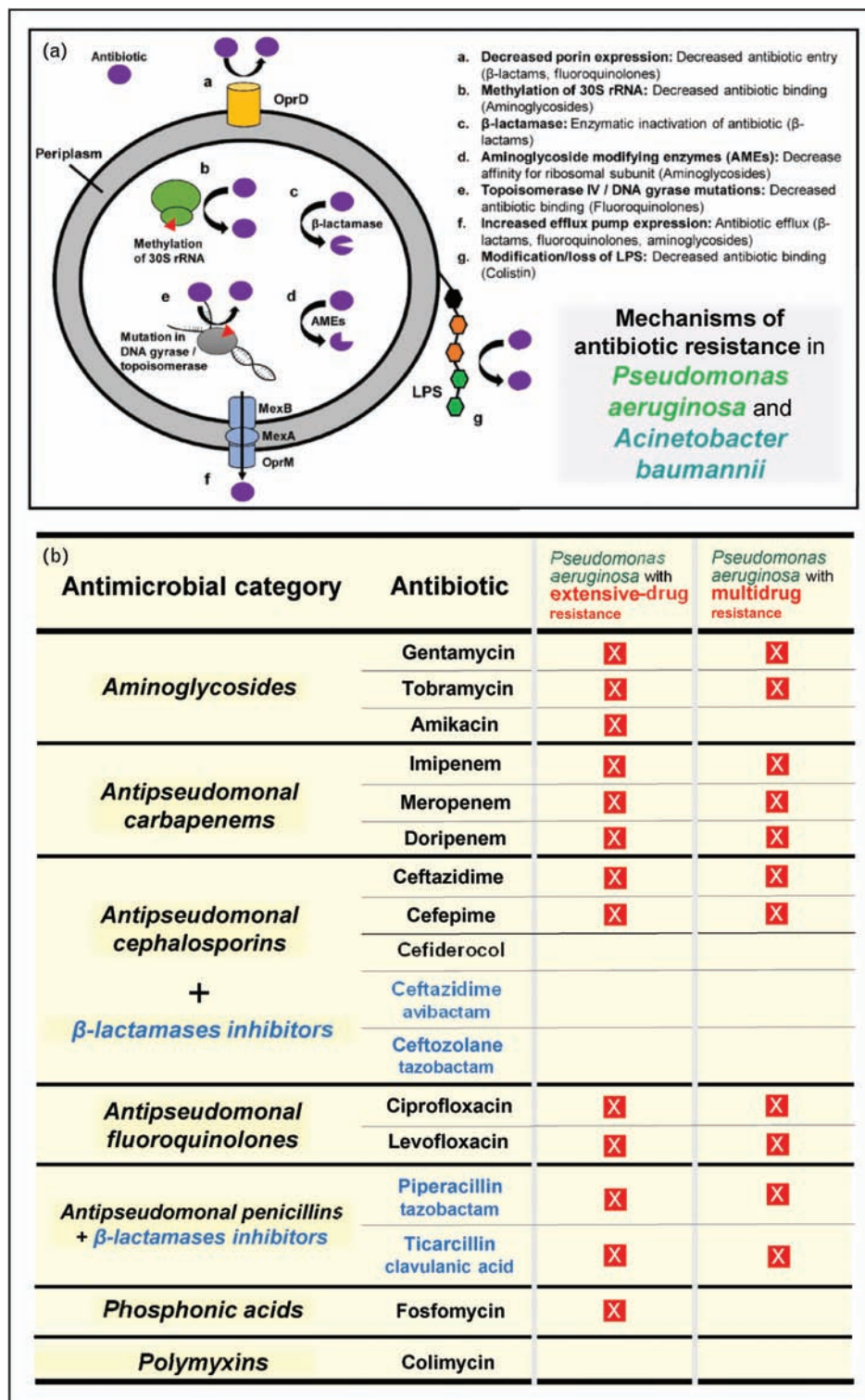


FIGURE 1. Resistance of Gram-negative bacteria causing ventilator-associated pneumonia. (a) Mechanisms of resistance for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*; (b) antibiotic sensitivity of two specimens of *Pseudomonas aeruginosa* with multidrug resistance and extensive – drug resistance. (a) – Reproduced with permission from Eichenberger EM, Thaden JT. Epidemiology and mechanisms of resistance of extensively drug resistant Gram-negative bacteria. *Antibiotics* 2019;8:pii: 37.

The limited penetration of nebulized antibiotics into consolidated pneumonic lung and the possible long delay before they reach the sites of infection, could justify the concomitant administration of nebulized and intravenous antibiotics in VAP where 'lobar' consolidation is often present. Experimentally, the alveolar deposition of nebulized antibiotics decreases with obstruction of distal bronchioles by purulent plugs, the histologic severity of pneumonia and the loss of lung aeration [1]. Severity of lung aeration loss has opposite effects depending on whether antibiotics are intravenously administered or nebulized: tissue concentrations increase in case of intravenous administration and decrease after nebulization [2,3,22]. Very likely, the increased permeability of the alveolar-capillary barrier in VAP, promotes intravenous amikacin penetration into the lung, whereas the multiple purulent plugs in distal bronchioles limit its alveolar deposition. However, within consolidated pneumonic lung regions, amikacin and colistin nebulized lung tissue concentrations remain largely above minimal inhibitory concentrations [3,22], raising the question how nebulized antibiotics reach infected lung parenchyma despite the lack of any pulmonary aeration. Intraparenchymal pseudocysts and bronchiolar distension frequently observed in consolidated lung areas of ventilated animals (and patients) with VAP [23], likely represent one of the routes by which nebulized antibiotics reach infected lung regions devoid of alveolar aeration. In addition, there is a continuum between the bronchial and the interstitial compartment. Any consolidation is contiguous with the bronchi which opens the door for nebulized antibiotics. According to these experimental data, it seems reasonable to foster nebulization alone.

Bacteremic VAP caused by XDR GNB is a clinical situation where nebulization and intravenous administration should be combined. Systemic diffusion of nebulized aminoglycosides and CMS do not achieve systemic bactericidal concentrations.

DETERMINATION OF THE OPTIMAL NEBULIZED DOSE

The understanding of mechanisms determining lung parenchymal deposition and the use of appropriate doses are key issues for therapeutic efficiency.

Extrapulmonary, bronchial and lung parenchymal deposition

In spontaneously breathing patients with cystic fibrosis, around 70% of nebulized antibiotics reach the infected bronchial tree. In ventilated patients

with VAP, less than 40% reach the infected lung parenchyma (Fig. 2) [24].

Massive inertial impaction of the aerosol in the ventilator circuits and tracheo-bronchial walls explains the limited pulmonary deposition. The retention in the nebulizer varies from 50%, with jet nebulizers to less than 5% with mesh nebulizers [24]. Heat and moisture exchangers significantly reduce the inhaled mass by trapping aerosolized particles in the filter [25]. Warming and humidifying inspired gas, increases aerosol particle size and induces a rainout effect in respiratory circuits and conducting airways. Non humidified aerosol increases inhaled mass delivery and lung deposition. In VAP, dry nebulization increased gentamicin, amikacin or vancomycin sputum levels by 3.63 compared with humidified nebulization [26]. With dry nebulization and optimized ventilator settings, circuit and bronchial deposition reach an average of 30 and 35%, respectively [24].

Bronchial contamination of the epithelial lining fluid

The bronchial deposition of nebulized antibiotics skews the epithelial lining fluid (ELF) concentrations [27^{*}]. In animals receiving a single aerosol dose of CMS or tobramycin, the ELF antibiotic concentrations measured 1 h after nebulization ranged between 700 and 4000 µg/ml [4^{**},21,28,29]. In healthy ewes receiving a 400-mg aerosol dose of tobramycin, the ELF concentrations were 100-fold higher than the interstitial space fluid concentrations measured using microdialysis [4^{**}], clearly suggesting a massive bronchial contamination during the bronchoalveolar lavage procedure [27^{*}]. In critically ill patients with VAP treated by nebulized CMS [30] or amikacin [31], bronchial concentrations above 1000 µg/ml were found.

To get samples representative of ELF, the fiberoptic is advanced as far as possible in the bronchial tree. Then, three to five aliquots of 20–60 ml saline are instilled and the aspirate from the third aliquot is used for ELF analysis. As shown in Fig. 3a, a 60 ml aliquot lavages a large segmental area [32]. Following nebulization, the tracheobronchial tree is coated with aerosolized antibiotic. The fiberoptic is contaminated during its passage and the ELF antibiotic concentrations reflect more bronchial than interstitial lung tissue concentrations. In sheep receiving 10 mg/kg nebulized amikacin, tracheobronchial concentrations were measured more than 10,000 µg/ml at the end of nebulization (Fig. 3b) [21]. In critically ill patients with VAP receiving 5 mg/kg of nebulized amikacin, tracheobronchial and ELF amikacin concentrations ranged between

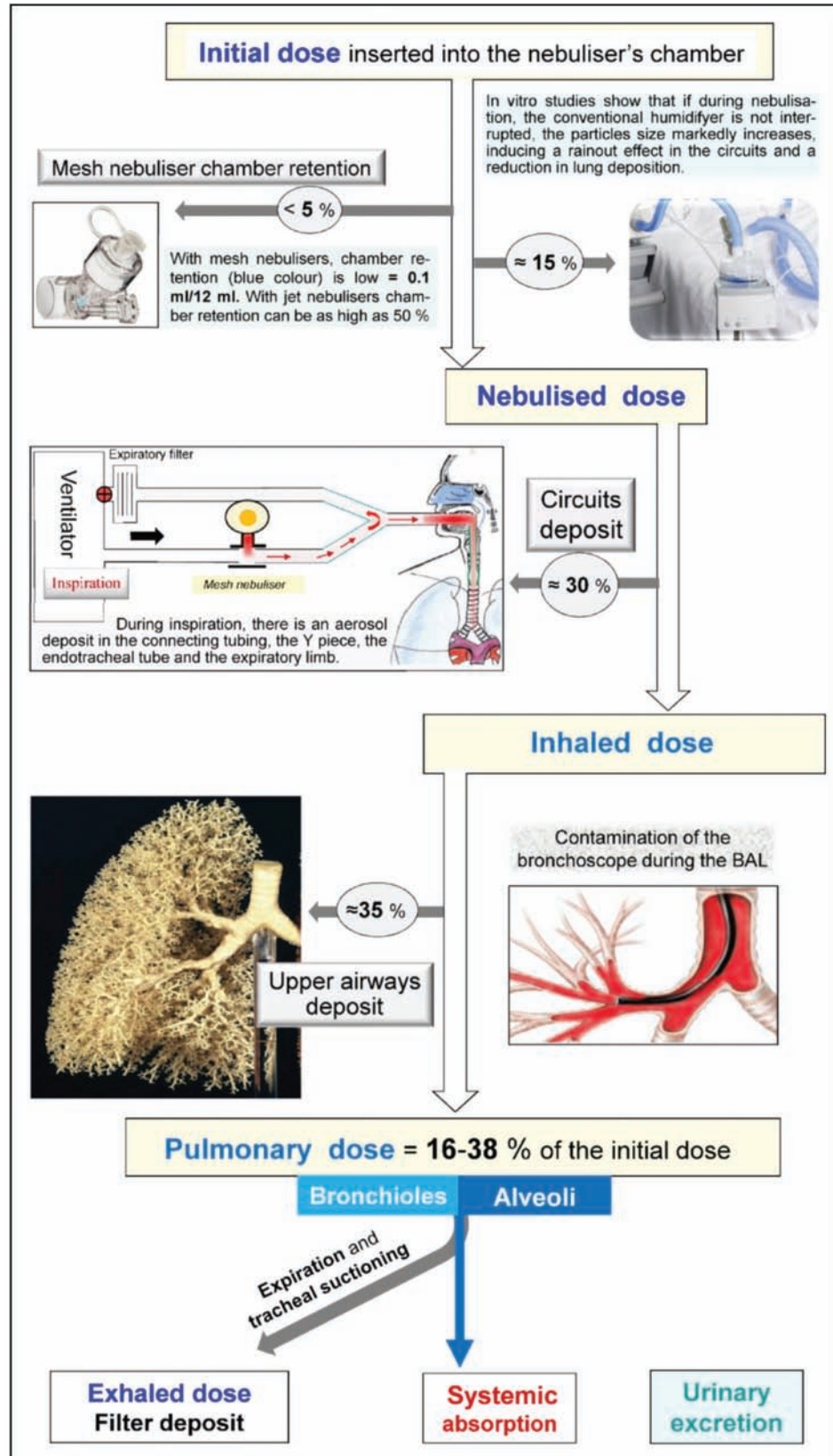


FIGURE 2. Extrapulmonary and pulmonary deposition of nebulized antibiotics. Reproduced with permission [50]. Copyright© 2020 Elsevier Masson SAS. All rights reserved.

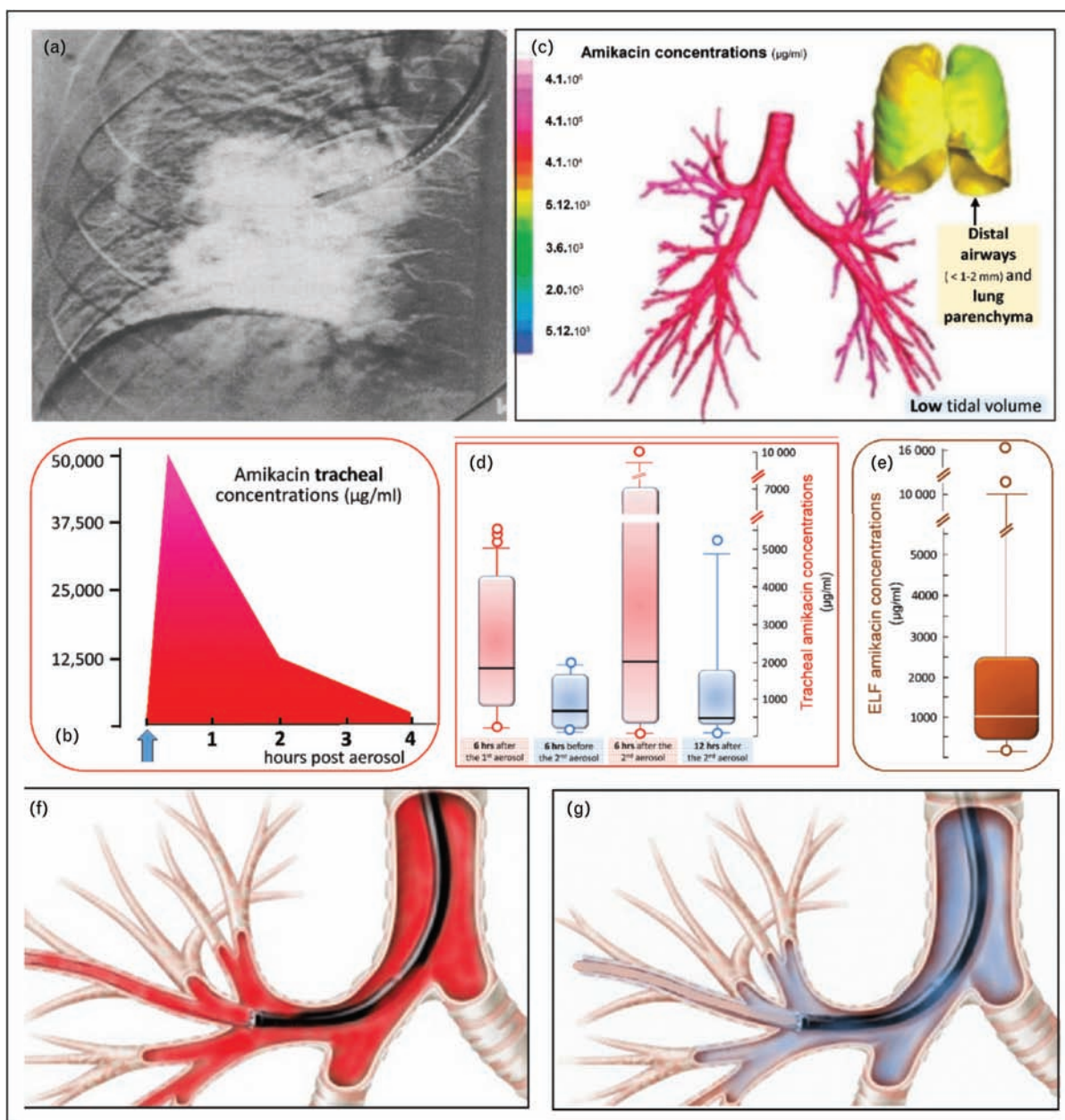


FIGURE 3. Bronchial contamination of the epithelial lining fluid during the fiberoptic bronchoalveolar lavage procedure. (a) Distribution of bronchoalveolar lavage fluid as assessed by digital subtraction radiography. The aspirate from the third 60-ml aliquot is issued from the entire volume of the medial segment of the middle lobe; (b) amikacin tracheal concentrations measured before and 10 min, 2 h and 4 h after a single nebulization of amikacin 300 mg in five pigs with *Pseudomonas aeruginosa* inoculation pneumonia; (c) distribution of tobramycin concentrations between proximal and lung parenchyma immediately after the nebulization of 600 mg in patients with cystic fibrosis (colour scale indicates amikacin concentrations ranging from 4,100,00 µg/ml to 512 µg/ml). Aerosol concentrations were computed using airway models reconstructed from computed tomography scans of patients with cystic fibrosis, in combination with computational fluid dynamic simulations. Proximal airways defined as bronchi with an internal diameter greater than 1 mm are represented as the tracheal bronchial tree, whereas distal airways are represented as lung parenchyma. Nebulization was simulated using a PARI-LCR Plus nebulizer (Midlothian, Texas, USA); (d) amikacin tracheal concentrations measured in 19 patients with ventilator-associated pneumonia treated by two daily aerosol doses of 400 mg, in the 6 h after the first and second aerosol of day 3 (*light red boxplots*), and in the 6 h preceding the second aerosol of day 3 and the first aerosol of day 4 (*light blue boxplots*); (e) epithelial lining fluid amikacin concentrations measured on day 3 of treatment in 28 patients (f) and (g) contamination of the fibroscope by high bronchial concentrations (red colour corresponding to the colour scale displayed in c) immediately after the end of the nebulization and by low bronchial concentrations (blue colour corresponding to the colour scale displayed in c) immediately before the next nebulization. Reproduced with permission [27*].

500 and 16,000 $\mu\text{g/ml}$ (Fig. 3d and e) [31]. Although simulation indicates a concentration gradient between proximal airways and lung parenchyma (Fig. 3c), tracheobronchial and ELF amikacin concentrations were increased in the same proportions (Fig. 3d and e), reinforcing the hypothesis of massive bronchial contamination. To quantify lung tissue concentrations and the 'bronchial contamination' over time, future experiments should compare bronchial, ELF using bronchoalveolar lavage and lung interstitial concentrations using microdialysis [4^{***}] after the single nebulization of a high dose of nebulized aminoglycoside or CMS to large animals with inoculation pneumonia.

In conclusion, ELF antibiotic concentrations in patients receiving nebulized antibiotics markedly overestimate lung interstitial concentrations and are not appropriate for assessing lung tissue concentrations. As microdialysis catheters cannot be inserted routinely in patients, microneedles and aptamer-based probes could be an attractive option [33].

Toxicity risk and rationale to determine the nebulized dose

Local and general toxicity of nebulized aminoglycosides and CMS depend on the nebulized dose and the systemic diffusion from the respiratory system. Whereas systemic diffusion of nebulized aminoglycosides is limited in healthy lung, it markedly increases when the alveolar-capillary barrier is disrupted by the inflammatory process [13^{*}]. In animals with inoculation pneumonia, trough amikacin concentrations are not different between nebulization and intravenous administration when the nebulized dose is equal to the intravenous dose augmented by extrapulmonary deposition [1,13^{*}]. As a consequence, the risk of amikacin toxicity is not reduced with nebulization. A possible rationale for dosing is to provide equivalent doses to the respiratory system either by the endotracheal tube (nebulization) or by the pulmonary artery (intravenous administration). In other words: nebulization dose = intravenous dose + extrapulmonary deposition dose (Fig. 4). High doses should therefore be administered, amounting 40 mg/kg/day. As aminoglycosides are concentration dependant antibiotics with a postantibiotic effect, a single nebulization per day may be preferred [13^{*}].

In contrast, systemic diffusion of nebulized CMS is low, even in presence of extensive inoculation pneumonia [3] or VAP [34]. As a consequence, the rationale for dosing is different, mainly determined by the bronchial tolerance of the aerosol. As nebulized CMS has a good tracheobronchial tolerability, doses can be increased far above the intravenous

dose augmented by extrapulmonary deposition. To increase the bactericidal activity (CMS is a concentration dependant antibiotic), up to 5 million international units (IU) can be nebulized each 8 h and compared with 3 million IU intravenously administered each 8 h.

Substitution rather than adjunctive therapy

The rationale for adjunctive therapy (nebulization and intravenous administration) appears limited [1]. For aminoglycosides, adjunctive therapy increases lung tissue and trough plasma concentrations. Therefore, the risk of toxicity likely increases. For CMS, adjunctive therapy increases lung tissue but not plasma concentrations. Therefore, it likely improves efficacy with a similar risk of toxicity. In contrast, substitution therapy markedly reduces colistin plasma concentrations and decreases the risk of toxicity as shown in a recent meta-analysis [35]. Therefore, the European Society of Clinical Microbiology and Infectious Diseases recommended to compare substitution therapy rather than adjunctive therapy with intravenous administration in future RCTs [36].

TECHNIQUE OF NEBULIZATION

To optimize lung deposition in ventilated patients, a continuous rather than breath-actuated nebulization should be provided using mesh nebulizers together with specific ventilator settings to reduce flow velocity and inertial impaction of aerosolized particles.

Continuous rather than inspiration-synchronized nebulization

Breath-synchronized mesh nebulizers are software-driven devices that monitor inspiratory flow, respiratory rate and inspiratory time. They increase the respirable mass [26,37] but markedly lengthen the time of nebulization by restricting aerosol generation to the inspiratory phase [38^{*}]. With nebulizers designed to synchronize aerosol generation to the first 75% of the inspiratory phase, the time of nebulization per minute is independent of the respiratory frequency and can be calculated as follows:

$$\begin{aligned} \text{Nebulization time (s/min)} \\ = 60 \cdot 0.75 \cdot T_i/T_{\text{tot}} \end{aligned}$$

Compared with a continuous mesh nebulizer, an inspiration-synchronized mesh nebulizer extends the time of nebulization by three to nine fold. Nebulization of amikacin 25 mg/kg takes 30–

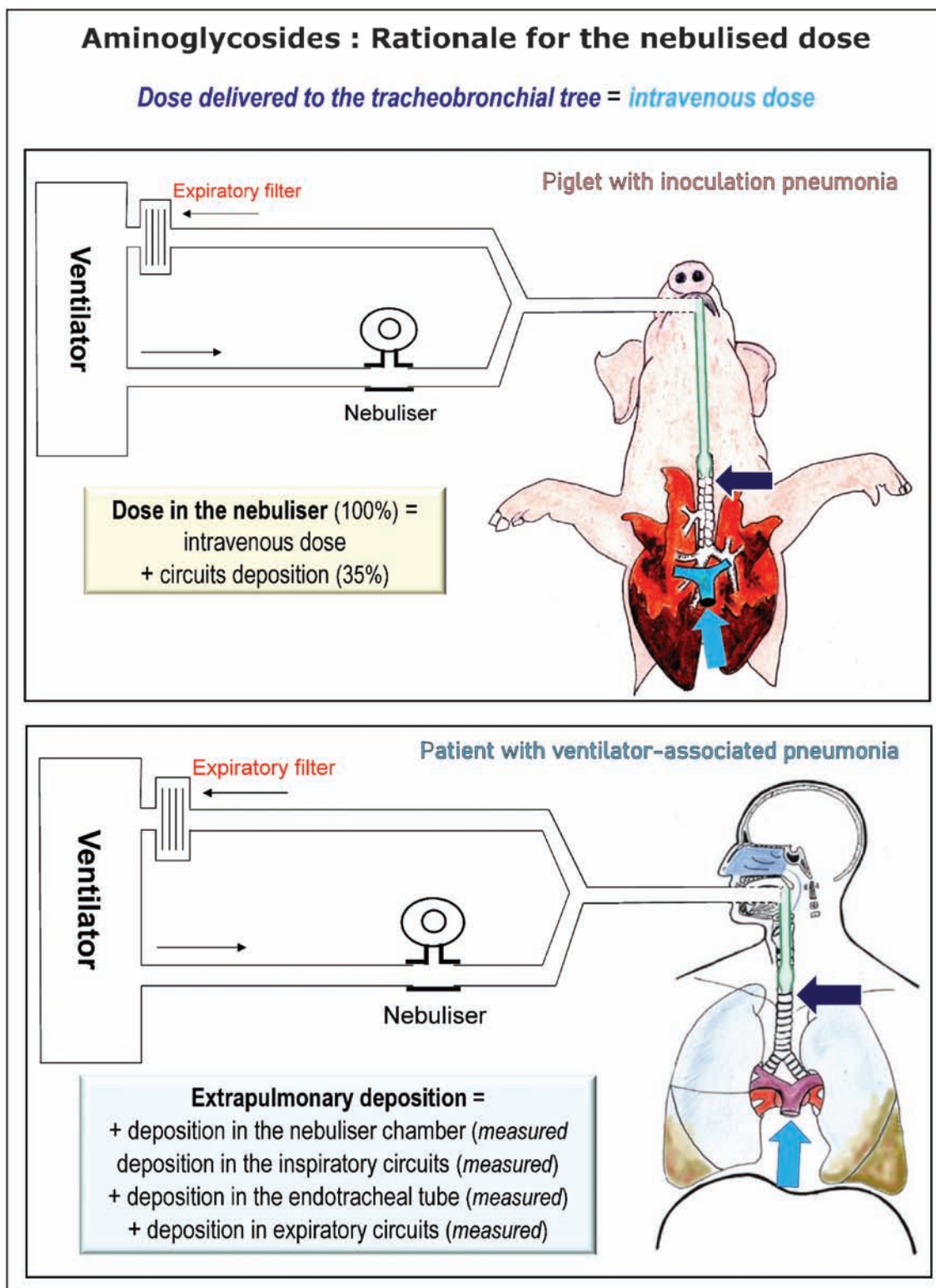


FIGURE 4. Rationale for determining equivalent dosing between nebulization and intravenous administration of aminoglycosides. Ventilated piglets with inoculation pneumonia and patients with ventilator associated pneumonia receive the same dose of aminoglycoside at the distal tip of the endotracheal tube (dark blue arrow, nebulization) and in the pulmonary artery (light blue arrow, intravenous administration). The dose inserted into the chamber of the nebulizer is equal to the intravenous dose and extrapulmonary deposition. Extrapulmonary deposition can be measured by washing out inspiratory and expiratory circuits and the endotracheal tube by a know volume of saline and measuring the mean concentration of amikacin in the collected liquid [39]. Reproduced and modified with permission [1].

45 min using continuous mesh nebulizers [39], whereas nebulization of 12 mg/kg takes 60 min using inspiration-synchronized mesh nebulizers [31]. As a consequence, nebulization of amikacin 40 mg/kg/day, the dose recommended in XDR GNB VAP, is unfeasible using inspiration-synchronized mesh nebulizers as it would require two 3–5 h nebulizations per day [38^a].

Continuous mesh nebulizers generate the antibiotic aerosol throughout the respiratory cycle. During expiration, the aerosol accumulates in the inspiratory limb and is propelled into the airways during the next inspiration (bolus effect). The 'bolus effect' contributes to the delivery of highly concentrated aerosol to the tracheobronchial tree and the distal lung and justifies the use of continuous mesh nebulizers in VAP.

Optimization of ventilator settings during the nebulization phase

Limiting inspiratory flow velocity reduces inertial impaction of the aerosol in the airways and optimizes lung deposition. To achieve that goal, it is recommended to use specifically designed smooth angles and inner surface tubings [36,39] and to select specific ventilator settings during the nebulization [36]: volume-controlled ventilation with a constant inspiratory flow, Inspiratory/Expiratory ratio at 1 : 1, respiratory rate at 12–15 bpm, tidal volume at 8 ml/kg, and absence or minimum bias flow (2 l/min). In patients with acute respiratory distress syndrome, such ventilator settings generate asynchronies which should be controlled by increasing sedation level transiently. A plateau end-inspiratory pause of 20% should be set to promote aerosol deposition on alveolar walls. Pressure support should be discouraged because the decelerating inspiratory flow produces turbulences [40]. The heat and moisture exchanger should be removed and heated humidifiers stopped to avoid hygroscopic growth of the aerosolized particles and a rainout effect in the endotracheal tube and airways. To avoid aerosol waste in the expiratory limb, the nebulizer should be positioned 15 cm before the Y piece, on the inspiratory limb [36,39].

Advantages of mesh nebulizers over jet nebulizers

In-vitro and in-vivo studies suggest the superiority of mesh over jet nebulizers for nebulizing antibiotics and bronchodilators [41–45]. With both types, mass median aerodynamic diameters remain below 5 µm [41–43], the threshold above which the majority of aerosolized particles cannot reach the deep lung. Fluorescence lung imaging [42] and scintigraphic studies [40,44], demonstrate that mesh nebulizers

provide a higher respirable inhaled mass than jet nebulizers. Another advantage is a much smaller residual volume (46% with jet nebulizers versus 4% with mesh nebulizers) that allows the administration of high doses in a shorter duration of time. In addition there is no interference with inhaled gas delivered by the ventilator. In spontaneously breathing anaesthetised mice inhaling salbutamol in an exposure chamber, postmortem tissue and serum concentrations were 60% higher with mesh compared with jet nebulizers [42], whereas residual volume was significantly reduced. In moderate to severe chronic obstructive pulmonary disease patients on noninvasive ventilation, mesh nebulizers deposited more than three-fold more radioaerosol into the lungs than jet nebulizers [44]. The technical advantages of mesh nebulizers may affect outcome. In a series of 1594 patients with asthma and chronic obstructive pulmonary disease admitted to a US Emergency Department and treated by bronchodilators, the use of mesh nebulizers (*n* = 715) was associated with fewer admissions to the hospital, shorter length of stay in the emergency department and a reduction in albuterol dose [45].

A note of caution, however, should be added concerning the viability of vibrating mesh technology. An unexpected 30% rate of premature cessation of aerosol production has been reported with the Aerogen mesh nebulizer [46]. Failure was associated with a wide range of residual volume averaging 21.3% of the charge compared with 1.5% of the charge when the nebulization was successful. In contrast, older jet nebulizers have been shown to be reliable with repeated use [47].

FUTURE RANDOMIZED CONTROLLED TRIALS

The reasons why the IASIS [5] and INHALE [6^a] multicenter RCTs failed, have been extensively analysed [38^a,48–50]: first, inclusion of patients with VAP caused by susceptible GNB; second, adjunctive therapy combining two even three antibiotics to treat VAP without shock and/or not caused by multiresistant GNB; third, use of inspiration-synchronized mesh nebulizers imposing the administration of low-dose amikacin; fourth, lack of optimization of mechanical ventilation during the nebulization phase; fifth, low-dose of nebulized amikacin based on high ELF concentrations reflecting rather bronchial than lung interstitial concentrations.

Future RCTs should compare the nebulization of amikacin and CMS with the parenteral administration of new cephalosporines/β-lactamase inhibitors in patients with VAP or VAT caused by XDR GNB. Ceftazidime avibactam and ceftolozane tazobactam

are active against *Enterobacteriales*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* producing carbapenemase and oxacillinase (a main challenge in Mediterranean countries), and cefiderocol or eravacycline are active against carbapenem-resistant *Acinetobacter baumannii*. If the GNB remains susceptible to aminoglycosides, nebulized amikacin should be compared with the intravenous cephalosporine/ β -lactamase inhibitor. If the GNB is resistant to aminoglycosides, nebulized CMS should be compared with the intravenous cephalosporine/ β -lactamase inhibitor. In VAP caused by documented pandrug resistant GNB, nebulized CMS should be compared with intravenous CMS (substitution therapy). Benefits that can be expected are a more rapid clinical cure, a reduction of duration of mechanical ventilation, a reduction of renal toxicity in case of substitution therapy using CMS, and a shorter duration of antibiotic administration. As lung deposition of nebulized amikacin decreases with lung aeration and severe forms of pneumonia [2,22], future RCTs should include patients at an early stage of VAP, which is often preceded by VAT. To design future RCTs, investigators should keep in mind that the European Medicines Evaluation Agency and the Food and Drug Administration approve drugs for new indications based on noninferiority and no more adverse events.

CONCLUSION

In future RCTs, high dose of nebulized amikacin (40 mg/kg/day) and nebulized colistimethate (three nebulizations of 5 million IU/day) should be delivered by nonsynchronized mesh nebulizers using volume controlled ventilation, optimized ventilator settings to limit inspiratory flow turbulences and appropriate sedation to avoid patient's asynchrony with the ventilator. Humidification and warming of inspired gas should be avoided during aerosol generation and therefore nebulization should not exceed 60 min. Monitoring of interstitial lung concentrations in patients treated with nebulized antibiotics is difficult as ELF concentrations are not reliable due to bronchial contamination. Main objective of future RCTs performed in patients with VAP and VAT caused by XDR and pandrug resistant GNB, should be the time to obtain clinical cure rate, the duration of mechanical ventilation and the duration of antibiotic administration. Short administration of high-dose nebulized amikacin or CMS (3–5 days) should be compared with 7-day administration of new cephalosporines/betalactamase inhibitors in patients with VAP or VAT caused by XDR GNB and to intravenous CMS in patients with VAP or VAT caused by pandrug resistant GNB.

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Members of the European Research Network for Nebulized Antibiotics in Ventilator-associated Pneumonia (ENAVAP)

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Conflicts of interest

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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

1. Rouby JJ, Bouhemad B, Monsel A, *et al.* Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies. *Anesthesiology* 2012; 117:1364–1380.
 2. Goldstein I, Wallez F, Nicolas-Robin A, *et al.* Lung deposition and efficiency of nebulized amikacin during *Escherichia coli* pneumonia in ventilated piglets. *Am J Respir Crit Care Med* 2002; 166:1375–1381.
 3. Lu Q, Girardi C, Zhang M, *et al.* Nebulized and intravenous colistin in experimental pneumonia caused by *Pseudomonas aeruginosa*. *Intensive Care Med* 2010; 36:1147–1155.
 4. Dhanani JA, Diab S, Chaudhary J, *et al.* Lung pharmacokinetics of tobramycin ■ by intravenous and nebulized dosing in a mechanically ventilated healthy ovine model. *Anesthesiology* 2019; 131:344–355.
- The experimental study in ventilated healthy ewes receiving nebulized tobramycin 400 mg, shows that epithelial lining fluid (ELF) concentrations grossly overestimate interstitial space fluid concentrations measured by microdialysis.
5. Kollef MH, Ricard JD, Roux D, *et al.* A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram negative ventilator-associated pneumonia: IASIS trial. *Chest* 2017; 151:1239–1246.
 6. Niederman MS, Alder J, Bassetti M, *et al.* Inhaled amikacin adjunctive to ■ intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative – pneumonia (INHALE): a double blind, randomised, placebo-controlled, phase 3, – superiority trial. *Lancet Infect Dis* 2020; 20:330–340.
- The INHALE multicentre double-blind randomized controlled study shows that the nebulization of amikacin 400 mg twice a day during 10 days using an inspiration-synchronized mesh nebulizer and combined with one or two intravenous antibiotics, is not superior to standard intravenous antibiotherapy to treat ventilator associated pneumonia caused by sensitive (50% of patients) or multidrug resistant (50% of patients) Gram-negative bacteria (GNB).
7. Stokker J, Karami M, Hoek R, *et al.* Effect of adjunctive tobramycin inhalation versus placebo on early clinical response in the treatment of ventilator-associated pneumonia: the VAPORISE randomized controlled trial. *Int Care Med* 2020; 46:546–548.
 8. Kalil AC, Metersky ML, Klompas M, *et al.* Executive summary: management of adults with hospital-acquired and ventilator associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63:575–582.
 9. Rello J, Solé-Leonart C, Rouby JJ, *et al.* Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect* 2017; 23:629–639.
 10. Torres A, Niederman MS, Chastre J, *et al.* International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J* 2017; 50:1700582.
 11. Leone M, Bouadma L, Bouhemad B, *et al.* Hospital-acquired pneumonia in ICU. *Anaesth Crit Care Pain Med* 2018; 37:83–98.
 12. Sweeney DA, Kalil AC. Why don't we have more inhaled antibiotics to treat ventilator-associated pneumonia? *Clin Microbiol Infect* 2019; 25:1195–1199.
 13. Rouby JJ, Sole-Leonart C, Rello J; European Investigators Network for Nebulized-Antibiotics in Ventilator-associated Pneumonia. Ventilator-associated pneumonia – caused by multidrug-resistant Gram-negative bacteria: understanding nebulization of – aminoglycosides and colistin. *Intensive Care Med* 2020; 46:766–770.
- The review on behalf of the members of the European Investigators Network for Nebulized Antibiotics for Ventilator-Associated Pneumonia shows that substitution therapy should be preferred to adjunctive therapy to show the benefit of nebulized aminoglycosides and colistin in ventilator-associated pneumonia (VAP) caused by multidrug resistant GNB and that mesh nebulizers should be preferred to jet nebulizers.
14. Rodvold KA, George JM, Yoo L. Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antibacterial agents. *Clin Pharmacokinet* 2011; 50:637–664.
 15. Morais CLM, Nascimento JW, Ribeiro AC, *et al.* Nebulization of vancomycin provides – higher lung tissue concentrations than intravenous administration in ventilated – female piglets with healthy lungs. *Anesthesiology* 2020; 132:1516–1527.
- The experimental study performed in ventilated healthy female animals shows that the nebulization of vancomycin 37.5 mg/kg results in vancomycin lung tissue concentrations 13-fold higher than those resulting from the intravenous administration of 15 mg/kg.

16. Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic mono therapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2014; 2014: CD003344.
 17. Arthur LE, Kizor RS, Selim AG, *et al.* Antibiotics for ventilator-associated pneumonia. *Cochrane Database Syst Rev* 2016; 10:CD004267.
 18. Abad CL, Kumar A, Safdar N. Antimicrobial therapy of sepsis and septic shock-when are two drugs better than one? *Crit Care Clin* 2011; 27:e1–e27.
 19. Magiorakos AP, Srinivasan A, Carey RB, *et al.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; 18:268–281.
 20. Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. *Am J Respir Crit Care Med* 2014; 189:1225–1233.
 21. Li Bassi G, Motos A, Fernandez-Barat L, *et al.* Nebulized amikacin and fosfomycin for severe *Pseudomonas aeruginosa* pneumonia: an experimental study. *Crit Care Med* 2019; 47:e470–e477.
 22. Elman M, Goldstein I, Marquette CH, *et al.* Influence of lung aeration on pulmonary concentrations of nebulized and intravenous amikacin in ventilated piglets with severe bronchopneumonia. *Anesthesiology* 2002; 97: 199–206.
 23. Goldstein I, Bughalo MT, Marquette CH, *et al.*, Experimental ICU Study Group. Mechanical ventilation-induced air-space enlargement during experimental pneumonia in piglets. *Am J Respir Crit Care Med* 2001; 163: 958–964.
 24. Dugemier J, Ehrmann S, Sottiaux T, *et al.* Aerosol delivery during invasive mechanical ventilation: a systematic review. *Crit Care* 2017; 21:264.
 25. Ari A, Dang T, Al Enazi FH, *et al.* Effect of heat moisture exchanger on aerosol drug delivery and airway resistance in simulated ventilator-dependent adults using jet and mesh nebulizers. *J Aerosol Med Pulm Drug Deliv* 2018; 31:42–48.
 26. Miller DD, Amin MM, Palmer LB, *et al.* Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med* 2003; 168:1205–1209.
 27. Rouby JJ, Monsel A. Nebulized antibiotics: epithelial lining fluid concentrations ■ overestimate lung tissue concentrations. *Anesthesiology* 2019; 131: 229–232.
- The editorial describes the data suggesting that ELF concentrations of nebulized antibiotics grossly overestimate interstitial lung fluid concentrations due to massive bronchial contamination of the fiberoptic during the bronchoalveolar lavage procedure.
28. Marchand S, Gregoire N, Brillault J, *et al.* Biopharmaceutical characterization of nebulized antimicrobial agents in rats: 3. Tobramycin. *Antimicrob Agents Chemother* 2015; 59:6646–6647.
 29. Landersdorfer CB, Nguyen TH, Lieu LT, *et al.* Substantial targeting advantage achieved by pulmonary administration of colistin methanesulfonate in a large-animal model. *Antimicrob Agents Chemother* 2016; 61:e01934–e1941.
 30. Boisson M, Jacobs M, Gregoire N, *et al.* Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. *Antimicrob Agents Chemother* 2014; 58:7331–7339.
 31. Luyt CE, Clavel M, Guntupalli K, *et al.* Pharmacokinetics and lung delivery of PDDS aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. *Crit Care* 2009; 13:R200.
 32. Kelly CA, Kotre CJ, Ward C, *et al.* Anatomical distribution of bronchoalveolar lavage fluid as assessed by digital subtraction radiography. *Thorax* 1987; 42:624–628.
 33. Rodvold KA, Hope WW, Boyd SE. Considerations for effect site pharmacokinetics to estimate drug exposure: concentrations of antibiotics in the lung. *Curr Opin Pharmacol* 2017; 36:114–123.
 34. Athanassa ZE, Markantonis SL, Fousteri MZ, *et al.* Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. *Intensive Care Med* 2012; 38:1779–1786.
 35. Solé-Leonart C, Rouby JJ, Blot S, *et al.* Nebulization of anti-infective agents in invasively mechanically ventilated adults: a systematic review and meta-analysis. *Anesthesiology* 2017; 126:890–908.
 36. Rello J, Rouby JJ, Sole-Leonart C, *et al.* Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients. *Clin Microbiol Infect* 2017; 23:640–646.
 37. Dhand R, Sohal H. Pulmonary drug delivery system for inhalation therapy in mechanically ventilated patients. *Expert Rev Med Devices* 2008; 5:9–18.
 38. Rouby JJ, Monsel A, Ehrmann S, *et al.* The INHALE trial: multiple reasons for a ■ negative result. *Lancet Infect Dis* 2020; 20:778–779.
- The letter describes the mechanisms by which inspiration-synchronized mesh nebulizers are unable to deliver appropriate dose of amikacin to patients with VAP.
39. Lu Q, Yang J, Liu Z, *et al.* Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. *Am J Respir Crit Care Med* 2011; 184:106–115.

Respiratory infections

40. Dugernier J, Reyckler G, Wittebole X, *et al.* Aerosol delivery with two ventilation modes during mechanical ventilation: a randomized study. *Ann Intensive Care* 2016; 6:73.
41. Mashat M, Clark BJ, Assi KH, Chrystyn H. In vitro aerodynamic characterization of the dose emitted during nebulization of tobramycin high strength solution by novel and jet nebulizer delivery systems. *Pulm Pharmacol Ther* 2016; 37:37e42.
42. Chang KH, Moon SH, Oh JY, *et al.* Comparison of salbutamol delivery efficiency for jet versus mesh nebulizer using mice. *Pharmaceutics* 2019; 11:192.
43. Liu CY, Ko HK, Fink JB, *et al.* Size distribution of colistin delivery by different type nebulizers and concentrations during mechanical ventilation. *Pharmaceutics* 2019; 11:459.
44. Galindo-Filho VC, Alcoforado L, Rattes C, *et al.* A mesh nebulizer is more effective than jet nebulizer to nebulize bronchodilators during noninvasive ventilation of subjects with COPD: a randomized controlled trial with radiolabeled aerosols. *Respir Med* 2019; 153:60–67.
45. Dunne RB, Shortt S. Comparison of bronchodilator administration with vibrating mesh nebulizer and standard jet nebulizer in the emergency department. *Am J Emerg Med* 2018; 36:641–646.
46. Gowda AA, Cuccia D, Smaldone GC. Reliability of vibrating mesh technology. *Respir Care* 2016; 62:65–69.
47. Skaria S, Smaldone GC. Omron NE U22: comparison between vibrating mesh and jet nebulizer. *J Aerosol Med Pulm Drug Deliv* 2010; 23:173–180.
48. Torres A, Motos A, Battaglini D, Li Bassi G. Inhaled amikacin for severe Gram-negative pulmonary infections in the intensive care unit: current status and future prospects. *Crit Care* 2018; 22:343.
49. Palmer LB. Why have trials of inhaled antibiotics for ventilator-associated infections failed? *Curr Opin Infect Dis* 2019; 32:163–168.
50. Rouby JJ, Monsel A, Leone M, *et al.* The IASIS, INHALE and VAPORISE trials. Reasons for a triple failure: study design, aminoglycosides dosing and technique of nebulisation. *Anaesth Crit Care Pain Med* 2020; 39:179–183.