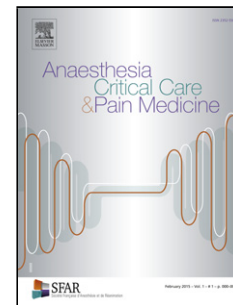


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**The IASIS, INHALE and VAPORISE trials. Reasons for a triple failure:
study design, aminoglycosides dosing and technique of nebulisation**

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Animal studies demonstrate that nebulised aminoglycosides and colimycin (polymyxin E) deliver higher antibiotic concentrations and greater bactericidal activity in the lung parenchyma infected by both sensitive and multidrug-resistant (MDR) Gram-negative bacteria (GNB) [1]. However, superiority of nebulised over intravenous (IV) aminoglycosides and colimycin in patients with ventilator-associated pneumonia (VAP) remains to be demonstrated. Clinical studies are sparse, heterogeneous in terms of aims and methods, and have enrolled a limited number of patients. As a consequence, recommendations from American and European academic societies for using nebulised antibiotics are limited, based on a weak level-of-evidence and sometimes divergent.

In 2016, the Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) edited Guidelines for VAP and suggested that VAP due to GNB, which are susceptible to only aminoglycosides or polymyxins, could be treated with both nebulised and IV agents [2]. In 2017, the European Society of Clinical Microbiology and Infectious Diseases published a position paper on the use of nebulised antibiotics in patients with VAP [3]. The panel of experts proposed: 1) to avoid the routine use of nebulised antibiotics (lack of evidence of their efficacy and risk of adverse respiratory events); 2) to use vibrating mesh nebulisers with optimised ventilator settings and specific ventilator

circuits to limit inertial impaction of aerosolised particles in the tracheobronchial tree and promote distal lung deposition [4]; 3) to perform randomised clinical trials (RCTs) of nebulised antibiotic therapy as part of a substitution approach to treatment of VAP caused by MDR GNB. In 2018, the French Society of Anaesthesia and Intensive Care Medicine and the French Intensive Care Society recommended nebulised colimycin and/or aminoglycosides in VAP caused by MDR GNB sensitive to colimycin and/or aminoglycosides, when no other antibiotics can be used (low level-of-evidence, strong agreement) [5]. In 2019, the 2016 American guidelines were extended and recommended nebulised amikacin or colimycin in patients with VAP due to GNB only susceptible to aminoglycosides or polymyxins on top of IV antibiotics, or in patients not responding to IV antibiotics alone, whether the responsible bacteria is MDR or not [6].

Between 2017 and 2020, three RCTs were published on the use of nebulised aminoglycosides combined with IV cephalosporins in VAP [7-9]: the IASIS (Aerosolized Amikacin and Fosfomycin in Mechanically Ventilated Patients with Gram-negative Pneumonia), INHALE (Inhaled amikacin adjunctive to IV standard-of-care antibiotics in mechanically ventilated patients with Gram-negative VAP), and VAPORISE (Adjunctive tobramycin inhalation vs placebo on early clinical response in the treatment of VAP) trials. The three RCTs failed to show benefit for nebulised aminoglycosides. They share methodological characteristics that likely explain the negative results.

Patients who may benefit from nebulised aminoglycosides combined to intravenous beta-lactams

The first concern is the identification of patients who may benefit from a combined nebulised and IV antibiotic therapy. Intravenous aminoglycosides or fluoroquinolones combined with β -lactams are not superior to IV β -lactams alone in VAP caused by sensitive GNB [10, 11]. According to the IDSA/ATS, VAP caused by or at risk of MDR pathogens is an indication for combining IV β -lactams with fluoroquinolones or aminoglycosides [2]. Therefore, European scientific societies recommended a combination of two IV antibiotics only for the initial empirical therapy since no study has shown that pursuing a therapy with two different classes of antibiotics remains beneficial [11,12]. The second concern is the penetration of IV antibiotics into the infected lung parenchyma. Most IV β -lactams and fluoroquinolones have an excellent pulmonary penetration. In contrast, IV aminoglycosides and colimycin have limited pulmonary diffusion, whereas high lung tissue deposition and parenchyma concentrations can be achieved using the nebulised route [1,13]. If a bitherapy with aminoglycoside is considered, it would therefore be logical to combine IV β -lactam and nebulised aminoglycoside.

As shown in Table 1, the IASIS, INHALE and VAPORISE trials shared common characteristics. The three were double-blind placebo-controlled RCTs. The proportion of VAP caused by MDR GNB varied from 0% (VAPORISE) to 49% (INHALE). A tritherapy was administered in the treatment group (one IV and two nebulised antibiotic in the IASIS trial and two IV plus one nebulised antibiotics in the INHALE and VAPORISE trials) whereas one or two IV antibiotics were administered in the placebo group. In the IASIS and INHALE trials, the VAP clinical cure rate in the placebo group was high, above 75% attesting of good efficacy of the IV therapy. Most of the identified VAP pathogens were sensitive to β -lactams and quinolones, therefore an additional benefit to add nebulised

aminoglycosides on top of IV antibiotics could reasonably not have been expected, explaining the failure of the trials.

An IV antibiotic therapy associating two antibiotics of different classes is likely to benefit to patients with VAP and septic shock [14] and, for that matter, is recommended by American and European guidelines [2,5,12]. Thus, nebulised aminoglycosides rather than a second IV antibiotic might be an attractive option in VAP with septic shock caused by sensitive GNB. Septic shock was an exclusion criterion in the IASIS study, whereas the proportion of patients with septic shock was not reported in the INHALE and VAPORISE studies. Therefore, septic shock cannot be considered as a rationale justifying the adjunction of nebulised aminoglycosides to IV antibiotic(s) in the IASIS, INHALE and VAPORISE trials. Another patient population may also benefit from nebulised aminoglycosides: patients with VAP caused by GNB resistant to beta-lactams and fluoroquinolones and still sensitive to aminoglycosides. In such patients, aminoglycosides should be nebulised as a substitution rather than adjunctive therapy. Future RCTs should select such populations of ventilated patients to show a benefit of nebulised antibiotics on VAP clinical cure rate and mortality.

Doses of nebulised aminoglycosides and conditions required to reach the infected lung parenchyma

In the IASIS and INHALE trials, nebulised doses of amikacin were low, ranging between 300 and 400 mg/day. Both bactericidal and post-antibiotic effects of aminoglycosides in GNB are concentration dependent, and peak interstitial concentrations determine bactericidal and the post-antibiotic effect duration [15]. As a consequence, high doses are recommended to treat VAP caused by sensitive or MDR GNB [16]. High doses are also justified by the fact that only a small proportion of aerosolised particles reach infectious sites in the lung.

As shown in the Fig. 1, the proportion of aerosol reaching the infected lung parenchyma ranges from 16 to 38% of the initial dose inserted into the nebuliser chamber [17]. The majority of aerosolised particles deposit on ventilator circuits, and tracheobronchial walls.

The retention in the nebuliser chamber is high, around 50 %, with jet nebulisers and low, less than 5 % with mesh nebulisers [17]. In vitro studies have clearly shown that humidification and warming of inspired gas by heat and moisture exchangers results in significant loss of aerosolised particles [18]. The effect of conventional humidifiers positioned on the initial part of the inspiratory limb remains debated. In vitro and in vivo data report an increased size of the aerosolised particles leading to a decrease in sputum deposition of nebulised aminoglycosides [19,20], whereas recent studies have shown that bronchial deposition of aerosolised salbutamol is not affected by the humidification and heating of inspired gas [21]. Another important issue is the optimisation of ventilator settings during the nebulisation phase. Limiting inspiratory flow turbulences decreases extrapulmonary deposition and promotes lung distal deposition [1,4,22]. It is therefore recommended to use specific ventilator settings during the nebulisation phase and to ensure a good coordination between the patient and the ventilator by using a short-acting sedative agent [4,22,23]. To decrease inspiratory flow turbulence and inertial impaction of aerosolised particles, volume-controlled ventilation should be preferred to pressure support ventilation. With a decelerating inspiratory flow, pulmonary deposition of radiolabeled particles is higher and extrapulmonary deposition lower than when a

constant inspiratory flow is used [23,24]. The prolongation of inspiratory time obtained by reducing the respiratory frequency to 12 cycles/min and fixing the inspiratory to expiratory ratio at 1:1, reduces turbulence and increases lung deposition [25]. Last but not least, an inspiratory pause of 20% promotes sedimentation of aerosolised particles in alveoli and decreases aerosol expiratory loss. Therefore, optimising ventilator settings during the nebulisation phase is strongly recommended [4]. Unfortunately, IASIS, INHALE and VAPORISE trials did not promote ventilator settings optimisation that could contribute to low deposition of the nebulised antibiotic.

The rationale for nebulising low dose aminoglycosides (600-800 mg per day of amikacin or 600 mg per day of tobramycin) resulted from a study performed in 28 patients with VAP treated by 800 mg of nebulised amikacin. In this study, epithelial lining fluid (ELF) amikacin concentrations were 20-fold greater than the minimum inhibitory concentration of sensitive GNB (4 mg/L) and 4-fold greater than the minimum inhibitory concentration of MDR GNB (128 mg/L) [26]. These high ELF concentrations were interpreted as reflecting high deep lung deposition and justified the administration of 800 mg per day in the INHALE trial. However, in a healthy ventilated sheep receiving a nebulised tobramycin dose of 400 mg (20 mg/kg), ELF concentrations were found 100 times greater than interstitial space fluid concentrations measured by microdialysis [13]. In a second group of animals receiving the same dose intravenously, ELF concentrations were found 10 times lower than concentrations measured in the interstitial space fluid. These data are highly suggestive of a massive contamination of the ELF concentrations by aerosolised particles present in the tracheobronchial tree [27]. As shown in the figure, the fiberscope used for sampling ELF as well as the successive aliquots instilled during the bronchoalveolar lavage are likely to be contaminated, and high ELF concentrations may reflect more bronchial rather than alveolar or interstitial concentrations.

Conclusions

Several reasons may explain the failure of the IASIS, INHALED and VAPORISE trials to show the clinical benefit of combining nebulised aminoglycosides to IV beta-lactams for treating VAP. 1) In critically ill patients with VAP mostly caused by sensitive GNB, IV beta-lactams are highly efficient, rendering unlikely an additional benefit from nebulised aminoglycosides. 2) The administration of low nebulised aminoglycoside doses, based on a false assumption of delivering high alveolar concentrations was likely associated with low lung deposition, and the lack of bactericidal effect at the infection site. 3) Ventilator settings should be optimised when administering nebulised antibiotics to achieve deep lung deposition, something that was not done in the three trials. Far from closing the door for nebulised antibiotics, the failure of IASIS, INHALE and VAPORISE trials calls for additional RCTs testing the superiority of high-doses nebulised (40 mg/kg) over IV (20 mg/kg) amikacin in VAP caused exclusively by MDR GNB and using optimised techniques of nebulisation. The primary aim of future RCTs could be a 15% increase in clinical cure rate of MDR VAP with nebulised aminoglycosides. If such a benefit is shown, then the impact on mortality could be studied in RCTs enrolling a very large number of patients with MDR Gram-negative ventilator-associated pneumonia.

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Table 1

Characteristics of the IASIS, INHALE and VAPORIS randomised controlled trials

Fig.1 Extrapulmonary and pulmonary deposition of nebulised aminoglycosides.