Other Therapeutic Modalities and Practices: Implications for Clinical Trials of Hospital-Acquired or Ventilator-Associated Pneumonia

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Direct delivery of antimicrobial agents to the site of infection via aerosolization may represent a valid option in patients with ventilator-associated pneumonia (VAP). Although promising and supported by the results of several recent investigations, antibiotic aerosolization to treat VAP has not yet entered the armamentarium for daily practice. Its potential efficacy should be first evaluated as an adjunctive therapy in a superiority trial in which all participants receive a standard-of-care intravenous regimen and then are randomized to receive additional antibiotics by aerosol or a placebo (eg, combination therapy trials). Inclusion criteria should specifically target patients with microbiologically proven VAP caused by potentially multidrug-resistant strains, because a clear benefit of aerosolized antibiotics is awaited in only this subpopulation. Until results of these trials are known, antibiotic aerosolization can be recommended only for treating patients with multidrug-resistant VAP, for which no effective intravenous regimen is available.

Ventilator-associated pneumonia (VAP) is responsible for approximately one-half of the infections acquired in the intensive care unit and represents one of the principal reasons for the prescription of antibiotics in this setting. Because insufficient dosing of antibiotics at the site of infection in patients with true bacterial infection may lead to clinical and microbiological failure, efforts to optimize pulmonary penetration of antimicrobial agents are warranted. Direct delivery of the drug to the site of infection via aerosolization may represent a valid option, providing that this technique actually allows improved lung tissue concentrations at the infected site. This mode of administration, by achieving high pulmonary antibiotic concentrations, could increase the antibacterial activity of concentration-dependent antibiotics, such as aminoglycosides, or restore the bactericidal activity of antibiotics against infections caused by pathogens with impaired drug susceptibility. Furthermore, by limiting systemic exposure, the administration of antibiotics characterized by a high systemic toxicity, such as polymyxins, can be allowed. This article will examine the potential benefits of aerosolized therapy for patients with VAP and/or hospital-acquired pneumonia (HAP) and the major issues that should be considered in the design of aerosol therapy trials for VAP.

Only a few studies have been conducted for evaluating aerosolized antibiotic delivery in patients receiving mechanical ventilation, either for prevention or for treatment of VAP [1–5]. Most of these trials were performed relatively long ago and essentially used jet nebulizers, which are not the most efficient devices for delivering an antimicrobial agent to the lower respiratory tract (see below). A meta-analysis including all comparative trials on prophylactic aerosolization (or tracheal instillation) of antibiotics for VAP prevention concluded that prophylactic administration of antibiotics via the respiratory tract was associated with fewer cases of intensive care unit–acquired VAP [6]. However, evidence from noncomparative studies and old trials suggest that this preventive strategy might lead to en-
hanced emergence of drug-resistant bacteria [6, 7]. Thus, the US Centers for Disease Control and Prevention and the Canadian Critical Care Society do not recommend the use of nebulized antibiotics for VAP prevention [8].

By pooling the results of the 5 randomized controlled trials that examined the potential benefit of inhaled or endotracheally instilled antibiotics for the treatment of patients with HAP and/or VAP, a statistically higher success rate was seen among patients receiving antimicrobial agents via the respiratory tract [4]. However, no difference in mortality could be documented, and the meta-analysis was based on a very limited number of patients. Of note, the bronchial deposition of aerosolized antibiotics might have rendered results of culture of endotracheal samples as false negative, which could have artificially increased the rate of success among patients randomized to receive aerosolized or endotracheally instilled antibiotics, casting some doubt on the validity of the results.

Several recent studies based on a new generation of nebulizers with improved technology have renewed the interest in aerosolized antibiotic therapy for patients with HAP and/or VAP [9–11]. In anesthetized piglets receiving prolonged mechanical ventilation for a severe experimental *Escherichia coli* bronchopneumonia, amikacin lung tissue concentrations were markedly higher after aerosolization than after intravenous administration [9]. Seventy-one percent of lung segments were found to be sterile after 2 nebulizations and 25 h of treatment, whereas result of cultures of lung segments were comparable in nontreated and intravenously treated animals. In a recent study using a new device with a vibrating plate and multiple apertures to produce an aerosol, Niederman et al [10] randomized 69 patients receiving mechanical ventilation who had VAP due to gram-negative pathogens to receive, in addition to intravenous antimicrobial therapy, 7–14 days of aerosolized amikacin (400 mg twice daily; *n* = 21), amikacin (400 mg once daily and placebo 12 h later [*n* = 26]), or placebo (twice daily; *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 [12, 13]. Moreover, aerosolized amikacin was well tolerated, without any severe adverse event, and patients who received amikacin twice daily required significantly less antibiotic therapy than did patients given placebo twice daily [10].

Data on the impact of antibiotic aerosolization active against gram-positive bacteria are scarce. In a placebo-controlled trial, Palmer et al [11] 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 on the basis of tracheal aspirate Gram stain results (vancomycin for gram-positive bacteria and gentamicin for gram-negative bacteria). Most of the patients had clinical signs of VAP and were receiving systemic antibiotic therapy at the time of randomization. Compared with placebo, antibiotic aerosolization led to faster resolution of clinical signs of pneumonia, fewer subsequent VAP episodes, less bacterial resistance and use of systemic antibiotics, and, perhaps, accelerated weaning from mechanical ventilation [11]. Aerosolized polymyxin has also been used increasingly, especially in the critical care setting, for treating patients with infections due to multidrug-resistant, gram-negative bacteria (mainly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*) [14, 15].

Thus, the results of recent investigations emphasize the potential contribution of antibiotic aerosolization to treat HAP and/or VAP as an efficient adjunctive therapy to intravenous antibiotics, but the clinical impact of such a strategy has not yet been definitively established. At present, antibiotic aerosolization can only be recommended for treatment of patients with multidrug-resistant VAP, for which no effective intravenous antibiotics are available. Indisputably, large prospective trials are needed to evaluate the potential usefulness of this therapeutic modality.

**HOW CAN THE DRUG BE OPTIMALLY DELIVERED TO THE LOWER RESPIRATORY TRACT?**

Although the clinical benefit of the aerosolization route has been poorly evaluated in humans, recent data have been published on this technique during mechanical ventilation and on the pharmacokinetics of aerosolized drugs, including regional distribution in normal and infected lung tissue. A nebulizer that generates 1–5-μm particles is required to optimize lung deposition of antibiotics during mechanical ventilation [16, 17]. Particles ≥5 μm are more likely to deposit in the ventilatory circuit or in the upper airways, whereas particles <1 μm are more likely to be eliminated during exhalation. During mechanical ventilation, laminar inspiratory flow provides better distal lung deposition than does turbulent flow. As a consequence, specific ventilator settings aimed at limiting inspiratory flow turbulences should be used during the aerosolization period. A volume-controlled mode should be preferred with the following ventilator settings: constant inspiratory flow, low minute ventilation, low respiratory frequency, and an inspiratory to expiratory ratio of 50%. Application of those recommendations together with recent improvements in aerosol technology has provided the possibility of delivery to the respiratory system of 30%–50% of the initial dose inserted in the aerosol chamber.

Jet nebulizers have serious drawbacks when used during mechanical ventilation. When operated continuously by an external gas flow, a high-speed turbulent gas flow is produced that promotes particle impaction on ventilator circuits, particularly during expiration. Ultrasonic nebulizers are more ap-
propriate for antibiotic aerosolization for several reasons: they are generally equipped with a large reservoir, they generate particles with a mass median aerodynamic diameter \(<5 \mu\)m through quartz vibrations, the aerosol is entrained in the inspiratory circuit by a low flow independent of the flow coming from the ventilator, and the aerosol is continuously generated, allowing the inspiratory administration of a bolus of aerosolized particles that accumulate in the inspiratory limb during the expiratory phase. Despite 15.6°–29.4°C heating of the solution, the stability of some antibiotics, such as aminoglycosides, colistin, and β-lactams, does not seem to be impaired. In vitro and in vivo data suggest that ultrasonic devices provide higher lung tissue deposition, compared with jet nebulizers [17, 18].

Recently, vibrating plate nebulizers have been developed and seem to also be appropriate for inhaled antibiotic therapy [13, 18]. The aerosol is generated by a ceramic vibrating element and a domed aperture plate through which the solution is micropumped and aerosolized. Vibrating plate aerosols have several potential advantages over ultrasonic nebulizers: at the end of aerosolization, the residual volume in the reservoir is negligible; the antibiotic solution is not heated; and the aerosol generation can be synchronized with inspiration, minimizing aerosol waste during exhalation.

Tissue Penetration of Aerosolized Antibiotics in Healthy and Infected Lungs

Little information is available on lung tissue concentrations of aerosolized antibiotics. In an animal model of prolonged mechanical ventilation mimicking the clinical conditions observed in critically ill patients, amikacin lung tissue concentration were 17-fold higher after aerosol administration than after intravenous administration [19]. The aerosol was homogeneously distributed between lobes, subcortical and perihilar lung regions, and dependent and nondependent lung segments. In all lung regions, tissue concentrations were higher than the minimum inhibitory concentrations of P. aeruginosa and A. baumannii. In the same experimental model, neither tissue nor systemic accumulation was observed after 4 days of daily aerosol administration [19].

Human and experimental VAP are characterized by multiple purulent pluses obstructing distal bronchioles. The resulting loss of lung aeration influences the penetration of inhaled antibiotics in the infected lung parenchyma. As demonstrated in piglets with severe E. coli pneumonia, the more severe the bronchopneumonia, the less the lung tissue deposition after aerosolization [9]. However, in that experimental model, it was still possible to reach effective concentrations of aerosolized antibiotics in the most severely infected lung regions [9]. Preliminary data obtained for patients with VAP corroborate these results [12]. Pulmonary infection increases permeability of the alveolar-capillary barrier and facilitates the diffusion of aerosolized antibiotics in the bloodstream. As a consequence, in patients with extended bronchopneumonia, antibiotic systemic bioavailability is markedly increased, thereby decreasing lung tissue concentrations and increasing the risk of toxicity [5]. The predominant renal clearance of aminoglycoside antibiotics also suggests a potential for elevated amikacin exposure after aerosol administration in patients with acute renal failure, which mandates careful monitoring of drug levels in such a context.

How Can the Benefit of Adjunctive Therapy Be Measured, and How Can Trials Be Designed to Show This Benefit?

At present, the standard of care for patients with VAP consists of administering adequate antibiotics by intravenous route as soon as possible, based of the pharmacokinetic and/or pharmacodynamic parameters and the drug susceptibility patterns of the responsible microorganisms [20, 21]. Clearly, the potential efficacy of aerosolized antibiotics in such a context should be first evaluated as an adjunctive therapy in a superiority trial in which all participants receive a standard-of-care intravenous regimen and then are randomized to receive additional antibiotics by aerosol or a placebo (eg, combination therapy trials).

Inclusion criteria in such a superiority trial should specifically target patients with microbiologically proven VAP caused by potentially multidrug-resistant strains. Although intravenous antibiotics can easily and rapidly sterilize lung tissue when the infection is caused by highly drug-susceptible pathogens, this is much more difficult to achieve when the infection is caused by multidrug-resistant strains, such as MRSA, P. aeruginosa, and other difficult-to-treat microorganisms, as shown in several studies [22–26]. Because aerosolized antibiotics might potentially facilitate the eradication of multidrug-resistant strains by achieving high antibiotic concentrations directly at the site of infection, a significant benefit is awaited in this subpopulation.

Use of only clinical criteria for enrollment of patients in clinical trials may potentially lead to inclusion of many patients with only proximal airway colonization and no true pulmonary infection and, thus, may dilute the potential impact of aerosolized antibiotics on VAP outcome [27]. Quantitative cultures of specimens obtained using bronchoscopic or nonbronchoscopic techniques, such as bronchoalveolar lavage and/or protected specimen brush, are more specific and could improve identification of patients with true VAP, avoiding this pitfall. Because trials evaluating aerosolized antibiotics preferentially target patients with a high probability of infection caused by potentially multidrug-resistant strains, baseline assessment before randomization should include a thorough appraisal of risk.
factors for difficult-to-treat microorganisms (ie, late-onset VAP, prior antimicrobial treatment, immunosuppression, and/or known airway colonization with such microorganisms), and microscopic examination of distal respiratory secretions with use of Gram staining. This strategy would permit randomization of only patients with a high probability of the disease of interest and, thus, avoid the potential bias that can result from secondary exclusions.

A key issue in trials investigating new treatment modalities in patients with VAP is how success or failure at test of cure is defined. Definitions should be carefully standardized and reproducible, avoiding any subjectivity. One possibility would be to use a modified Clinical Pulmonary Infection Score (CPIS) incorporating 5 parameters measured during follow-up (body temperature, leukocyte count, tracheal secretion characteristics, oxygenation ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, and pulmonary radiograph findings) as an objective marker of a good outcome when the score rapidly improves, in adjunction to the parameters that are usually used for defining success and failure, such as lack of need for additional antibiotics and survival [22, 28]. Duration of treatment by aerosol and intravenous antibiotics should also be determined a priori at the time at which test of cure is assessed. Failure at test of cure could then be defined as a composite of an increase in the CPIS on day 3, a failure of the CPIS to decrease by at least a certain number of points at the end of the predefined period of intravenous antibiotic therapy, continuation of intravenous antibiotic therapy after the predefined period, restart of intravenous antibiotic therapy before the test of cure, and all-cause mortality.

As discussed above, follow-up evaluation of the proximal airways with use of microbiological cultures is meaningless when aerosolized antibiotics are used, because their bronchial deposition may render results of culture of respiratory samples to be false negative although the lung parenchyma is still positive. Results of culture of endotracheal aspirate specimens should therefore not be part of the criteria used to define success in trials investigating aerosolized antimicrobial agents.

Among many patients with VAP, risk of relapse after discontinuation of antibiotics is high, especially among patients not weaned from the mechanical ventilator; thus, secondary end points should be evaluated after a fixed and sufficiently long period for all patients (eg, at 28 days) [29]. This is particularly relevant when evaluating aerosolized antibiotics, because a major advantage of this modality of treatment is dramatic reduction of the relapse rate among patients with VAP as a result of the suppression of bacteria colonizing the proximal airways by the very high antibiotic concentrations obtained at that level. These end points should include the number of mechanical ventilation-free days, the number of intensive care unit–free days, the number of antibiotic-free days, the clinical relapse rates, and all-cause mortality rates—all measured in the 2 arms at day 28. Because procalcitonin kinetic has been shown to have a high prognostic value in such a context, its use as a secondary end point in such trials may be warranted [30]. Obviously, the safety and tolerability of aerosolized antibiotics would also need to be carefully analyzed.

**CONCLUSION**

Although promising, antibiotic aerosolization for treatment of VAP has not yet entered the armamentarium for daily practice. The results of recent investigations emphasize its potential contribution as an interesting adjunctive therapy to intravenous antibiotics, but the clinical impact of such a strategy has not yet been definitively established. Before performance of randomized, double-blinded, multicenter studies assessing the impact of aerosolized versus intravenous antibiotics on clinical outcome of patients receiving mechanical ventilation who have lung infection, several issues must be addressed, particularly regarding how to optimize the delivery of aerosolized antibiotics and how to design a trial. At present, antibiotic aerosolization can be recommended only for treatment of patients with multidrug-resistant VAP, for which effective intravenously administered antibiotics are not available.

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