

Inhaled antibiotics for ventilator-associated pneumonia: treatment or prophylaxis?

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SUMMARY

Ventilator associated pneumonia (VAP) and Ventilator associated Tracheobronchitis (VAT) are the most common infections in patients admitted to the ICU who required mechanical ventilation. However, VAP is considered the leading cause of death related to infection in mechanically ventilated patients. Multidrug resistant (MDR) pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., Extended spectrum beta-lactamases and *Staphylococcus aureus* represent the most important group of pathogens causing VAP. This group of pathogens represents the biggest challenge in the management of patients with hospital-acquired infections around the globe. The high resistant rates and the lack of available antibiotics generate the need to identify mechanisms to deliver in the site of infection antimicrobial agents that could potentially lead to improved outcomes in patients requiring mechanical ventilation. In pneumonia, adjunctive therapies with aerosolized antibiotics are a high topic due to the difficulties associated with the management of patients with MDR pathogens that may be failing to systemic therapies. Recent guidelines from the Infectious Diseases Society of America and the American Thoracic Society recommend to evaluate the risk factors associated with MDR VAP. The most common risk factors associated with MDR VAP include previous antibiotic use within 90 days of hospitalization, septic shock at the time of VAP, Acute Respiratory Distress Syndrome (ARDS) preceding the VAP episode, five or more days of hospitalization prior to the occurrence of VAP, and acute renal replacement therapy prior to VAP onset. A survey that evaluated the indications for nebulized antibiotics in patients mechanically ventilated found that VAT was used in 67% of the time, followed by VAP in 64% of the patients. The antibiotics most commonly used in clinical practice for patients with VAP include aminoglycosides and colistin/polymyxin B. These antibiotics could be deposited in the lungs due to the small particle size (1-5 μ m) that made optimal for delivery to the lower airways and the lung parenchyma. The best aerosolized antibiotics are highly active, concentration-dependent, with post-antibiotic effect, delivered at high concentrations causing minimal toxicity, and with the ability to penetrate infected sputum, without being inactivated by other medications administered in the airway or systemically. In addition to the characteristics of the antibiotics, is the method of delivery, in which vibrating mesh nebulizers seem to have the best results compared to jet nebulizers.

Prevention of VAP

Nebulized antibiotics that could prevent VAP are something of great clinical interest. However, after reviewing the literature the IDSA/ATS clinical practice guidelines recommend not to use preventive antibiotics to avoid VAP. Several small studies suggested that the use of aerosolized antibiotics prevented VAP, but there is a valid concern of emergence of bacterial resistance during treatment. In small trials aerosolized antibiotics were able to reduce the rate of *P. aeruginosa* colonization without higher serious drug related toxicity.

Treatment of VAP

The IDSA/ATS clinical practice guidelines recommend for patients with VAP due to Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B) the use

of both inhaled and systemic antibiotics, rather than systemic antibiotics alone. In patients with HAP/VAP caused by *Acinetobacter* species that is sensitive only to polymyxins, the IDSA/ATS recommend intravenous polymyxin (colistin or polymyxin B). In patients with HAP/VAP caused by carbapenem-resistant pathogen that is sensitive only to polymyxins, the IDSA/ATS clinical practice guidelines recommend intravenous polymyxins (colistin or polymyxin B), and they suggest the use of adjunctive inhaled colistin. However, the guidelines recommend against the use of any form of antibiotic therapy for patients with VAT.

Adverse events

The major concern about the use of aerosolized antibiotics include side effects such as bronchospasm and the development of further resistant pathogens, particularly when used as prophylactic agents rather than as treatment of acute infection. Falagas et al reported in a meta-analysis from RCTs that aerosolized antibiotics reduce the rate of VAP, but had no effect on mortality and conclude that there is insufficient evidence to assess the effect on bacterial colonization. However, this analysis included older prophylactic studies with different delivery systems and different rates of baseline incidence of MDR pathogens that may not represent the current epidemiology and ecology of VAP patients.

Conclusion

Therefore, it is recommended that aerosolized antibiotics be use as adjunctive therapy in mechanically ventilated patients with infections due to highly resistant pathogens to the majority of available systemic antibiotic agents.

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