Inhaled antibiotics: strengths and fears

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AIMS

To review the current clinical data available about efficacy of this mode of delivery and the potential benefits

• Why may inhaled antibiotic therapy be an important mode of treating ventilator-associated infections?
• Are there Improved outcomes in treatment of respiratory infections with inhaled therapy?
• Is there an effect on bacterial resistance?
• Can systemic antibiotic use be reduced?

SUMMARY

Ventilator-associated pneumonia (VAP) remains the leading cause of death related to infection in critically ill patients and more than 50% of the antibiotic use in the intensive care unit is administered for this infection. The morbidity and mortality related to respiratory infections remain significant despite reports of a zero incidence of VAP in some publications.

Increasing microbial resistance of Gram-negative pathogens in the ICU is a major challenge for critical care physicians because it is driven primarily by systemic antibiotics used to treat infections in these critically ill patients. Rates of resistance correlate directly with amounts of antibiotic used. The increasing difficulty of treatment of multidrug-resistant organisms (MDROs) is occurring at a time when there is a dearth of new systemic antibiotics available. In the past 40 years, there have been only 2 new available classes of antibiotics introduced, oxazolidinones (linezolid) and the cyclic lipopeptides (daptomycin). Both these antibiotics are used for the treatment of gram-positive organisms, leaving options for resistant gram-negative organisms even more limited. This shrinking armamentarium of systemic antibiotics in a sea of rising minimum inhibitory concentrations (MICs) compels us to examine the current data on the efficacy of inhaled antibiotics.

History of inhaled antibiotics

The earliest studies of topical antibiotic therapy were driven by the same clinical problem that plagues us more than 40 years later. Resistant Gram-negative organisms, in particular Pseudomonas species, were causing respiratory infections in intubated patients and patients with tracheostomy, and clinical response to intravenous (IV) therapy was poor. At that time, aminoglycosides given intravenously were the primary treatment. These antibiotics have poor lung penetration and treatment failure occurred in up to 60% of patients. This led to the use of targeted therapy to the lung which could provide increased concentrations. These early trials were promising. Early investigations used endotracheal instillation of the antibiotic. The concentrations of the aminoglycoside in the bronchial secretions were shown to be 1000-fold higher than the serum concentrations of patients receiving IV therapy, and bactericidal activity was more than 30-fold greater than that in serum. These investigators had also demonstrated the clinical benefit from the instillation of aminoglycosides for
the treatment of bronchial infections in intubated patients, which is now called ventilator-associated tracheobronchitis (VAT), as well as in bronchopneumonia.

**Gamechanger**

But a large prophylactic trial of atomized polymyxin in the 1970’s raised concerns that inhaled therapy would lead to highly resistant organisms causing life threatening pneumonia. Little attention was paid to further exploring the use of this mode of delivery for almost 40 years. Now that the treatment of MDRO has become increasingly problematic, targeted therapy to the lung is being revisited.

**Rationale for using inhaled antibiotics**

The theoretical reasons for using targeted antimicrobial therapy in mechanically ventilated patients are compelling. With proper delivery, the drug is delivered directly to the site of infection, concentrations in the lung are high, and systemic toxicity is minimized. Furthermore, the microflora of the gut is unlikely to be altered, thus reducing the emergence of MDRO and infection with Clostridium difficile. The high antibiotic concentrations achieved with targeted therapy far exceed the MIC and result in a large ratio of maximum concentration to MIC, an index shown to be important for eradication of these organisms in the milieu of thick purulent secretions, biofilm, and diminished mucociliary clearance. Conversely, if only IV therapy is used and concentrations are not bactericidal, biofilm formation may be induced, making the infections even harder to eradicate. There is some early evidence that the use of these aerosolized agents with systemic antibiotics may reduce the need for additional systemic antibiotic added for poor response to initial treatment.

**Devices**

Devices used for aerosolized delivery have never been held to the same rigorous FDA regulations to which medications are subject. Medications given intravenously with appropriate attention to dosing are not subject to large variability of concentrations in the blood stream. Unlike IV therapy, whereby dose is primarily related to concentration in the blood and the blood flow within the infected organ, inhaled delivery is affected by particle size, humidity, flow rates and multiple other factors. Furthermore delivery devices and mechanical ventilators are designed with increasingly complex interactive technology that may alter drug deposition. Devices have evolved from a simple syringe or atomizer to jet and ultrasonic nebulizers, vibrating mesh technology, and, in animal studies, magnetic field–guided aerosols with superparamagnetic iron oxide nanoparticles in the solutions to be aerosolized.

**Device/drug combination**

Despite all these variables that may influence lung dose and site of deposition, there are no specific standards for aerosolized drug delivery in intubated patients. Because of the complexity of all these variables, currently available proprietary drugs are sold as a combination drug and device product to optimize the delivery of the antimicrobial.

In this session we will go over the currently available clinical data and emphasize both the merits of this mode of delivery as well as the specific areas where more research is needed.

**REFERENCES**

**Systematic reviews and meta-analyses**


Reviews on the use of inhaled antibiotics in ventilator patients