Inhaled Antibiotics for Hospital-Acquired and Ventilator-Associated Pneumonia

To the Editor—We would like to comment on the hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) guidelines recently published in *Clinical Infectious Diseases* [1]. These guidelines recommend inhaled antibiotics for patients with VAP due to gram-negative bacilli susceptible only to aminoglycosides or polymyxins and for patients not responding to intravenous (IV) antibiotics. It also suggests adjunctive inhaled colistin for HAP or VAP due to *Acinetobacter* strains susceptible only to polymyxins. Several important considerations related to inhaled antibiotics were not addressed.

In the United States, only 3 inhaled antibiotics are approved by the US Food and Drug Administration (FDA) and commercially available: aztreonam, tobramycin solution, and tobramycin powder. One additional product, colistin dry powder for inhalation, is approved by the European Medicines Agency. None of these products are approved for the treatment of HAP or VAP (Table 1). The limited number of available antibiotics for inhalation, along with the increasing incidence of respiratory infections caused by multidrug-resistant (MDR) organisms, has prompted the practice of using IV antibiotics for inhaled administration. We believe this practice should generally be discouraged.

Inhalation and IV formulations of the same drug are not interchangeable. Inhalation of antibiotics not formulated for this route of administration has led to adverse effects, including death [2–5]. Currently approved inhaled antibiotics have been designed to optimize delivery to the lung. This has been achieved through modification of various properties for enhanced lung deposition [6]. The formulation should also be paired with the appropriate inhaler or nebulizer to ensure proper particle size for lung distribution and to provide dose consistency. Commercially available inhaled antibiotics have also been formulated for improved tolerability. For example, IV aztreonam contains arginine that, when administered via inhalation, has been associated with declining lung function in patients with cystic fibrosis. For this reason, aztreonam inhalation solution was formulated without arginine [7]. Preservatives contained in some IV antibiotics can also contribute to airway irritation [8].

The administration of inhaled antibiotics in mechanically ventilated patients requires specialized skill, often requiring adjustments to ventilator settings to optimize drug delivery and ventilator performance. These adjustments may also necessitate increased sedation that may, in turn, prolong mechanical ventilation and negatively impact patient outcomes [9].

Another concern is the potential for loss of drug into the environment with nebulized therapy, leading to inadvertent exposure to antibiotics by healthcare personnel. This could lead to adverse effects such as bronchospasm in healthy individuals. Environmental distribution of antibiotics could also lead to altered microbiota among exposed individuals as well as environmental spread of antibiotic-resistance genes. The latter concern is significant because many nebulized antibiotics, such as amikacin and colistin, have important clinical applications for treating MDR infections.

Evidence supporting the use of inhaled antibiotics for HAP and VAP is limited, consisting mostly of retrospective and observational studies [10]. We recommend that off-label use of inhaled antibiotics be evaluated for approval by the healthcare facility's pharmacy and therapeutics committee in collaboration with the respiratory care department. Consideration should be given to providing off-label inhaled antibiotics for use under an FDA investigational new drug application and with approval from the healthcare facility's institutional review board. Larger studies to evaluate the safety and efficacy of inhaled antimicrobial therapy for the treatment of pneumonia are needed.

Table 1. Current Commercially Available Inhaled Antibiotics

Antibiotic	Indication	Approving Agency	Availability in the United States
Aztreonam for inhalation solution	To improve respiratory symptoms in cystic fibrosis patients aged ≥7 years with *Pseudomonas aeruginosa*	FDA	Available
Tobramycin inhalation solution	Management of cystic fibrosis patients aged ≥6 years with *Pseudomonas aeruginosa*	FDA	Available
Tobramycin inhalation powder	Management of cystic fibrosis patients aged ≥6 years with *Pseudomonas aeruginosa*	FDA	Available
Colistimethate dry powder for inhalation	Management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged ≥6 years	European Medicines Agency	Not available

Abbreviation: FDA, US Food and Drug Administration.

Note

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