Aerosolized Antibiotics in the Intensive Care Unit

Lucy B. Palmer, MD

KEYWORDS

- Aerosolized antibiotics
- Ventilator-associated tracheobronchitis
- Ventilator-associated pneumonia • Bacterial resistance

Ventilator-associated pneumonia (VAP) is the leading cause of death related to infection in critically ill patients and accounts for more than 50% of the antibiotic use in the intensive care unit (ICU).[1–8] The morbidity and mortality related to respiratory infections remain significant. In a 2010 review of clinical outcomes of health care–related infection in European ICUs, 4457 patients were identified with VAP caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, or *Staphylococcus aureus*.[9] The excess risk of death from VAP (hazard ratio) was 1.7 (95% confidence interval [CI], 1.4–1.9) for drug-sensitive *S aureus* and 3.5 (95% CI, 2.9–4.2) for ceftazidime-resistant *Pseudomonas*. Increasing microbial resistance in the ICU is a major challenge for physicians because it is driven primarily by systemic antibiotic use. Rates of resistance correlate directly with amounts of antibiotic used.[6,10–12] 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. Furthermore, few new antibiotics are in development in the pipelines of the pharmaceutical industry. In the past 40 years, there have been only 2 new 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.[13–15] This shrinking armamentarium of systemic antibiotics in a battlefield of rising minimum inhibitory concentrations (MICs) compels us to examine the current data on the efficacy of aerosolized antibiotics. At present, the American Thoracic Society (ATS) guidelines suggest, "adjunctive therapy with an inhaled aminoglycoside or polymyxin for MDR Gram-negative pneumonia should be considered, especially in patients who are not improving on systemic therapy"[1] and cite 1 nonrandomized trial[16] because these guidelines were written in 2005. In this article, the author reviews the literature with emphasis on the most recent data concerning the following questions:

1. What is the evidence that aerosolized antibiotics result in improved outcome in the treatment of respiratory tract infection in mechanically ventilated patients in the ICU?
2. What should be the indication for aerosolized antibiotics?
3. Are there data available that suggest this method of delivery decreases or increases the emergence of MDROs?

The earliest studies of topical antibiotic therapy were driven by the same clinical problem that plagues us more than 40 years later.[17–21] 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

Disclosure: Dr Lucy B Palmer and her associate Dr Gerald Smaldone have a patent with the Research Foundation of SUNY Stony Brook for the use endobronchial antibiotics, which is licensed to Nektar Therapeutics.
Pulmonary, Critical Care and Sleep Division, SUNY at Stony Brook, HSC T17-040, Stony Brook, NY 11794-8172, USA
E-mail address: lbpalmer@notes.cc.sunysb.edu

Clin Chest Med 32 (2011) 559–574
doi:10.1016/j.ccm.2011.05.012
0272-5231/11/$ – see front matter © 2011 Elsevier Inc. All rights reserved.

chestmed.theclinics.com

treatment of gram-negative organisms, and treatment failure occurred in up to 60% of patients.[19–21] These poor outcomes were thought primarily to be caused by poor penetration of the aminoglycosides into the lung, so the methods of increasing the concentration in the lung were studied.

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.[20] 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.[19,20] At that time the investigators wrote, "endotracheal administration might thus represent the ideal adjunct to systemic antimicrobial therapy for bronchopneumonina." Despite these initial positive studies in the 1970s, there have been no large multisite clinical randomized trials of aerosolized antimicrobials for the treatment of respiratory infection in mechanically ventilated patients.

Why have advances in antibiotic delivery to the lung in ventilated patients progressed so slowly? There have been several drugs approved for patients with cystic fibrosis, but almost all aerosol treatments of VAT or VAP have been off label. There has been only one phase 2 randomized controlled trial (RCT) in ventilated patients for VAP.[22] This delay of research and development in aerosolized antibiotics for the ventilated patient was primarily driven by the negative results of an investigation of topical antibiotics used for the prevention of pneumonia in critically ill patients in the 1970s.[23,24] It is worthwhile reviewing this work because the data teach the importance of methods of delivery and the duration of prophylactic or treatment protocols.

Two seminal studies came out in 1975 using polymyxin B, a potent cationic cyclic polypeptide antibiotic against gram-negative organisms.[23,24] In a preliminary observational study, all patients in the ICU, whether intubated or not, were given prophylactic polymyxin B. The polymyxin B was administered via an atomizer to the oropharynx or, if the patients were intubated, for 2-month cycles with both atomizer and instillation, alternating with 2-month cycles with no polymyxin B. A total of 744 patients were enrolled.[23] The results were encouraging because both colonization rates with *Pseudomonas* and the incidence of VAP were decreased. The same investigators then published a follow-up study,[24] which gave the same regimen in a 7-month trial to 292 patients, but now the antibiotic was given continuously to all the patients without any 2-month cycles off the antibiotic. This study had markedly different results. There was an increase in the incidence of VAP with organisms resistant to polymyxin, including *Flavobacterium*, *Serratia*, and *Streptococcus* species, and the mortality from VAP was 64% (7 of the 11 patients who acquired pneumonia during the study died). The investigators stated that continuous topical antibiotics were a dangerous form of therapy. These results led to reluctance to further study topical therapy, and there were no significant advances in aerosolized antibiotic treatment trials for nearly 30 years. In retrospect, analysis of the design of this trial predicts the development of resistant organisms. As the investigators themselves noted, it was the continuous use of polymyxin given to all patients, all the time, whether intubated or not, that was problematic. Also, dose and deposition site were not well defined with the use of an atomizer and instillation. All these factors may have contributed to the emergence of resistant organisms.

Now that the treatment of MDRO has become increasingly problematic, targeted therapy to the lung is being revisited. The first RCTs in targeted delivery to the lung were treatment protocols in spontaneously breathing patients with cystic fibrosis. In these patients with chronic airway infection, aerosolized antibiotics are a mainstay of therapy, and investigations have shown decreased hospitalizations and preservation of lung function.[25,26] These studies have led to 2 Food and Drug Administration (FDA)-approved aerosolized antibiotics with defined delivery devices.

Mechanically ventilated patients' airways and respiratory infections share many attributes of those of patients with cystic fibrosis once VAT is present. Both groups present an airway epithelium that is injured and inflamed with poor mucociliary clearance, and, in addition, it is well known now that the endotracheal tube develops a biofilm similar to that found in the airways of patients with cystic fibrosis.[27,28] Biofilm may also be present in ventilated patients' airways (**Fig. 1**). Furthermore, increasingly resistant *Pseudomonas* species and *S aureus* are important pathogens in both groups. These similarities suggest that the aerosolized delivery of antimicrobial therapy should be of benefit for mechanically ventilated patients as well.The off-label, FDA-approved, and phase 2 trial drugs used for these 2 groups of patients are shown in **Box 1**. Toxicities associated with the use of these antibiotics are shown in **Box 2**.

Download English Version:

https://daneshyari.com/en/article/4207348

Download Persian Version:

https://daneshyari.com/article/4207348

Daneshyari.com