Review of Use of Inhaled Aminoglycosides Outside of Cystic Fibrosis

Madeleine King, PharmD
April Yarbrough, PharmD, BCPS

Inhaled antimicrobials have become a mainstay for the treatment of pulmonary exacerbations in patients with cystic fibrosis (CF) and have led to improved clinical outcomes.[5] The use of nebulized aminoglycosides in patients with CF has been shown to be safe and effective.[1] However, their role in treatment for other respiratory conditions has not been established. Over the past few decades, inhaled antimicrobials have been used for indications such as ventilator associated pneumonia and tracheitis.[1,3,4,5] The rationale for use in these patients is maximizing drug delivery directly to the site of infection while minimizing potential for systemic side effects.[5] However, safety and efficacy profiles for nebulized antimicrobials have not been established outside of their use in cystic fibrosis.[1]

Guidelines published in 2016 for the management of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) by the Infectious Diseases Society of America and the American Thoracic Society contain recommendations for use of inhaled antimicrobials. These guidelines recommend the use of inhaled antibiotics in conjunction with systemic antibiotics for patients with VAP due to Gram-negative bacilli that are only susceptible to aminoglycosides or polymyxins. This document also concluded that inhaled antibiotics could be used as a treatment of last resort in patients not responding to intravenous antibiotics. The basis for these recommendations included five randomized controlled trials and four observational studies. These studies found that addition of inhaled antibiotics to systemic antibiotics in these scenarios improved clinical cure rates but had no definitive effects on mortality. The adult HAP and VAP guidelines do not recommend the use of inhaled antimicrobial monotherapy. Therefore, inhaled antimicrobials should only be used for VAP in conjunction with systemic antibiotics if a patient is not responding or in cases of infection with resistant pathogen that only displays susceptibility to aminoglycosides or colistin.[3]

One concern with the widespread and inappropriate use of inhaled antimicrobials is the development of antibacterial resistance. Pathogens such as *Pseudomonas, Stenotrophomonas,* and *Acinetobacter* have a high potential for the intrinsic resistance or the development of resistance on exposure to sub-therapeutic drug levels.[2] Of the 9 studies evaluated that utilized adjunctive inhaled antimicrobials in the 2016 HAP and VAP IDSA guidelines, only 2 studies addressed microbiological resistance. They found no difference in development of antibiotic resistance in those groups treated with both systemic and inhaled antibiotics.[3] Additional meta-analyses and Cochrane reviews of the use of inhaled antibiotics for non-CF bronchiectasis have not revealed an increase in resistance. Most of the data that does report increased resistance with inhaled antibiotic use has come from the CF population who have been treated with extensively long courses.[6]

Tracheitis is another disease state where inhaled aminoglycosides are being used. However, currently, there are no guidelines for the treatment for bacterial tracheitis. The CDC defines tracheitis as a positive culture obtained by tracheal aspirate or bronchoscopy along with at least

two of the following other clinical signs and symptoms with no other recognizable cause: fever, cough, new or increased sputum production, rhonchi, and wheezing. Additionally, the CDC requires there to be no evidence of pneumonia on a chest X-ray. Pseudomonas is one of the most commonly isolated organisms from trach aspirates.[1] Inhaled aminoglycosides are sometimes utilized for tracheitis treatment with the intent to achieve bactericidal activity directly at the site of infection against an organism that can often develop resistance to systemic antibiotics.[1,4] In a retrospective review of 34 pediatric rehab patients who received inhaled gentamicin or tobramycin for 1 to 3 weeks for bacterial tracheitis, patients were noted to have a resolution of tracheitis after a mean of 3 days of treatment. However, tracheitis has recurred or relapsed in most patients within several weeks of completion of the inhaled aminoglycoside treatment. In addition to the retrospective nature, this study did not assess the potential for development of antimicrobial resistance.[1]

In conclusion, the use of inhaled antimicrobials outside of the cystic fibrosis population is not supported by the data. Current recommendations for VAP include the use of inhaled aminoglycosides only for limited indications in conjunction with systemic antibiotics.[3] The benefits of inhaled aminoglycosides for the treatment of tracheitis have not been determined in prospective, randomized controlled trials. Although the direct delivery of the drug to the site of infection is potential benefit of the inhaled aminoglycoside therapy, their use outside of cystic fibrosis should be limited because of the lack of clinical evidence.

References

1. Chen JK, Martin-McNew BL, & Lubsch LM. Nebulized gentamicin as an alternative to nebulized tobramycin for tracheitis in pediatric patients. *J Pediatr Pharmacol Ther.* 2017 Jan-Feb; 22(1): 9 – 14.
2. Ghannam DE, Rodriguez GH, Radd II, et al. Inhaled aminoglycosides in cancer patients with ventilator-associated Gram-negative bacterial pneumonia: safety and feasibility in the era of escalating drug resistance. *Eur J Clin Microbiol Infect Dis.* 2009 Mar; 28(3): 253 – 9.
3. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1 1;63(5):e61-e111.
4. Maselli DJ, Keyt H, Restrepo MI. Inhaled antibiotic therapy in chronic respiratory diseases. *Int J Mol Sci.* 2017 May; 18(5): 1062.
5. Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. *Ann Am Thorac Soc.* 2014 Mar; 11(3): 425-434.
6. Wenzler E, Fraidenburg DR, Scardina T, et al. Inhaled antibiotics for gram-negative respiratory infections. *Clin Microbiol Rev.* 2016 Jul; 29(3): 581 – 632.