Aerosolized antibiotics: the past, present and future, with a special emphasis on inhaled colistin

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Inhaled antibiotics, such as TOBI (a tobramycin solution), gentamicin, colistin and aztreonam lysine (Cayston) have been effectively administered with safety and efficacy in patients with cystic fibrosis and bronchiectasis. In addition, inhaled antibiotics have been administered with safety and efficacy for the prevention and treatment of patients with ventilator-associated tracheobronchitis or pneumonia due to multidrug-resistant Gram-negative bacteria (mainly *Pseudomonas aeruginosa* or *Acinetobacter baumannii).* Original studies showed that inhaled colistin resulted in treatment success of nosocomial pneumonia or ventilator-associated pneumonia (VAP) due to multidrug-resistant Gram-negative bacteria. However, although aerosolized colistin seems to be safe and effective for the eradication of *P. aeruginosa* and the management of pneumonia in cystic fibrosis patients, hospital-acquired pneumonia and VAP due to multidrug-resistant Gram-negative bacteria, it is still unclear if it provides additional benefit in all-cause hospital mortality, or VAP-related mortality rates. For this reason, randomized controlled trials (RCTs) are necessary to validate the efficacy and safety of aerosolized colistin, mainly in patients with nosocomial pneumonia or VAP. In addition, RCTs are necessary to determine the appropriate inhaled colistin dose and the optimal delivery device.

Keywords: aerosolized antibiotics, aerosolized colistin, inhaled colistin, inhaled polymyxins

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Dioskurides, (ca 40 – 90) an ancient Greek physician, pharmacologist and botanist is considered the father of aerosolized medicine. Many medications have been administered by inhalation such as bronchodilators, steroids, adrenaline, milrinone, prostacyclin analogs, nitric oxide (NO), xylocaine, morphine, nitroglycerin, IFN-A, the majority of antibiotics (penicillin, ceftazidime, aztreonam, ciprofloxacin, aminoglycosides, streptomycin, polymyxins and vancomycin), antiviral agents such as ribavirin and zanamivir as well as pentamidine and amphotericin.

In modern medicine, the first reports on administration of antibiotics via the respiratory tract (nebulized – aerosolized) in clinical practice were made in 1950s [1,2]. TOBI (a tobramycin solution for inhalation) is the first antibiotic that was approved by the Food and Drug Administration (FDA) on December 1997 as an inhaled antibiotic for the treatment of respiratory tract infections due to *Pseudomonas aeruginosa* in cystic fibrosis patients [3]. Later on, TOBI was licensed in Europe and has been administered in cystic fibrosis patients with early *P. aeruginosa* colonization [4]. Apart from tobramycin, inhaled gentamicin or colistin has also been administered in children with cystic fibrosis [5]. Lately, in February 2010, Gilead Sciences, Inc. (Foster City, CA, USA) received FDA approval for aztreonam lysine for inhalation (Cayston) for improvement of

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respiratory symptoms in cystic fibrosis patients above 7 years old with *P. aeruginosa* infection. The drug is administered as 75 mg dose within 2 – 3 min, three times daily [6,7].

Apart from the maintenance treatment of patients with cystic fibrosis, inhaled antibiotics have been administered with safety and efficacy for the prevention and treatment of respiratory tract infections in patients with bronchiectasis or ventilator-associated tracheobronchitis or pneumonia due to multidrug-resistant Gram-negative bacteria. A meta-analysis including five randomized controlled trials (RCTs) showed that the administration of antimicrobials via the respiratory tract (either inhaled or endotracheally instilled) was associated with better outcome in non-cystic fibrosis patients with nosocomial pneumonia. There were no statistically significant differences between therapeutic regimens regarding all-cause mortality, microbiological success and toxicity. The author suggested that a combination of aerosolized and systematic antimicrobial treatment may be considered, especially in patients slowly responsive or unresponsive to standard therapy [8]. The formation of a biofilm on the inner surface of the endotracheal tubes is considered as an important factor for the development of ventilator-associated pneumonia (VAP). The intravenous antibiotic administration results in low antibiotic concentrations within the airway lumen thus facilitating the biofilm formation. By contrast, inhaled antibiotics achieve high local antibiotic concentrations that suppress biofilm formation and inhibit bacterial growth within the biofilm [9,10].

Inhaled antimicrobial therapy is an attractive alternative to systemic administration because it is associated with main advantages such as ability to achieve high concentrations of antimicrobials in sputum, the bronchial and pulmonary tissue the alveolar macrophages and in the epithelial lining fluid at the site of respiratory tract infection; and ability to reach minimum inhibitory concentrations (MICs) at lower dosages compared with intravenous formulations. In addition, this route of administration is often associated with superior penetrability and bactericidal efficacy at the infection level and has the advantage of a targeted delivery of lower doses of antibiotics compared with those used with parenteral administration. It is also associated with little systemic absorption, thereby minimizing systemic toxicity [11]. The most common adverse effects are bronchospasm and cough [8]. Despite previous concerns regarding the association of emergence of antimicrobial resistance with aerosolized antibiotics, recent studies did not support such concerns.

The success of aerosolized antimicrobial therapy mainly depends on the administered antibiotic, its aerosolized formulation and the delivery system [12]. Newer inhaled drug delivery systems enable inhaled administration of high antibiotic concentrations to small airways. The choice of nebulizer remains an important factor. Jet nebulizers are the most widely used in intensive care units since they are disposable and produce sufficient particle size. However, ultrasonic nebulizers can perform better than jet nebulizers in producing better particle size and shorter administration times. On the other hand, ventilators used for antibiotic delivery in patients with VAP should have a flow rate greater than 6 l/min and they should nebulize during inspiration exclusively.

During the last decade, inhaled colistin has been effectively used for the treatment of hospital-acquired pneumonia or VAP due to multidrug-resistant Gram-negative bacteria, mostly *Pseudomonas* and *Acinetobacter baumannii*, in order to improve lung parenchyma penetration and achieve sufficient antibiotic concentrations locally [13,14]. However, it should be mentioned that no study has been performed to assess colistin concentrations in the pulmonary epithelial lining fluid, which is the target site of antibiotics for the treatment of pneumonia/VAP. The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) HAP guidelines recommend that adjunctive therapy with inhaled aminoglycoside or colistin should be considered in patients with multidrug-resistant Gram-negative pneumonia, especially for those who are not improving (Level III) [15]. The recommendations by the Society of Infectious Diseases Pharmacists are similar [16]. However, it should be mentioned that aerosolized antibiotics have not been proven to have value in the therapy of VAP in general (Level I). Furthermore, this type of treatment has not yet been approved by the FDA.

The author of this review article presents several studies showing the efficacy and safety of inhaled colistin (sulfate or colistimethate sodium, CMS) in patients with cystic fibrosis, non-cystic fibrosis bronchiectasis, hospital-acquired pneumonia (HAP) or VAP [17]. Both formulations of colistin (colistin sulfate and CMS) have been used for aerosol treatment. However, CMS is associated with fewer adverse effects such as chest tightness, throat irritation and cough compared with colistin sulfate [18]. CMS powder should be diluted for nebulization in 4 ml of sterile normal saline 0.9% and should be administered as soon as possible after dilution.

Previous studies showed that the administration of colistin via the respiratory tract was associated with significant improvement of VAP outcome and the use of inhaled colistin was an independent predictor of infection cure [14,19,20].

In conclusion, the role of inhaled colistin seems to be clear for the eradication of *P. aeruginosa* and the effective management of respiratory tract infection due to multidrug-resistant Gram-negative bacteria in patients with cystic fibrosis or bronchiectasis. In addition, inhaled colistin has a beneficial role in the management of HAP or VAP due to multidrug-resistant Gram-negative bacteria although it is still unclear if it provides an additional benefit in all-cause or VAP-related mortality rate. It should be noted that RCTs dealing with inhaled colistin are necessary in order to determine the appropriate colistin dose, the optimal delivery device and to validate the efficacy, safety,

advantages and disadvantages of this challenging therapeutic approach in order to maximize clinical efficacy and minimize the risk of colistin resistance, mainly in patients with HAP or VAP.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

Bibliography

1. Nikiforov VN. Inhalation of penicillin, streptomycin, and novocaine solution aerosols in the treatment of resistant diphtherial bacterial carriers. Pediatriia 1954;4:53-4
2. Venerando A, Maffei R. Use of combined trypsin and antibiotics in inhalation therapy of some bronchial diseases. Minerva Med 1955;46(67-68):385-9
3. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 1999;340(1):23-30
4. Ratjen F, Doring G, Nikolaizik WH. Effect of inhaled tobramycin on early Pseudomonas aeruginosa colonisation in patients with cystic fibrosis. Lancet 2001;358(9286):983-4
5. Hansen CR, Pressler T, Hoiby N. Early aggressive eradication therapy for intermittent Pseudomonas aeruginosa airway colonization in cystic fibrosis patients: 15 years experience. J Cyst Fibros 2008;7(6):523-30
6. Drugs.com. FDA Approves Dulera. Available from: www.drugs.com/newdrugs/~ [Accessed 17 November 2010]
7. European Medicines Agency. Aztreonam lysine (Cayston®) powder and solvent for nebulizer solution: summary of product characteristics. Available from: www.ema.europa.eu/ema/index.jsp?curl=search.jsp~ [Accessed 16 July 2010]
8. Ioannidou E, Siempos II, Falagas ME. Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. J Antimicrob Chemother 2007;60(6):1216-26
9. Sermet-Gaudelus I, Le Cocguic Y, Ferroni A, et al. Nebulized antibiotics in cystic fibrosis. Paediatr Drugs 2002;4(7):455-67
10. Geller DE. Aerosol antibiotics in cystic fibrosis. Respir Care 2009;54(5):658-70
11. Wood GC, Swanson JM. Aerosolised antibacterials for the prevention and treatment of hospital-acquired pneumonia. Drugs 2007;67:903-14
12. Michalopoulos A, Metaxas EI, Falagas ME. Aerosol Delivery of Antimicrobial Agents During Mechanical Ventilation: current Practice and Perspectives. Curr Drug Deliv 2011;8(2):208-12
13. Michalopoulos A, Fotakis D, Virtzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. Respir Med 2008;102(3):407-12
14. Korbila I, Michalopoulos A, Rafailidis P, et al. Inhaled colistin as adjunctive to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. Clin Microbiol Infect 2010;16(8):1230-6
15. American Thoracic Society/Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcareassociated pneumonia. Am J Respir Crit Care 2005;171:388-416
16. Le J, Ashley ED, Newhauser MM, et al. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Pharmacother 2010;30:562-84
17. Antoniu SA, Cojocaru I. Inhaled colistin for lower respiratory tract infections. Expert Opin Drug Deliv 2012;9(3):333-42
18. Michalopoulos A, Kasiakou S, Falagas M. The significance of different formulations of aerosolized colistin. Crit Care 2005;9:417-18
19. Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of pseudomonas aeruginosa and Acinetobacter baumannii ventilator-associated pneumonia. Respir Care 2012; Epub ahead of print
20. Lin CC, Liu TC, Kuo CF, et al. Aerosolized colistin for the treatment of multidrug-resistant Acinetobacter baumannii pneumonia: experience in a tertiary care hospital in northern Taiwan. J Microbiol Immunol Infect 2010;43(4):323-31

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