REVIEW

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Aerosolized antibiotics in the treatment of hospital-acquired pneumonia/ventilator-associated pneumonia

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Aerosolized antibiotics are being increasingly used to treat respiratory infections, especially those caused by drug-resistant pathogens. Their use in the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia in critically ill patients is especially significant. They are also used as an efficient alternative to overcome the issues caused by systemic administration of antibiotics, including the occurrence of drug-resistant strains, drug toxicity, and insufficient drug concentration at the target site. However, the rationale for the use of aerosolized antibiotics is limited owing to their insufficient efficacy and the potential for underestimated risks of developing side effects. Despite the lack of availability of high-quality evidence, the use of aerosolized antibiotics is considered as an attractive alternative treatment approach, especially in patients with multidrug-resistant pathogens. In this review, we have discussed the effectiveness and side effects of aerosolized antibiotics as well as the latest advancements in this field and usage in the Republic of Korea.

Keywords: Aerosolized antibiotics; Hospital-acquired pneumonia; Ventilator-associated pneumonia; Multidrug-resistant

INTRODUCTION

Respiratory infections, including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), are important causes of morbidity and mortality in intensive care units (ICUs) despite the improvements in prevention and treatment [1-3]. HAP/VAP also leads to prolonged ICU stay, and increased medical costs and mortality rates, particularly when it is associated with infections caused by multidrug-resistant (MDR) strains [4]. The majority of VAP-related deaths occur as a direct consequence of the infection, with cases caused by glucose non-fermenting gram-negative bacilli (GNB) such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, exhibiting a higher mortality rate [5-7]. Moreover, there has been a significant increase in the occurrence of infections caused by MDR gram-negative pathogens, which pose challenges in treatment and pathogen eradication. According to the Korean National Healthcare-associated Infections Surveillance (KONIS) data, *A. baumannii* and *P. aeruginosa* were isolated from 33.1% and 13.0%, respectively, of the clinical samples obtained from patients admitted in the ICU with respiratory infections, as the causative organism, while the carbapenem resistance rates were 89.3% and 52.7%, respectively [8]. This emphasizes the need for ensuring an appropriate use and development of new strategies to enhance the effectiveness of antibiotics.

Depending upon the type of antibiotics used, antibiotics administered via systemic administration may not penetrate the parenchymal lung tissue and bronchial secretions, resulting in insufficient drug concentration at the target site [9]. Moreover, altered antibiotic pharmacokinetics in critically ill patients has been recognized as an important factor that

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Table 1. FDA-approved aerosolized antibiotics

Drug	Indication	FDA-approved year [13]	Dose/Frequency	Availability in the Republic of Korea
Tobramycin (TOBI®/Bethkis®)	CF	1997/2012	300 mg twice a day	No
AZLI (Cayston®)	CF	2010	75 mg three times a day	No
ALIS (Arikayce®)	MAC-LD	2018	590 mg once a day	No

FDA, U.S. Food and Drug Administration; CF, cystic fibrosis; AZLI, aztreonam lysine inhalation solution; ALIS, amikacin liposome inhalation suspension; MAC-LD, *Mycobacterium avium* complex lung disease.

compromises optimal drug penetration [10]. Inadequate concentration of antibiotics at the infection site may result in poor treatment outcomes, particularly when MDR pathogens are the etiology [11]. Therefore, there is a requirement for drugs that can demonstrate the achievement of high concentrations at the site of infection, while also reducing the risk of systemic toxicity caused by intravenously administered antibiotics. Accordingly, aerosolized antibiotics have been used as a rescue or adjuvant therapy in patients who do not exhibit responses to systemic treatment alone [3].

Since aerosolized antibiotics were first reported in the 1940s, tobramycin and aztreonam have been approved for inhalation in cystic fibrosis (CF), and amikacin liposome inhalation suspension (ALIS) was approved for use in *Mycobacterium avium* complex lung disease (MAC-LD) by the U.S. Food and Drug Administration (FDA) in 2018 (Table 1) [12-14]. Although not FDA-approved for inhalation, inhaled colistin is also being used to treat patients with CF or VAP. Similarly, the European Cystic Fibrosis Society Consensus Group recommended the use of aerosolized antibiotics for eradication of early *P. aeruginosa* infection and prevention of chronic *P. aeruginosa* infection in CF patients [15]. Tobramycin and colistin preparations are recommended for inhalation either as monotherapy or in combination with systemic antibiotics. Since its role in CF has been established, there is an increase in the exploration and utilization of aerosolized antibiotics among intensivists, although clinical evidence regarding their efficacy in the treatment of respiratory infections in critically ill patients is limited. Particularly, treatment with aerosolized antibiotics has emerged as an important adjunctive therapy to increase the treatment efficacy and tissue concentration of antibiotics, and to prevent systemic toxicity during the treatment of respiratory infections caused by MDR pathogens.

In this review, we have focused on the effectiveness of aerosolized antibiotics and considerations for their use, especially in HAP/VAP in critically ill patients. Additionally, we have discussed the recent advances in this field and their utilization in the Republic of Korea.

EFFECTIVENESS

To overcome the limitations of intravenous (IV) antibiotics, aerosolized antibiotics were suggested as a promising alternative approach for drug delivery in respiratory infections. These antibiotics demonstrate potential applicability in the prevention or treatment of HAP/VAP, and aminoglycosides and colistin are considered representative drugs.

Aminoglycosides

Aminoglycosides have a narrow therapeutic index and hydrophilic concentration-dependent kill characteristics. In critically ill patients, aminoglycosides frequently result in an increased volume of distribution (Vd) that can reduce their maximum concentration (Cmax) [16,17]. In fact, IV antibiotics administered are often underdosed, resulting in insufficient lung tissue distribution in critically ill patients with VAP [18]. Furthermore, several *in vitro* and *in vivo* studies have reported that the concentration of nebulized aminoglycosides in lung interstitial space fluid and median epithelial lining fluid (ELF) is higher than that of IV aminoglycosides, with no evidence of systemic toxicity [19-23]. Niederman et al. [24] investigated 69 mechanically ventilated patients with gram-negative pneumonia who received inhaled amikacin solution (BAY 41-6551) in combination with systemic antibiotics. The findings of this randomized control trial (RCT) revealed that amikacin distributed well throughout the lung parenchyma, with extremely high tracheal and alveolar concentrations, while sustaining IV concentrations below the

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Table 2. Clinical studies on aerosolized antibiotics

Study	Design	No. of patients/type of infection	Intervention	Outcomes
Ioannidou et al. (2007) [25]	Meta-analysis (5 RCTs)	176/HAP	AS or endotracheally instilled aminoglycosides vs. placebo, with IV or IM antibiotics	High success rates with intervention; no difference in mortality, microbial eradication rate, and drug-related adverse event
Sole-Lleonart et al. (2017) [26]	Meta-analysis (6 RCTs + 5 observational studies)	826/VAP or VAT	AS aminoglycosides or colistin ± IV aminoglycosides or colistin vs. IV aminoglycosides or colistin, with IV antibiotics	High clinical cure rates with AS antibiotics in VAP with drug-resistant pathogens, less nephrotoxicity; no difference in mortality, MV duration; compromised MV in hypoxemic patients
Hassan et al. (2018) [27]	Open label RCT	133/Postcardiac surgery, HAP, or VAP	AS amikacin 400 mg BID vs. IV amikacin 20 mg/kg once daily, with IV piperacillin/tazobactam	High clinical cure rates with AS amikacin on day 7, shortened ICU stay and MV duration, less nephrotoxicity; no difference in mortality
Kollef et al. (2017) [28]	Double-blind RCT	143/VAP	AS amikacin 300 mg/fosfomycin 120 mg BID vs. placebo, with IV meropenem or imipenem	Few positive tracheal cultures on days 3 and 7 with AS amikacin/fosfomycin; no difference in CPIS change, mortality, and clinical relapse rates
Niederman et al. (2020) [29]	Double-blind RCT	725/Gram-negative pneumonia under MV	AS amikacin 400 mg BID vs. placebo, with IV antibiotics	No difference in survival until day 28–32, pneumonia-related mortality, duration of MV and ICU stay, and drug-related adverse events
Rattanaumpawan et al. (2010) [43]	Open label RCT	100/VAP	AS colistin (CBA 75 mg) BID vs. placebo, with IV antibiotics	High microbial eradication rate with AS colistin; no difference in clinical outcome overall
Abdellatif et al. (2016) [44]	Single-blind RCT	149/VAP	AS colistin 4 MIU TID vs. IV colistin LD 9 MIU + 4.5 MIU BID, with IV imipenem	Improvement in respiratory failure (PaO_2/FiO_2 ratio), shortened time to microbial eradication, early weaning from MV, less nephrotoxicity with AS colistin; no difference in clinical cure rates, length of stay, and 28-day mortality
Valachis et al. (2015) [45]	Meta-analysis (7 observational cohort or case-control studies + 1 RCT)	690/VAP	AS colistin + IV colistin vs. IV Colistin alone	Improvement in clinical response, microbial eradication rate, and infection-related mortality with AS + IV colistin; no difference in overall mortality

RCT, randomized control trial; HAP, hospital-acquired pneumonia; AS, aerosolized; IV, intravenous; IM, intramuscular; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; MV, mechanical ventilation; BID, twice daily; ICU, intensive care units; CPIS, clinical pulmonary infection score; CBA, colistin base activity; MIU, million international units; TID, three times daily; LD, loading dose.

threshold of renal toxicity. Based on these findings, several experimental and clinical studies were conducted to evaluate the effects of aerosolized aminoglycosides in HAP/VAP.

In a meta-analysis of five RCTs that involved the administration of adjunctive aminoglycosides or alternatives via the respiratory tract in intubated patients with HAP caused by gram-negative bacteria, the administration via respiratory tract therapy showed a high success rate compared to the control (odds ratio [OR], 2.39; 95% confidence interval [CI], 1.29 to 4.44) (Table 2) [25]. However, it did not exhib-

it any statistically significant difference in mortality rates. A systemic review and meta-analysis of 11 studies including six RCTs reported that treatment with aerosolized aminoglycosides and colistin could be highly effective in respiratory infections, especially in those caused by resistant pathogens (OR, 1.96; 95% CI, 1.30 to 2.96), with decreased nephrotoxicity, but could compromise mechanical ventilation, especially in hypoxemic patients [26]. However, the results did not demonstrate any significant reduction in mortality rates or mechanical ventilation duration. In the study reported by Hassan et al. [27], the efficacy of nebulized (400 mg twice daily) versus IV (20 mg/kg once daily) amikacin, in adjunct with IV piperacillin-tazobactam, in HAP/VAP caused by MDR GNB strains, was evaluated in a prospective RCT involving 133 postcardiac surgery patients. The nebulized amikacin group showed better clinical cure rates and shorter ICU stays compared to the IV group. However, this study also did not demonstrate significant differences in mortality rates.

Meanwhile, other randomized trials did not present favorable results. An RCT conducted on adjunctive treatment with 300 mg amikacin/120 mg fosfomycin inhalation in 143 VAP patients with gram-negative infection (IASIS trial) did not yield effective results regarding the improvement of clinical outcomes compared to the treatment with standard IV antibiotics, despite demonstrating a reduction in the bacterial burden [28]. In this study, a well-designed formulation containing amikacin, with optimum particle size to ensure deposition in lung tissue, was administered using the highly efficient vibrating mesh nebulizers. The treatment group presented with significantly fewer positive tracheal cultures on days 3 and 7 compared to the placebo group, especially for pan-drug-resistant *Acinetobacter*. However, similar to the results reported by other studies, this study also showed no difference in either mortality or clinical improvement rates between the two groups at day 14. The recently concluded INHALE program, a global phase III RCT of inhaled amikacin solution (BAY 41-6551) in mechanically ventilated patients with gram-negative pneumonia, did not demonstrate the superiority of standard of care and aerosolized antibiotics compared to the placebo [29]. This program involved 725 patients with gram-negative pneumonia, who were administered with either 400 mg of aerosolized amikacin or saline placebo, both of which were administered every 12 hours for a period of 10 days, along with administration of standard of care IV antibiotics. The results did not demonstrate between-group difference in survival until days 28 to 32 (OR, 0.84; 95% CI, 0.55 to 1.28; $p = 0.43$). Furthermore, the inhaled amikacin group showed no significant benefits for the secondary endpoints, including pneumonia-related mortality, and duration of mechanical ventilation and ICU stay. Subgroup analyses revealed that no population group benefitted from the use of inhaled amikacin.

The effectiveness of aerosolized antibiotics is affected not only by the drug, but also by the types of nebulizers. In general, vibrating mesh nebulizers deliver antibiotics more efficiently than jet or ultrasonic nebulizers [30-32]. This is because jet nebulizers remain a large amount of medication in its chamber at the end of nebulization, and ultrasonic nebulizers can overheat the antibiotic solution and thus, degrade heat-sensitive drugs. In addition, in terms of application of the nebulizers, inspiratory synchronization of nebulizers is better reduces drug loss than continuous nebulization [33,34]. Therefore, to optimize the delivery of antibiotics by nebulization in mechanically ventilated patients, vibrating mesh nebulizers and inspiratory synchronization should be employed. However, there exists a practical difficulty when vibrating mesh nebulizers are not available.

Colistin

Colistin, a formerly 'abandoned' antibiotic, is gradually gaining popularity because of its potential to overcome VAP caused by MDR pathogens. Owing to physicochemical characteristics, such as high molecular weight, hydrophobicity, and cationic nature of the decapetide, it exhibits low lung tissue penetration when administered through the IV route [9]. Moreover, IV colistin is also associated with incidences of increased nephrotoxicity and neurotoxicity [35]. In studies conducted on animals, colistin administered via inhalation demonstrated higher concentrations in the lung tissue or ELF compared with IV administration [36,37]. Furthermore, several small retrospective studies that evaluated the effects of inhaled colistin in mechanically ventilated patients with MDR pneumonia, reported high rates of clinical response and pathogen eradication [38-40]. These encouraging findings have increased expectations that aerosolized colistin may contribute to the treatment of VAP that does not exhibit responses to conventional treatment methods.

In a pharmacokinetics study conducted on nebulized colistin, a single dose of 80 mg of colistimethate sodium (CMS) (equivalent to 30 mg of colistin base activity [CBA]) led to the achievement of high colistin concentrations in the ELF for up to 4 hours (median 6.7 and 3.9 μg/mL at 1 and

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4 hours, respectively), and concentrations were higher than the minimum inhibitory concentration (MIC) breakpoint (2 μg/mL) for *A. baumannii* and *Klebsiella pneumoniae* as indicated by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [41]. However, the median concentration at 4 hours was below the MIC breakpoint (4 μg/mL) for *P. aeruginosa*. In another study, Boisson et al. [42] showed that following administration of a dose with 2 million international units (MIU) of inhaled CMS (equivalent to 60 mg of CBA), the concentrations of colistin in the ELF were even higher (9.53 to 1,137 mg/L) than those in the plasma (0.15 to 0.73 mg/L), which indicated low systemic exposure and toxicity.

Several clinical studies that have evaluated the benefits of aerosolized colistin in patients with pneumonia have reported mixed results, with randomized trials not demonstrating any significant improvements in clinical cure rates. A randomized trial compared aerosolized colistin with saline in addition to IV antibiotics among 100 patients with VAP caused by MDR *P. aeruginosa* and/or *A. baumannii* [43]. Although aerosolized colistin increased microbial eradication (60.9% vs. 38.2%, $p = 0.03$), no difference was observed in the clinical outcomes (51% vs. 53.1%, $p = 0.84$). In another randomized single-blind trial involving 149 patients with gram-negative VAP, aerosolized colistin plus IV imipenem administration resulted in a more favorable improvement in respiratory failure (PaO_2/FiO_2 ratio 349 vs. 316 at day 14, $p = 0.012$), shortened time to microbial eradication (9.89 days vs. 11.26 days, $p = 0.023$) and earlier weaning from ventilator compared to IV colistin plus IV imipenem administration [44]. However, no difference was observed in the clinical cure rates (67.1% vs. 72%, $p = 0.59$), the length of stay, and the 28-day mortality between the two groups. Moreover, the study findings showed that the efficacy of aerosolized colistin was not inferior to that of IV colistin administered in the treatment of VAP caused by MDR bacilli, with lower nephrotoxicity.

Similarly, in the meta-analysis conducted by Valachis et al. [45], adjunctive therapy with aerosolized colistin showed significant improvements in clinical outcome (OR, 1.57; 95% CI, 1.14 to 2.15; $p = 0.006$), microbial eradication (OR, 1.61; 95% CI, 1.11 to 2.35; $p = 0.01$), and infection-related mortality (OR, 0.58; 95% CI, 0.34 to 0.96; $p = 0.04$), compared to IV administration only. However, adjunctive therapy with aerosolized colistin did not improve the overall mortality (OR, 0.74; 95% CI, 0.54 to 1.01; $p = 0.06$).

Despite the above-mentioned limitations, the clinical and microbiological findings of these studies seem to be encouraging. Thus, further investigation is warranted to consider an approach based on inhaled colistin for the treatment of respiratory infections caused by MDR *P. aeruginosa* and *A. baumannii*.

Prophylaxis

The use of aerosolized antibiotics for the purpose of prophylaxis for VAP has not been well established, and there are many concerns regarding antibiotic resistance. In the meta-analysis conducted by Falagas et al. [46], the authors reviewed eight comparative trials (five RCTs and three non-RCTs) that evaluated the prophylactic effects of several antibiotics administered via the respiratory tract. Among these, analysis of the five RCTs showed a low prevalence of ICU-acquired pneumonia among patients who received antibiotic prophylaxis (OR, 0.49; 95% CI, 0.32 to 0.76), whereas no difference in mortality was observed between the compared groups (OR, 0.86; 95% CI, 0.55 to 1.32). However, analysis of the data for evidence regarding antibiotic resistance was not conducted for this study.

Karvouniaris et al. [47] conducted an RCT involving 168 subjects to ascertain whether prophylactic aerosolized colistin would reduce the prevalence rates of VAP caused by gram-negative pathogens. The results did not demonstrate a significant difference in VAP incidence between the colistin group and saline group (16.7% vs. 29.8%, $p = 0.07$). Additionally, there was no significant difference in the incidence of ventilator-associated tracheobronchitis and colonization rates. Evidence of increased colistin or multidrug resistance was also not reported in the study. Recently, a systematic review and meta-analysis conducted by Povoa et al. [48] presented an evaluation of the role of aerosolized antibiotics in the prevention of VAP in mechanically ventilated patients. Six comparative trials involving 1,158 patients were included in the analysis and it was concluded that the prophylactic use of aerosolized antibiotics reduced the occurrence of VAP (OR, 0.46; 95% CI, 0.22 to 0.97), without any significant change in ICU mortality or incidence of VAP caused by MDR pathogens. However, the current guidelines of both United States and Europe do not recommend the use of aerosolized antibiotics for prophylactic treatment [3,49].

Guidelines

As per the recent HAP/VAP guidelines (2016) of the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS), adjunctive therapy with aerosolized antibiotics is recommended along with the administration of systemic antibiotics rather than systemic antibiotics alone for patients with gram-negative VAP (not HAP) 'only' susceptible to aminoglycosides or colistin [3]. They also suggested that this therapy could be provided as a last resort for patients who do not exhibit responses to IV antibiotics alone, whether the irrespective of the drug resistance status of the infecting organism. In 2017, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommended that the use of aerosolized antibiotics should be avoided in clinical practice because of insufficient evidence regarding their efficacy and high potential for underestimating risks of developing side effects [50]. Currently, there are no recommendations available for using aerosolized antibiotics as routine adjunctive therapy in HAP/VAP patients.

Studies conducted in the Republic of Korea

Currently, there is no insurance coverage for inhaled antibiotic therapy in the Republic of Korea, and aerosolized formulations of antibiotics are not commercialized. Nevertheless, there have been several retrospective studies conducted in Korea regarding the nephrotoxicity caused by aerosolized colistin use and the effects of inhaled colistin monotherapy and, more recently, a comparative study on the use of loading dose (LD) with inhaled or IV colistin has been reported.

In one retrospective study, therapy with adjunctive aerosolized colistin resulted in a high negative bacterial conversion rate (84.6%) and was relatively safe in terms of nephrotoxicity [51]. A daily dose of 300 mg of CBA was administered to 25 patients with VAP caused by MDR gram-negative bacteria in the ICU. Min et al. [52], in a retrospective study, compared the incidence of nephrotoxicity following administration of IV versus aerosolized colistin in a cohort of 464 patients. The results showed that the aerosolized colistin group exhibited a significantly lower incidence of nephrotoxicity compared to the IV group (7.84% vs. 20.26%, $p < 0.001$).

In another retrospective study that was conducted to investigate the efficacy of nebulized colistin monotherapy, 219 patients with VAP due to carbapenem-resistant *A. baumannii* were treated with either IV (n = 93) or aerosolized colistin (n = 126) and were evaluated through propensity score matching [53]. The findings showed that the aerosolized colistin group was not inferior to the IV group in terms of clinical failure (adjusted OR [aOR], 0.48; 95% CI, 0.19 to 1.19, $p = 0.11$) or ICU mortality rates (aOR, 0.36; 95% CI, 0.12 to 1.09; $p = 0.070$), while a significantly lower incidence of acute kidney injury was observed in the aerosolized colistin group (18% vs. 49%, $p = 0.004$). Recently, Choe et al. [54] reviewed the retrospective progress in 191 critically ill patients with HAP/VAP caused by carbapenem-resistant gram-negative bacteria. The patients were divided into the following three groups: LD IV group (IV colistin with LD), non-LD IV group (IV colistin without LD), and additional aerosolized (AS)-LD group (AS colistin and IV colistin with LD). No difference was observed in the clinical outcomes of the three groups. However, the microbial eradication rate was markedly higher in the AS-LD group than that in the LD IV and non-LD IV groups (60%, 33%, and 31%, respectively; $p = 0.010$). Additionally, patients in the AS-LD group demonstrated a significantly lower all-cause mortality rate at 30 days than the patients treated with IV colistin alone (aOR, 0.338; 95% CI, 0.132 to 0.864; $p = 0.024$). However, no change in nephrotoxicity was observed in the LD or AS-LD groups ($p = 0.100$).

However, all such studies are single-center and retrospective, and since these studies did not report the use of a standardized dose or inhalation method, the limitations are evident.

Additionally, because of the pharmacokinetic/pharmacodynamics (PK/PD) data of colistin for Koreans were still insufficient, the dose standardization should be prioritized and conduction of a well-designed RCT is warranted to standardize an appropriate antibiotic inhalation protocol.

ADVERSE EFFECTS

Inhalational drug administration is known to reduce serious side effects and safety risks, compared to administration by injection. However, there is a potential for the development of systemic toxicity and localized side effects related to inhalation.

Systemic effects

Through inhalation, the concentration of drugs that enter the systemic blood circulation can be significantly reduced,

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thereby preventing the occurrence of serious side effects, the most important of which is nephrotoxicity.

In an RCT of HAP/VAP among postcardiac surgery patients conducted by Hassan et al. [27], nebulized amikacin therapy demonstrated reduced nephrotoxicity associated with lower deterioration in kidney function compared to systemic amikacin therapy. However, caution should be exercised in patients with impaired baseline kidney function. Although aerosolized aminoglycosides are generally safe for usage under normal circumstances, systemic absorption may be substantial in patients with renal dysfunction, and thus drug monitoring is recommended for aminoglycoside use [55,56].

In the study conducted by Min et al. [52], although aerosolized colistin was not associated with any significant risk factors for nephrotoxicity, the duration of colistin use and underlying renal function might affect the development of nephrotoxicity. Therefore, the authors recommended a short-term use of aerosolized colistin and evaluation of underlying renal function before treatment to reduce nephrotoxicity. Another retrospective study reported that although aerosolized colistin was considered to be safe for usage, and the incidence of acute kidney injury was high when it was administered with other nephrotoxic drugs, especially aminoglycosides [51].

In summary, aerosolized antibiotics are generally safe in terms of systemic side effects, especially nephrotoxicity. However, the duration of drug administration and underlying renal conditions may affect drug toxicity. Additionally, caution should be exercised when other nephrotoxic drugs are used concurrently, and drug monitoring should be conducted.

Local side effects

Nebulization can lead to the development of direct mucosal toxicity. Particularly, long-term exposure to high concentrations of inhaled antibiotics can cause bronchial toxicity and alveolar damage. Though transient benign cough is common, bronchospasm is a more serious but rare side effect that is reportedly occurs during antibiotic nebulization [23,43,57,58]. In an RCT involving 74 patients with bronchiectasis, along with identification of *P. aeruginosa* in sputum, patients who were administered with aerosolized tobramycin reported increased cough, wheezing, dyspnea, and non-cardiac chest pain as local side effects, compared to placebo patients, but the symptoms did not pose limitations to the treatment [58]. In another RCT involving 100 patients with gram-negative VAP, all patients received systemic antibiotics and were randomized to receive an additional therapy with nebulized colistin or sterile normal saline for the entire duration of the systemic antibiotic therapy. Bronchospasm was observed in 7.8% of the colistin group and 2.0% of the control group, but there was no statistical significance reported ($p = 0.36$) [43]. The occurrence of bronchospasm can be diminished by conducting pretreatment with a short-acting bronchodilator. In general, preventive treatment with bronchodilators is not necessary for all patients, although the occurrence of bronchospasm results in aerosol interruption, which necessitates the conduction of bronchodilator nebulization. In this regard, European Respiratory Society guidelines for bronchiectasis state that prior treatment with a bronchodilator is advisable [59].

In conclusion, therapy with aerosolized antibiotics often causes local side effects including mild respiratory symptoms, although the occurrence of serious side effects such as bronchospasm is rare. Therefore, in patients with a high probability of bronchospasm, preventive treatment with bronchodilator may be considered.

Other related complications

In addition to the potential toxicity associated with systemic absorption and local side effects, complications related to nebulization also should be considered. Filtering devices are used during mechanical ventilation to avoid dysfunction of flow and pressure transducers and to contain airborne microorganisms [60,61]. Residual nebulization particles may cause ventilator dysfunction and circuit obstructions. These particles are usually larger than mist and can cause obstruction of the filters, which may lead to increased resistance, and thus, this resistance may serve as auto-positive end-expiratory pressure, leading to increased airway pressure [62,63]. In a randomized phase II trial conducted on VAP caused by *P. aeruginosa*, nebulization with amikacin or ceftazidime resulted in the obstruction of the exhalation filter in three out of 20 patients [57]. One of these patients experienced cardiac arrest due to the obstruction but recovered completely after cardiopulmonary resuscitation.

Additionally, nebulization is a potential hazard due to the generation of aerosols and droplets that cause infection transmission. In particular, in the current coronavirus disease 2019 (COVID-19) pandemic, concerns about the risk of virus transmission to healthcare workers when using aerosolized

antibiotics should be fully considered. According to an *in vitro* study, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains viable and infectious in aerosols for 3 hours post-nebulization, and is stably maintained on plastic surface for up to 72 hours [64]. In the same context, Global Initiative for Asthma (GINA) guidelines (updated 2021) recommended avoiding aerosol generating procedures, including nebulization, where possible, to reduce the risk of spreading the virus during the COVID-19 pandemic [65]. Nevertheless, if nebulization therapy is required, as a way to reduce transmission of infection to the ambient environment, the use of HEPA filters on the exhaled limb of the ventilator and/or a disposable nebulizer is recommended [66,67]. In addition, maximum protection of the healthcare workers is required for more than 3 hours post-nebulization, and the risk of contamination of the ambient environment by nebulized aerosols should also be considered.

In brief, aerosolized antibiotic usage may cause complications such as exhalation filter obstruction and, therefore, it is necessary to regularly monitor the saturation level of the filter, in addition to frequent changes in cases where optimal ventilation is critical. Furthermore, it should be borne in mind that nebulization can pose a potential hazard due to the generation of aerosols and droplets that cause infection transmission.

DRUG RESISTANCE

The grave concern regarding antibiotic use is the emergence of antimicrobial resistance [68-70]. Aerosolized antibiotics are generally recommended for administration via adjuvant therapy with systemic antibiotics rather than as a monotherapy, as their role in the emergence of new drug resistance is unclear.

In a meta-analysis conducted in 2007 involving five RCTs, Ioannidou et al. [25] found that three (6.5%) out of the 46 patients who received antibiotic therapy via the respiratory tract, presenting with an initially susceptible pathogen, demonstrated the presence of a resistant pathogen after the completion of the treatment. In a double-blind, randomized, placebo-controlled single-center trial conducted on patients with VAP, Palmer and Smaldone [71] found that the conduction of adjunctive therapy with aerosolized antibiotics successfully eradicated existing MDR pathogens while also reducing the emergence of new drug resistance, compared to the use of systemic antibiotics alone. In this study, the use of aerosolized antibiotics eradicated the original resistant organism present in the cultures and gram stains of samples in 14 out of the 16 patients, compared with only one out of the 11 patients in the placebo group ($p < 0.001$). While new resistance to aerosolized antibiotics did not occur, there was a significant increase in resistance to systemic antibiotics in the placebo group ($p = 0.03$).

Aerosolized antibiotics caused fewer cases of drug resistance compared to systemic administration; however, the risk increases with the increase in the duration of use. In an RCT involving 520 patients with CF, the patients were treated with either aerosolized antibiotics (tobramycin) or placebo. It was seen that the percentage of patients from whom *P. aeruginosa*, with the MIC of tobramycin greater than or equal to 8 μg/mL, was isolated, increased from 25% to 32% in the tobramycin group, while it decreased from 20% to 17% in the placebo group, at week 0 and 24, respectively [72]. Long-term follow-up of cases in this study in an open-labeled clinical trial showed that the resistance to tobramycin continued to develop and increase with the passage of time [73]. At the end of 12 treatment cycles (92 weeks), the percentage of patients with an MIC above 16 μg/mL for tobramycin, in the most tolerant isolates, increased from 10% to 41%. Despite these findings, the patients exhibited clinical benefits such as improved pulmonary function and weight gain.

Though the use of aerosolized antibiotics tends to reduce the emergence of new drug resistance, it should be noted that resistance may develop with long-term use.

CONCLUSIONS

Many studies have been conducted to test the efficacy and safety of aerosolized antibiotics, including aminoglycosides and colistin, in the treatment of HAP/VAP. Though these studies have demonstrated a good efficacy and bacterial eradication, information on their effect on mortality is still insufficient. Hence, aerosolized antibiotics should not be used in routine empirical therapy and may only be considered as rescue or adjuvant therapy in patients with resistant pathogens not exhibiting responses to systemic treatment alone.

Although high-quality evidence remains limited, the use of aerosolized antibiotics may represent an attractive alter-

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native treatment approach, particularly for patients with MDR pathogens. Further studies should be conducted to investigate various drugs and methods for the use of aerosolized antibiotics. Non-standardized antibiotic inhalation should be conducted with caution, and further research is warranted to validate their use in clinical practice. Additionally, research on the PK/PD data of antibiotics for Koreans with well-designed RCTs should be conducted to validate the use of aerosolized antibiotics in Korea.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Klompas M, Khan Y, Kleinman K, et al. Multicenter evaluation of a novel surveillance paradigm for complications of mechanical ventilation. PLoS One 2011;6:e18062.
2. Bor C, Demirag K, Okcu O, Cankayali I, Uyar M. Ventilator-associated pneumonia in critically ill patients with intensive antibiotic usage. Pak J Med Sci 2015;31:1441-1446.
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;63:e61-e111.
4. Schreiber MP, Shorr AF. Challenges and opportunities in the treatment of ventilator-associated pneumonia. Expert Rev Anti Infect Ther 2017;15:23-32.
5. Micek ST, Wunderink RG, Kollef MH, et al. An international multicenter retrospective study of Pseudomonas aeruginosa nosocomial pneumonia: impact of multidrug resistance. Crit Care 2015;19:219.
6. Garnacho-Montero J, Ortiz-Leyba C, Fernandez-Hinojosa E, et al. Acinetobacter baumannii ventilator-associated pneumonia: epidemiological and clinical findings. Intensive Care Med 2005;31:649-655.
7. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;18:318-327.
8. Kim EJ, Kwak YG, Kwak SH, et al. Korean National Healthcare-associated Infections Surveillance system, intensive care unit module report: summary of data from July 2018 to June 2019. Korean J Healthcare Assoc Infect Control Prev 2020;25:115-127.
9. Imberti R, Cusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically Ill patients after IV colistin methanesulfonate administration. Chest 2010;138:1333-1339.
10. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072-1083.
11. Luyt CE, Brechot N, Combes A, Trouillet JL, Chastre J. Delivering antibiotics to the lungs of patients with ventilator-associated pneumonia: an update. Expert Rev Anti Infect Ther 2013;11:511-521.
12. Kuhn RJ. Formulation of aerosolized therapeutics. Chest 2001;120(3 Suppl):94S-98S.
13. U.S. Department of Health and Human Services. Approved drug products with therapeutic equivalence evaluations [Internet]. Silver Spring (MD): U.S. Food & Drugs Administration, 2020 [cited 2021 Jun 25]. Available from: https://www.fda.gov/media/136324/download.
14. Swenson C, Del Parigi A. Amikacin liposome inhalation suspension as a treatment option for refractory nontuberculous mycobacterial lung disease caused by Mycobacterium avium complex. Mayo Clin Proc 2020;95:201-202.
15. Heijerman H, Westerman E, Conway S, Touw D, Doring G; consensus working group. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. J Cyst Fibros 2009;8:295-315.
16. Beckhouse MJ, Whyte IM, Byth PL, Napier JC, Smith AJ. Altered aminoglycoside pharmacokinetics in the critically ill. Anaesth Intensive Care 1988;16:418-422.
17. Triginer C, Izquierdo I, Fernandez R, et al. Changes in gentamicin pharmacokinetic profiles induced by mechanical ventilation. Eur J Clin Pharmacol 1991;40:297-302.
18. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37:840-851.
19. Dhanani JA, Diab S, Chaudhary J, et al. Lung pharmacokinetics of tobramycin by intravenous and nebulized dosing in a mechanically ventilated healthy ovine model. Anesthesiology 2019;131:344-355.
20. Ehrmann S, Mercier E, Vecellio L, Ternant D, Paintaud G, Dequin PF. Pharmacokinetics of high-dose nebulized amikacin in mechanically ventilated healthy subjects. Intensive Care Med 2008;34:755-762.
21. Rouby JJ, Bouhemad B, Monsel A, et al. Aerosolized antibiot-

ics for ventilator-associated pneumonia: lessons from experimental studies. Anesthesiology 2012;117:1364-1380.
22. Goldstein I, Wallet F, Nicolas-Robin A, Ferrari F, Marquette CH, Rouby JJ. Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets. Am J Respir Crit Care Med 2002;166:1375-1381.
23. Luyt CE, Clavel M, Guntupalli K, et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. Crit Care 2009;13:R200.
24. Niederman MS, Chastre J, Corkery K, Fink JB, Luyt CE, Garcia MS. BAY41-6551 Achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. Intensive Care Med 2012;38:263-271.
25. 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;60:1216-1226.
26. Sole-Lleonart C, Rouby JJ, Blot S, et al. Nebulization of anti-infective agents in invasively mechanically ventilated adults: a systematic review and meta-analysis. Anesthesiology 2017;126:890-908.
27. Hassan NA, Awdallah FF, Abbassi MM, Sabry NA. Nebulized versus IV amikacin as adjunctive antibiotic for hospital and ventilator-acquired pneumonia postcardiac surgeries: a randomized controlled trial. Crit Care Med 2018;46:45-52.
28. Kollef MH, Ricard JD, Roux D, et al. A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of gram-negative ventilator-associated pneumonia: IASIS trial. Chest 2017;151:1239-1246.
29. Niederman MS, Alder J, Bassetti M, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. Lancet Infect Dis 2020;20:330-340.
30. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, Fink JB. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. Respir Care 2010;55:845-851.
31. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SH, Nunan TO, Treacher DF. Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation. Eur Respir J 1997;10:905-909.
32. Ferrari F, Liu ZH, Lu Q, et al. Comparison of lung tissue concentrations of nebulized ceftazidime in ventilated piglets: ultrasonic versus vibrating plate nebulizers. Intensive Care Med 2008;34:1718-1723.
33. Miller DD, Amin MM, Palmer LB, Shah AR, Smaldone GC. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. Am J Respir Crit Care Med 2003;168:1205-1209.
34. Michotte JB, Staderini E, Le Pennec D, et al. In vitro comparison of a vibrating mesh nebulizer operating in inspiratory synchronized and continuous nebulization modes during noninvasive ventilation. J Aerosol Med Pulm Drug Deliv 2016;29:328-336.
35. Vardakas KZ, Voulgaris GL, Samonis G, Falagas ME. Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: a systematic review and meta-analysis. Int J Antimicrob Agents 2018;51:1-9.
36. Lu Q, Girardi C, Zhang M, et al. Nebulized and intravenous colistin in experimental pneumonia caused by Pseudomonas aeruginosa. Intensive Care Med 2010;36:1147-1155.
37. Gontijo AV, Gregoire N, Lamarche I, Gobin P, Couet W, Marchand S. Biopharmaceutical characterization of nebulized antimicrobial agents in rats: 2. Colistin. Antimicrob Agents Chemother 2014;58:3950-3956.
38. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa. Clin Infect Dis 2005;41:754-757.
39. Naesens R, Vlieghe E, Verbrugghe W, Jorens P, Ieven M. A retrospective observational study on the efficacy of colistin by inhalation as compared to parenteral administration for the treatment of nosocomial pneumonia associated with multidrug-resistant Pseudomonas aeruginosa. BMC Infect Dis 2011;11:317.
40. Lin CC, Liu TC, Kuo CF, Liu CP, Lee CM. 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;43:323-331.
41. Athanassa ZE, Markantonis SL, Fousteri MZ, et al. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. Intensive Care Med 2012;38:1779-1786.
42. Boisson M, Jacobs M, Gregoire N, et al. Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients.

https://doi.org/10.3904/kjim.2021.277

Antimicrob Agents Chemother 2014;58:7331-7339.
43. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. J Antimicrob Chemother 2010;65:2645-2649.
44. Abdellatif S, Trifi A, Daly F, Mahjoub K, Nasri R, Ben Lakhal S. Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial. Ann Intensive Care 2016;6:26.
45. Valachis A, Samonis G, Kofteridis DP. The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and metaanalysis. Crit Care Med 2015;43:527-533.
46. Falagas ME, Siempos II, Bliziotis IA, Michalopoulos A. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. Crit Care 2006;10:R123.
47. Karvouniaris M, Makris D, Zygoulis P, et al. Nebulised colistin for ventilator-associated pneumonia prevention. Eur Respir J 2015;46:1732-1739.
48. Povoa FCC, Cardinal-Fernandez P, Maia IS, Reboredo MM, Pinheiro BV. Effect of antibiotics administered via the respiratory tract in the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. J Crit Care 2018;43:240-245.
49. Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). Eur Respir J 2017;50:1700582.
50. Rello J, Sole-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect 2017;23:629-639.
51. Park SY, Park MS, Chung CR, Kim JS, Park SJ, Lee HB. Clinical effectiveness and nephrotoxicity of aerosolized colistin treatment in multidrug-resistant Gram-negative pneumonia. Korean J Crit Care Med 2016;31:208-220.
52. Min KL, Son ES, Kim JS, Kim SH, Jung SM, Chang MJ. Risk factors of colistin safety according to administration routes: Intravenous and aerosolized colistin. PLoS One 2018;13:e0207588.
53. Kim YK, Lee JH, Lee HK, et al. Efficacy of nebulized colistin-based therapy without concurrent intravenous colistin for ventilator-associated pneumonia caused by carbapenem-resistant Acinetobacter baumannii. J Thorac Dis 2017;9:555-567.
54. Choe J, Sohn YM, Jeong SH, et al. Inhalation with intravenous loading dose of colistin in critically ill patients with pneumonia caused by carbapenem-resistant gram-negative bacteria. Ther Adv Respir Dis 2019;13:1753466619885529.
55. Kahler DA, Schowengerdt KO, Fricker FJ, Mansfield M, Visner GA, Faro A. Toxic serum trough concentrations after administration of nebulized tobramycin. Pharmacotherapy 2003;23:543-545.
56. Petitcollin A, Dequin PF, Darrouzain F, et al. Pharmacokinetics of high-dose nebulized amikacin in ventilated critically ill patients. J Antimicrob Chemother 2016;71:3482-3486.
57. Lu Q, Yang J, Liu Z, et al. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa. Am J Respir Crit Care Med 2011;184:106-115.
58. Barker AF, Couch L, Fiel SB, et al. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. Am J Respir Crit Care Med 2000;162(2 Pt 1):481-485.
59. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 2017;50:1700629.
60. Demers RR. Bacterial/viral filtration: let the breather beware! Chest 2001;120:1377-1389.
61. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. Crit Care Med 1998;26:31-39.
62. Davies JB, Bromilow J. Bacterial filter obstruction with the use of ultrasonic nebulisation. Anaesthesia 2011;66:394-395.
63. Lucato JJ, Tucci MR, Schettino GP, et al. Evaluation of resistance in 8 different heat-and-moisture exchangers: effects of saturation and flow rate/profile. Respir Care 2005;50:636-643.
64. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020;382:1564-1567.
65. Global Initiative for Asthma. GINA report: global strategy for asthma management and prevention (updated 2021) [Internet]. Fontana (WI): Global Initiative for Asthma, 2021 [cited 2021 Jun 25]. Available from: https://ginasthma.org/wp-con-

tent/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf.
66. Ari A. Practical strategies for a safe and effective delivery of aerosolized medications to patients with COVID-19. Respir Med 2020;167:105987.
67. Reychler G, Vecellio L, Dubus JC; 'group Aerosoltherapy GAT' of the French Language Respiratory Society-Société de Pneumologie de Langue Française SPLF. Nebulization: a potential source of SARS-CoV-2 transmission. Respir Med Res 2020;78:100778.
68. Alanis AJ. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res 2005;36:697-705.
69. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155-164.
70. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323-2329.
71. Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am J Respir Crit Care Med 2014;189:1225-1233.
72. 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;340:23-30.
73. Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest 2002;121:55-63.

https://doi.org/10.3904/kjim.2021.277