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The safety and efficacy of inhaled antibiotics use among mechanically ventilated patients: A brief review of evidence.

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Abstract

Mechanical Ventilation (MV) is one of many life-supporting machines used in the Intensive Care Unit (ICU) for acutely ill patients. Most reported MV complications are lung injuries and Ventilator-Associated Pneumonia (VAP). VAP is defined as pneumonia developing in a mechanically ventilated patient ≥ 48 h after tracheal intubation. In addition to high mortality rates reported with VAP, patients with VAP are at higher risk of pulmonary complications. Poor lung penetration of some intravenous antibiotics could result in therapy failure. Many randomized clinical trials and retrospective analyses examined the theoretical benefit of using inhaled antibiotics for VAP treatment. The use of inhaled antibiotics has the advantage of providing a higher lung concentration, minimized systemic toxicities, and a lower risk of induction resistance. The objective of our review article is to provide a review of the safety and efficacy of inhaled antibiotics use among manically ventilated patients in the ICU based on the most recently published evidence.

The main purpose of a mechanical ventilator is to allow the patient time to heal. Usually, as soon as a patient can breathe effectively on their own, they are taken off the mechanical ventilator. Normal inspiration generates negative intrapleural pressure, which creates a pressure gradient between the atmosphere and the alveoli, resulting in air inflow. In mechanical ventilation, the pressure gradient results from increased (positive) pressure of the air source.

Keywords: Mechanical ventilation, Inhaled antibiotics, Nebulized antibiotics.

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Introduction

Mechanical Ventilation (MV) is a life-saving intervention used for several indications in the ICU [1-3]. MV is commonly used as a saving measure for hypercapnia and/or hypoxia [1-3]. Other indications include but are not limited to upper airway obstruction and inability to protect the airway [2,3]. MV provides sufficient oxygenation and ventilation among patients who fail to maintain adequate alveolar ventilation and suffer from respiratory failure. Respiratory failure is further classified as hypoxic or hypercapnic. Hypoxic respiratory failure is defined as the patient's inability to maintain enough oxygenation. However, hypercapnic respiratory failure is related to carbon dioxide accumulation and inadequate ventilation [2,3].

Although MV is a life-saving modality for most patients, it has many complications that could be detrimental and result in a higher mortality rate in the ICU. Most reported

complications are barotrauma, decreased cardiac output, unintended respiratory alkalosis, increased intracranial pressure, and Ventilator-Associated Pneumonia (VAP) [1,2]. VAP is defined as pneumonia occurring at least 48-72 hours after endotracheal intubation [4]. In addition to high mortality rates reported with VAP, patients with VAP are at higher risk of prolonged ICU stay, multi-drug resistance infections, septic shock, malnutrition, and pulmonary complications [1,4]. Current guidelines recommend systemic antibiotics as first-line therapy for VAP treatment and inhaled antibiotics as adjunctive therapy [4]. However, the use of systemic antibiotics therapy is not feasible among some patients due to undesirable side effects, such as acute kidney injury [4]. Moreover, poor lung penetration of some intravenous antibiotics could result in therapy failure [4]. Inhaled antibiotics could be utilized for such patients [2,4].

In theory, inhaled antibiotics use provides a higher drug concentration at the site of infection, resulting in a favourable pharmacokinetic/pharmacodynamic profile [2,4]. Optimizing the pharmacokinetic/pharmacodynamic profile was shown to reduce the risk of induction resistance [2,4-6]. Additionally, avoiding systemic intravenous antibiotics is desirable among the critically ill with kidney injury [2,4]. Nonetheless, studies have reported worsening wheezing and bronchospasm following the use of inhaled antibiotics [2,4]. The aim of our review article is to review the evidence behind the safety and efficacy of inhaled antibiotics among mechanically ventilated patients.

Although use of inhaled antibiotics is the standard of care in cystic fibrosis, there is insufficient evidence to support use of inhaled antibiotics in patients with bronchiectasis not due to cystic fibrosis. We aimed to assess the efficacy and safety of inhaled antibiotics for the long-term treatment of adults with bronchiectasis and chronic respiratory tract infections.

We did a systematic review and meta-analysis of all randomised controlled trials of inhaled-antibiotic use in adult patients with bronchiectasis and chronic respiratory tract infections. Eligible publications were identified by searching MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov. Randomised controlled trials of inhaled antibiotics were included if the patients were adults with stable bronchiectasis diagnosed by CT or bronchography, the trials had treatment a duration of at least 4 weeks, and their outcomes met at least one of the endpoints of interest.

Search strategy

Eligible publications were identified by searching the PubMed, EMBASE, Cochrane, and Google Scholar databases. We included Randomized Controlled Trials (RCT) and retrospective studies. Case reports were excluded. Eligible trials had to meet our defined PICO criteria (Participants, Intervention, Comparator, and Outcome). Participants were adults with confirmed ventilator-associated pneumonia. The intervention included the use of inhaled antibiotics for the treatment, compared with standard care or placebo as mono- or combined-therapy, without inhaled antibiotics. Studies must have reported clinical cure or mortality as one of the outcomes. Search keywords included ventilator-associated pneumonia OR VAP OR respiratory infection AND aerolised antibiotics OR aerosolized antibiotics OR inhaled antibiotics OR nebulised antibiotics OR nebulized antibiotics. Studies were included if patients were diagnosed with VAP, and inhaled antibiotics were used. All studies published between January 1st, 2000 until December 31st, 2021 were included.

Although nebulization is an appealing way for delivering a treatment to the lungs, lots of pitfalls have to be avoided, in particular related to mechanical ventilation when one aims to treat VAP. Indeed, not taking into account the constraints of aerosolization may lead to inefficient therapy, due to insufficient lung deposition. One should keep in mind that the amount of antibiotic loaded in the nebulizer is not the amount of drug deposited in the lung. The residual volume remaining in the nebulizer chamber at the end of delivery, extra-pulmonary deposition and aerosol exhalation influence the dose finally deposited in the lung. To optimize nebulization, several parameters have to be taken into account.

Quality assessment

The credibility of the included meta-analyses was independently evaluated by two authors (Aldhaeefi M and Alaqil AA), and any disparities were resolved by the third author (Alanazi HM). The quality of all included studies were assessed by using AMSTAR 2 tool, which contained 16 items [7]. The answers for each item are "yes," "partial yes," and "no".

Review of evidence

Out of 356 articles identified, 17 articles were included based on our inclusion criteria. Most studies surrounding the use of inhaled antibiotics among patients diagnosed with VAP utilized inhaled antibiotics as adjuvant therapy to IV standard of care. The high VAP mortality rate in the ICU could explain this study design and current clinical practice.

A single-center RCT was conducted in a 36-bed general ICU and included patients with confirmed Multidrug-Resistant Gram-Negative Bacteria (MDR-GNB VAP) [8]. This study showed that aerosolized amikacin use, in addition to standard of care therapy, resulted in a shorter time to culture clearance [8]. The use of aerosolized amikacin had no significant effect on systemic side effects. However, there was no improvement in the mortality rate [8]. Moreover, another study confirmed the addition of inhaled amikacin to IV amikacin therapy resulted in better oxygenation, organism clearance, less nephrotoxicity, less duration of mechanical ventilation, and ICU stay [9].

Another major study found that adding inhaled amikacin plus ceftazidime to IV meropenem, levofloxacin, and linezolid enhanced culture clearance and a lower resistance rate. Similar to other studies, patients had similar mortality and side effect rates [6,10].

Another RCT demonstrated that using nebulized colistimethate combined with the standard of care therapy resulted in a higher rate of culture clearance [11]. However, patients who received nebulized colistimethate had a higher rate of bronchospasm and renal impairment [11]. A pilot study that included a small number of patients showed that inhaled tobramycin increased the rate of VAP clinical resolution in the ICU when it was added to IV tobramycin therapy. However, two patients had a statistically significant increase in serum creatinine [12]. Another retrospective analysis included patients with *Pseudomonas aeruginosa* ARDS and demonstrated that inhaled tobramycin and systemic antibiotics combination therapy resulted in a lower recurrence infection and mortality rates [13].

Furthermore, inhaled vancomycin resulted in a better culture clearance when added to IV vancomycin therapy among patients diagnosed with Methicillin-Resistant Staphylococcus Aureus (MRSA) VAP [14]. Another study conducted in a cardiac surgery ICU found that patients treated with inhaled amikacin plus systemic piperacillin/tazobactam had better clinical cure rates, shorter ICU stay, and a quicker recovery than systemic amikacin and piperacillin/tazobactam [15]. Similar to other studies, inhaled amikacin had less nephrotoxicity [15]. Another study concluded that inhaled combination therapy of amikacin and Fosfomycin with systemic therapy resulted in an improved microbiological clearance without finding any other significant clinical outcomes difference compared to systemic therapy alone [16]. Comparable to this study, aerosolized amikacin improved microbiological culture clearance without improvement in mortality when used among patients with pneumonia caused by multidrug-resistant gram-negative bacteria [17].

Three studies utilized inhaled antibiotics as monotherapy among VAP patients [18-20]. Lower nephrotoxicity, improved P/F ratio, quicker MV weaning, clinical resolution, reduced bacterial resistance, and a better microbiological clearance time were found [18-21]. However, patients treated with aerosolized colistin had more throat irritation, cough, and bronchospasm [18]. A lower rate for induction of microbial resistance was reported in one study [20].

Conclusion

VAP has significant morbidity and mortality among adult patients in the ICU. The standard of care, systemic antibiotics, could have serious side effects even when used properly. The clinical benefit of inhaled antibiotics among VAP patients remains unclear. The mortality benefit of inhaled antibiotics is undetermined, and the routine use of inhaled antibiotics is controversial. Inhaled antibiotics might facilitate the microbiological culture clearance. Powered randomized controlled trials are needed to assess the efficacy of inhaled antibiotic therapy for VAP.

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