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INNOVATION IN THE TREATMENT OF VAP (VENTILATOR-ASSOCIATED PNEUMONIA): THE ROLE OF INHALED ANTIBIOTICS

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Abstract: **Objective:** To discuss the effectiveness of using inhaled antibiotics to prevent pneumonia associated with mechanical ventilation. **Methodology:** The searches were conducted in the PubMed Central (PMC) database, using a combination of terms related to the condition of interest and the treatments investigated, resulting in 58 articles, of which 16 were selected for this work. **Review:** Several contemporary studies have explored the efficacy and safety of inhaled antibiotics. Currently, the Food and Drug Administration (FDA) has approved only four inhaled antibiotics, each with specific indications. Amikacin is indicated to treat lung disease caused by the *Mycobacterium avium* complex, while Aztreonam, Colistin, and Tobramycin are used for infections in patients with cystic fibrosis. However, the efficacy of drug delivery to the lungs can be compromised by inadequately sized particles that do not reach the lower airways. **Final Considerations:** The use of inhaled antibiotics in the prevention of ventilator-associated pneumonia has limited efficacy, with exceptions in specific subgroups, such as patients treated with aerosolized Colistin. On the other hand, inhaled amikacin shows no significant impact on survival compared to controls, indicating variability in the pulmonary distribution of the drug. Due to these limitations and uncertainties in efficacy and risks of adverse effects, recommendations for the use of these antibiotics are limited.

Keywords: Pneumonia Associated with Mechanical Ventilation; Inhaled Antibiotic; Amikacin.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a severe complication in patients undergoing invasive mechanical ventilation for at least 48 hours. This condition, part of intensive care unit (ICU)-acquired pneumonia, is characterized by infection of the lung parenchyma and is associated with high rates of morbidity and mortality, contributing to increased length of stay and hospital costs. The main microorganisms involved include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, several strains of *Acinetobacter,* and *Staphylococcus aureus*, with the diagnosis generally confirmed by clinical and radiographic signs and microbiological culture results (Papazian, Klompas & Luyt, 2020).

Respiratory infections related to mechanical ventilation pose significant challenges, especially given the growing problem of antimicrobial resistance. Agents such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are of particular concern due to their ability to resist conventional treatments, complicating the appropriate therapeutic choice (Schreiber & Shorr, 2019).

In this context, inhaled antibiotics are a promising approach, offering the possibility of delivering therapeutic doses directly to the lungs, minimizing systemic exposure and associated side effects. Among the studied agents, aminoglycosides and colistin have shown potential benefits in both the prevention and treatment of VAP. However, there are still challenges related to the adverse effects of these medications, such as bronchospasm and dysphonia, in addition to the need for further studies to fully validate their efficacy and safety (Wong; Dudney; Dhand, 2019; Palmer, 2019; Jung; Kim; Choi, 2022).

Although scientific evidence legitimizing the efficacy of inhaled antibiotic therapy is strictly aimed at actions against multi-resistant pathogens, reducing adverse effects caused by systemic antibiotics, and better concentration in lung tissues without significant systemic toxicity, methodological and scientific analyses of clinical trials have demonstrated subtle predominance in reducing mortality. There is a lack of studies with current scientific support that prove its real efficacy in clinical improvement and prevention, thus, its clinical use continues to be reserved for adjuvant contexts for more severe cases involving multidrug resistance (Jung; Kim; Choi, 2022).

Administration of the correct dose to the necessary site without harming the patient may not be possible without the aid of inhalation therapy in an intubated patient. However, it is important to use a device that has been well characterized in terms of particle size, site of delivery, and concentration at the site of infection, in addition to being affected by the type of nebulizer, opting for the use of a vibrating mesh compared to jet or ultrasound (Palmer, 2019). This literature review aimed to discuss the use of inhaled antibiotics in the prevention of ventilator-associated pneumonia (VAP).

METHODOLOGY

The present study was a narrative literature review developed based on the PVO strategy, which includes an analysis of the population or research problem, the variables of interest, and the expected outcomes. The guiding question of this study was: "What are the effectiveness, safety, and potential clinical applications of using inhaled antibiotics in preventing ventilator-associated pneumonia (VAP)?" The population comprises patients undergoing mechanical ventilation treated with inhaled antibiotics, specifically amikacin, as a preventive measure against VAP. Searches were conducted in the PubMed Central (PMC) database, using a combination of terms related to the condition of interest and

the treatments investigated. The search terms used were combined using the following search strategy: ("Ventilator-Associated Pneumonia") AND (((Anti-bacterial agents) OR (amikacin)) AND (Inhaled)). The search was facilitated by the use of Boolean operators "AND" and "OR" to refine the results with a total of 58 articles. Initially, 31 potentially relevant articles were identified. The inclusion criteria adopted were: articles published between 2019 and 2024, which directly discuss the topics of interest in this study, including experimental, observational works, clinical trials, and reviews, available in full. Duplicate articles, those with only in summary format that did not directly address the proposal, and articles that did not meet the other inclusion criteria were excluded from the analysis. After applying these criteria, 16 articles were selected for detailed analysis in the present study.

DISCUSSION

Ventilator-associated pneumonia (VAP) is a severe complication affecting up to 40% of patients undergoing invasive mechanical ventilation (IMV) for more than 48 hours. The infection, predominantly caused by Gram-negative bacteria such as *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, and *Acinetobacter* sp. often involves multidrug-resistant strains. The diagnosis of VAP is still a topic of debate, for which the Clinical Pulmonary Infection Score (CPIS) is a tool used for assessment, although its applicability remains controversial. Traditionally, treatment begins with the administration of third-generation cephalosporins, adjusted according to the patient's response.

Historically, inhaled antibiotic therapy was introduced in the 1940s but has been largely replaced due to the associated risk of significant adverse effects. Recently, however, with increasing resistance to systemic antibiotics, inhaled administration has re-emerged as a promising strategy for direct delivery of antimicrobial agents to the lung, minimizing the risks of bacterial resistance due to low serum concentrations of the drugs. Several contemporary studies have explored the efficacy and safety of inhaled antibiotics. For example, the AMIKINHAL study and the clinical trial by Niederman et al. (2020) investigated the impact of using inhaled amikacin on patients with VAP. Niederman et al. reported that survival in patients treated with inhaled amikacin did not differ significantly from that of the control group, suggesting that while inhaled administration achieves adequate concentrations in tracheal aspirate, its distribution in the lungs may be variable.

Another point of interest is the analysis of drug formulation and administration devices. The efficacy of drug delivery to the lungs can be compromised by inadequately sized particles that do not reach the lower airways. Schreiber and Shorr (2019) highlighted that, although the combination of inhaled Amikacin with Piperacillin and Tazobactam has shown higher cure rates compared to intravenous treatment, concerns about the uniformity of drug delivery remain. In terms of tolerability, the most common side effects associated with the use of inhaled antibiotics include coughing and bronchospasm. These effects are generally manageable, but highlight the need for vigilance in the management of patients receiving this type of therapy.

VAP is one of the most prevalent nosocomial infections, representing approximately 39% of these cases. The development of therapeutic strategies such as inhaled antibiotics (IA) is, therefore, crucial for the effective treatment of VAP, minimizing adverse systemic consequences. Currently, the Food and Drug Administration (FDA) has approved only four inhaled antibiotics, each with

specific indications. Amikacin, for example, is indicated to treat lung disease caused by the *Mycobacterium avium* complex, while aztreonam, colistin, and tobramycin are used for infections in patients with cystic fibrosis. These approvals outline the scope of use but also highlight the need to expand indications to other clinical contexts, such as VAP (Tavernier et al., 2021).

The efficacy, cost, dosage, toxicity, safety, indications, and mortality of IA are generally evaluated through rigorous clinical trials. These studies are essential to produce robust evidence to guide therapeutic decisions and clinical practices. Notably, the American Thoracic Society (IDSA/ATS) Guidelines analyzed nine studies in a meta-analysis, revealing that inhaled colistin significantly improved clinical outcomes compared with intravenous antibiotics, especially in patients with infections with highly resistant organisms.

Based on this evidence, IDSA/ATS now recommends the use of inhaled colistin to treat VAP caused by Gram-negative bacilli sensitive to this antibiotic. Other meta-analyses, incorporating data from studies such as INHALE, IASIS, and IDSA/ATS, corroborate the benefits of IA as adjuvant therapy in patients with multidrug-resistant pathogens.

Recently, Angermair et al. (2023) highlighted the potential of inhaled tobramycin in a phase 2A clinical trial for the treatment of VAP caused by multidrug-resistant Gram-negative agents. The authors observed a significant eradication of pathogens in the group treated with inhaled tobramycin, with a minimized risk of systemic side effects, due to localized application that reduces selection pressure on the intestinal flora.

In contrast, the study by Benítez-Cano et al. (2019) on the use of colistimethate sodium showed that high administered doses remained below the toxicity threshold, indicating significant efficacy with minimal impact on patients, without deterioration in renal function or the emergence of neurotoxicity and bronchospasm. Such studies highlight the promising use of inhaled antibiotics in the treatment of VAP, especially in the context of multidrug-resistant infections. Nevertheless, more research is needed to optimize formulations, minimize adverse effects, and extend the use of IA to other clinical contexts. Well-designed clinical trials will continue to be critical in elucidating the potential benefits and limitations of these innovative therapies.

VAP represents a significant challenge in intensive care units and the emergence of multidrug-resistant organisms intensifies the need for innovative therapies, such as IA, which show potential both in studies and in clinical practice. A systematic review and meta-analysis by Tang et al. (2021) and Qin et al. (2021), respectively, revealed that adjuvant IAs improve clinical cure rates in patients with VAP, mainly due to the high concentration of antibiotics directly in the respiratory tract. This localized administration provides comparable or superior therapeutic efficacy with a fraction of the systemic dose, thus reducing the risks of severe side effects associated with intravenous administration.

However, studies such as those by Desgrouas and Ehrmann (2021) and Qin et al. (2021) also draw attention to the lack of significant impact of IA in reducing mortality and the length of ICU stay or ventilation time. These findings emphasize the need for caution in interpreting positive results, considering the moderate heterogeneity observed in clinical trials, potentially due to variations in the pathogenic bacteria involved and definitions of clinical response.

Mahmood and Shorr (2021) and Tang et al. (2021) state the importance of carefully evaluating the safety of IA, pointing out risks such as irritation of the respiratory mucosa,

allergic reactions, pulmonary dysbiosis, bacterial resistance, and systemic effects, including nephrotoxicity. Although IAs have not increased the risk of renal failure, in some studies they have been associated with bronchospasms, indicating the need for close monitoring during therapy.

In addition to clinical challenges, technical factors such as aerosol particle size, nebulizer type, characteristics of the carrier gas, and respiratory settings are crucial to the efficacy of pulmonary drug deposition. Quin et al. (2021) and Desgrouas and Ehrmann (2021) emphasize that the amount of antibiotic loaded into the nebulizer does not always correspond to the amount deposited in the lung, with the residual volume in the nebulizer chamber and extrapulmonary deposition influencing the effective dose. Therefore, further research and development must be carried out to optimize IA administration, aiming to maximize therapeutic efficacy and minimize risks. The adoption of IA as part of VAP management should be guided by robust evidence-based guidelines and continuous updates as new findings emerge. Improvements in nebulization technology and a better understanding of the pharmacokinetic and pharmacodynamic interactions of IAs in the lung may open new avenues for the effective treatment of VAP.

The use of IA for VAP has gained prominence in scientific research, mainly to address the increase in lung infections caused by multidrug-resistant bacteria. The work of Dhand (2022) explores this approach, focusing on the potential reduction of adverse effects associated with systemic therapies, through direct application to the target organ. However, their results indicate that the combination of intravenous and inhaled therapy does not provide advantages over systemic therapy alone in patients with VAP caused by Gram-negative bacteria, reinforcing the recommendations for the restricted use of inhaled antibiotics in patients susceptible to aminoglycosides and polymyxins.

In contrast, the study by Szychowiak, Desgrouas, and Ehrmann (2022) focuses on nebulizer application techniques and how factors such as equipment positioning, fan temperature, and humidity can influence treatment effectiveness. This study also addressed the use of inhaled antibiotics in preventing VAP, finding limited effects on overall incidence and mortality, but positive results in specific subgroups, such as patients receiving aerosolized colistin. Despite this, the main infectious and thoracic disease societies recommend caution and limit the indication of these practices to specific patients only.

Hakamifard et al. (2023) present data from a comparative study on the use of inhaled tobramycin and fosfomycin versus colistin in patients with VAP caused by multidrug-resistant *Acinetobacter baumannii*. Their results indicate a shorter treatment and a significant advantage in recovery time for the group treated with inhaled tobramycin and fosfomycin, although they highlight the need to consider variables such as the history of hospitalization, comorbidities and previous use of antibiotics, which could influence the results. The limitation due to the small sample size suggests the need for larger studies to validate these findings. In summary, while inhaled antibiotics provide significant theoretical advantages for targeted administration and reduction of adverse systemic effects, practical applicability, and current recommendations are limited due to uncertainties related to overall efficacy, risks of localized adverse effects, and variability in clinical outcomes. Future guidelines should be informed by a more robust evidence base that clarifies the situations in which this therapeutic modality is most effective and safe.

FINAL CONSIDERATIONS

Ventilator-associated pneumonia (VAP) is a common nosocomial infection in ICUs, affecting around 40% of intubated patients and increasing mortality and length of stay. Therefore, the development of effective therapeutic strategies is crucial. Recently, the application of inhaled antibiotics (IAs) has been explored, especially to treat infections caused by multidrug-resistant bacteria. The efficacy of these IAs, however, depends on several technical factors, such as the size of the aerosol particles and the type of nebulizer. Although the combination of inhaled amikacin with piperacillin and tazobactam has shown higher cure rates than intravenous treatment in certain studies, uniformity in drug delivery is still a concern. Variable results and the lack of significant advantages over systemic therapy in some cases reinforce the need for cautious and restricted use of these antibiotics. The use of inhaled colistimethate sodium has shown efficacy without reaching toxicity thresholds, proving promising especially for multidrug-resistant infections. However, the overall efficacy of inhaled antibiotics in reducing the incidence and mortality of VAP is limited, with notable benefits only in specific subgroups, such as patients treated with aerosolized colistin. This heterogeneity in results, possibly due to variations in pathogenic bacteria and definitions of clinical response, highlights the need for further research. Future studies should focus on optimizing the administration of IAs to maximize efficacy and minimize risks, such as local adverse effects and bacterial resistance. Advances in nebulization technology and a better understanding of pharmacokinetic and pharmacodynamic dynamics may open new avenues for the effective treatment of VAP.

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