Considerations in nursing regarding nebulized antibiotics in adults with ventilator-associated pneumonia

Consideraciones de enfermería sobre antibióticos nebulizados en adultos con neumonía asociada a ventilación mecánica invasiva

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Abstract

Introduction: Ventilator-associated pneumonia (VAP) is the most common hospital-acquired respiratory infection, making it a significant health problem due to its associated increase in morbidity and mortality, higher medical financial burden, and a substantial impact on public health and the economy. Amongst the benefits of administering nebulized antibiotics for respiratory tract infections, one of the highlights is the ability to deliver effective concentrations of such drugs directly to the site of infection while minimizing systemic adverse effects. **Objective:** To identify nursing considerations regarding the use of nebulized antibiotics in adults with invasive ventilator-associated pneumonia through a literature review. **Methodology:** A literature review was conducted using databases such as PubMed, Epistemonikos, and Trip. The search strategy included the MESH terms ventilator-associated pneumonia, nosocomial pneumonia, nebulized antibiotics, and inhaled antibiotics, combined with boolean operators. The PRISMA guidelines were employed for classification and screening. **Results:** The research showed favorable results from the use of nebulized antibiotics. However, there is a disparity between the large amount of experimental evidence supporting the administration of nebulized antibiotics and the scarcity of clinical studies confirming the efficacy and safety of these drugs and, more importantly, the lack of scientific material published by nursing staff regarding the nursing care to be taken into account.

Keywords: Nosocomial pneumonia, mechanical ventilation, intensive care unit, nebulized antibiotics, nursing care

Resumen

Introducción: La neumonía asociada a la ventilación mecánica (NAVM) es la infección respiratoria hospitalaria más frecuente, es un problema grave de salud por el aumento de morbimortalidad, elevación de gastos médicos y de tratamiento, con grave impacto en la salud pública y la economía. Las ventajas de la administración de un antibiótico nebulizado en las infecciones del tracto respiratorio incluyen la posibilidad de administrar concentraciones efectivas del fármaco en el lugar de la infección y minimiza los efectos adversos sistémicos. **Objetivo:** Identificar las consideraciones de enfermería sobre el uso de antibióticos nebulizados en adultos con neumonía asociada a ventilación mecánica invasiva por medio de una revisión de literatura. **Metodología:** se realizó una revisión de información en bases de datos: Pubmed, Epistemonikos y Trip utilizando como estrategia de búsqueda los términos MESH *ventilator-associated pneumonia, nosocomial pneumonia, (nebulized antibiotics, inhaled antibiotics;* combinados con los operadores booleanos. Para la clasificación y cribado se utilizaron las directrices PRISMA. **Resultados:** en las investigaciones realizadas se evidencia resultados favorables del uso de antibióticos nebulizados. Sin embargo, existe disparidad entre la gran cantidad de pruebas experimentales que respaldan la administración de antibióticos nebulizados y la escasez de estudios clínicos que confirmen la eficacia y la seguridad de estos fármacos y sobre todo la inexistencia de información científica publicada por personal de enfermería con respecto a los cuidados de enfermería a tener en cuenta.

Palabras clave: Neumonía nosocomial, ventilación mecánica, unidad de cuidados intensivos, antibióticos nebulizados, cuidados de enfermería

Introduction

Nosocomial pneumonias are infections acquired during a hospital stay. They constitute a significant global health burden due to their impact in morbidity, mortality, and prolonging hospital stays. Likewise, nosocomial infections also increase the use of antibiotics, raising the risk of developing multi-resistant bacteria[1,2]. Ventilator-associated pneumonia (VAP) is responsible for high morbidity and mortality in critically ill patients, and they are the most prevalent hospital-acquired infection in intensive care units (ICU)[3].

The mortality rate for patients developing VAP is nearly 20%, while also increasing the duration of need for mechanical ventilation and the duration of ICU stay. Its incidence ranges from 1.9 to 3.8 per 1000 ventilation days in the United States, and it far exceeds 18 per 1000 ventilation days in Europe. According to data from the National Hospital Infection Surveillance Program in Argentina, incidence rate reached 12.4 per 1000 ventilation days in 2016, indicating that proper management of this disease is crucial in medical units, not only due to its morbimortality but also because of its frequency[4,5].

Typically, nebulized antibiotics are not considered the first choice of treatment in patients with VAP. However, due to the rising prevalence of multi-resistant strains, their use is becoming more and more common for treating lung infections in critically ill patients. The advantages of nebulized antibiotics include higher concentrations at the infection site while also maintaining reduced systemic exposure. Likewise, nebulized antibiotics are of great interest in patients infected with microorganisms resistant to various drugs. The aforementioned approach could have a positive impact in reducing the emergence of antibiotic resistance and minimizing adverse effects[6,7]. Currently, inhalational administration of antibiotics is primarily done through wet nebulization. However, this method of antibiotic delivery is laborious, susceptible to reinfection, and can lead to the development of resistance in the device[6,7].

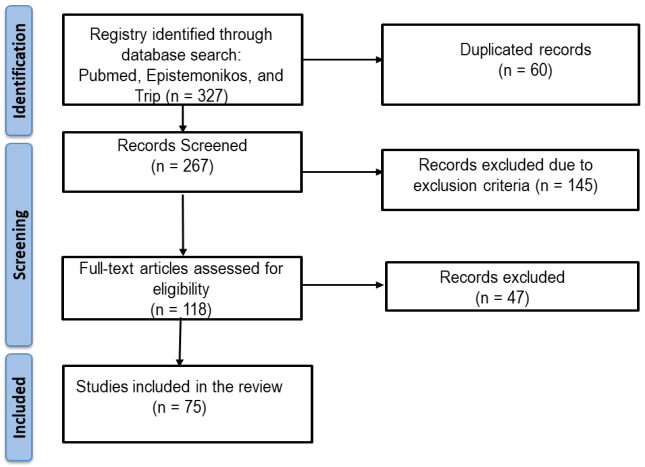
Available data has shown that incidence of VAP is significantly higher in the ICU. This growing problem highlights the need to investigate the benefits and contributions of each healthcare professional in this therapeutic measure. Therefore, the objective of this research is to evaluate nursing considerations regarding the use of nebulized antibiotics in adults with VAP through a literature review.

Materials and methods

A bibliographic review was conducted both in English and Spanish based on scientific articles and other sources of information related to “Nursing considerations on nebulized antibiotics in adults with ventilator-associated pneumonia.” The search strategy implemented PICO structured questions aiming to include the adult population with VAP subjected to the use of nebulized antibiotics, while comparing their efficacy and obtaining favorable results in the treatment of nosocomial pneumonia.

The strategies for data collection included using keywords based on Health Sciences Descriptors (DeCS/MesSH), combined with the use of boolean operators AND and OR (((ventilator-associated pneumonia [Title/Abstract]) OR (nosocomial pneumonia [Title/Abstract])) AND (nebulized antibiotics [Title/Abstract])) OR (inhaled antibiotics [Title/Abstract]). Information was sought in scientific articles published from 2013 to 2023 in the PubMed, Epistemonikos, and Trip databases. For classification and screening, the guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) were used as shown in **Figure 1**.

Figure 1. Diagram of research selection according to the PRISMA guidelines



Exclusion Criteria

- Research articles conducted on children
- Theses, monograph documents, and university essays
- Studies conducted on patients without a diagnosis of ventilator-associated pneumonia

NEBULIZED ANTIBIOTICS IN VENTILATOR-ASSOCIATED PNEUMONIA

Critically ill patients in the ICU have some of the highest mortality rates, sometimes due to the severity of the underlying illness and other times due to hospital-acquired infections[10]. Lower respiratory infections comprise various infectious conditions affecting the respiratory tract from the bronchi to the alveoli and, ultimately, the lung parenchyma. These are classified into community-acquired pneumonia, hospital-acquired pneumonia, and VAP[11].

In the context of intensive care, the need for invasive ventilatory measures is highly frequent, which is itself a risk factor for infections. Consequently, placement of an endotracheal tube increases the risk of developing VAP by 6 to 20 times[12]. VAP is defined as pneumonia that occurs after 48 hours of hospital admission[13]. The previous entity is known for increasing the duration of mechanical ventilation and extending the stay in the ICU[14]. It also leads to higher costs in both medication and supplies[15].

There are two types of VAP: early-onset VAP, which occurs within the first four days of admission in previously healthy patients who are not on antibiotics, and late-onset VAP, which occurs after at least five days of hospitalization[16]. VAP is suspected when the patient presents with severe hypoxemia, changes in the characteristics and volume of secretions, fever, leukocytosis, elevated C-reactive protein, and features suggestive of pneumonia on radiography. Moreover, in hemodynamically unstable patients, ventilatory parameters have a trend to increase in requirements[17].

The most frequent microorganisms responsible for VAP include Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, as well as Gram-positive microorganisms such a *Staphylococcus aureus*[18]. However, Gram-negative bacteria are the most prevalent cause of VAP[19].

The primordial aspect in the management of VAP should be to accurately identify the pulmonary infection, while determining the etiologic agent, to provide early targeted antimicrobial therapy[20]. Antibiotic resistance is a key determinant in the outcomes of patients with severe infections, along with pathogen virulence. It is important to highlight that within the ICU setting, VAP is often caused by multidrug-resistant bacteria[21].

In critically ill patients, emerging data suggests that nebulized antibiotics could provide an advantage in the treatment of VAP caused by multidrug-resistant bacteria. However, these antibiotics are prescribed alongside intravenous antibiotics and rarely as single therapy. Currently, antibiotics are available for administration via nebulization or inhalation; nebulized if the drug is in the form of suspension or solution, and dry powder. Both have shown similar efficacy outcomes, although dry powder forms tend to have higher rates of coughing, sometimes leading to the discontinuation of treatment. Systemic antibiotics remain as the mainstay treatment used for managing healthcare-associated pneumonia. However, recent evidence indicates that nebulized antibiotics have yielded promising results in treating VAP in critically ill patients. Administering antimicrobials directly to the respiratory tract offers key advantages over the maximum intravenous dose, including higher sputum concentrations and reduced systemic exposure. Furthermore, inhaled antibiotics are rapidly cleared from the lungs, reducing the risk of emerging resistance to antimicrobial treatment[22-25].

Direct drug administration, such as using inhaled antibiotics, reduces the risks of systemic adverse effects because of the limited systemic absorption. Likewise, since they are directly delivered to the respiratory tract, the onset of action is significantly shorter, while also reaching concentrations 100 times higher than the minimum inhibitory concentration achieved by the systemic route. Furthermore, the risk of antimicrobial resistance is eliminated or at least significantly reduced. Additionally, adverse side effects are significantly fewer than with systemic administration[26].

Nebulization is a strategic way to deliver medication to the lungs. However, there are several factors that can lead to therapeutic failure which must be avoided, primarily those related to mechanical ventilation. Ignoring these factors will surely lead to ineffective therapy due to insufficient pulmonary deposition. Notably, the amount of antibiotic loaded in the nebulizer is not the amount that will be deposited in the lung. When the nebulizer's residual volume is large, the loaded drug in the nebulizer must be increased by increasing the drug's concentration in the solution loaded into the nebulizer's reservoir. This can affect particle size and pharmaceutical deposition, prolonging nebulization duration, potentially causing drug stability issues[27].

Other factors that affect the efficacy of the administration of nebulized antibiotics with mechanical ventilation include the physicochemical properties of the antibiotic formulation such as surface tension and viscosity. Likewise, other mechanical factors such as size and type of endotracheal tube used can significantly influence pharmacokinetics[28].

Nebulizers are devices that produce an inhalable drug aerosol from a solution or suspension. Effective nebulization depends on the medication's characteristics, airway anatomy, nebulization technique, and the nebulization system. For instance, particles measuring between 1 and 5 μm are more likely to reach the site of infection and achieve the desired therapeutic effect. By definition, nebulizers convert the liquid into small particles that can be inhaled into the lower respiratory tract. The aerosol is transported by the mechanical ventilation flow, and the gas flow rate decreases from the trachea to the terminal bronchioles. The deposition of inhaled antibiotics is de-

termined by three mechanisms: impaction, sedimentation, and diffusion[29].

Antibiotics administered through inhalation must have an osmolality between 150-1200 mOsm/L, as higher values can cause bronchospasm and cough. On the other hand, pH must range between 4.0-8.0, and they must be sterile, preservative-free, and pyrogen-free. Other important properties include electrical charge, lipophilicity, solubility, and molecular weight[30].

During the selection of an antibiotic for nebulization, it is vital to consider several factors. Along these lines, the agent must be hydrosoluble, bactericidal, remain active in lung tissue, retain its properties during the nebulization process, penetrate pulmonary secretions and sputum, have minimal systemic absorption, and produce minimal harm to the airway surface. Additionally, it should be an antibiotic that does not reach high levels in the lung when administered intravenously. Likewise, other factors influencing the proper delivery of drugs to the lung include the patient's position, drug formulation, endotracheal tube size, room temperature, ventilatory asynchronies, respiratory rate, flow pattern, dose and frequency of administration, as well as nebulizer position[31].

Moreover, the nebulizer must produce particles of the appropriate size; therefore, not every nebulizer is viable for this therapy. Nebulizers generally take longer to deliver standard doses compared to other devices, making this alternative time-dependent. The choice of nebulizer should be based on where the drug will be administered and the pharmacological formulation. Jet nebulizers are the most commonly used nebulization devices. Continuous nebulization can affect the delivered tidal volume resulting in significant drug loss during expiration. Therefore, mechanical ventilators have integrated jet nebulization systems that synchronize during inspiration to maintain constant tidal volume[32].

Ultrasonic and vibrating mesh nebulizers should be placed 15 cm from the Y-piece in the inspiratory limb of the ventilation circuit, in order to achieve better drug delivery in a constant flow ventilation pattern. However, jet nebulizers perform better when placed closer to the ventilator due to the effect of continuous gas flow loading the circuit, acting as an aerosol reservoir[33].

In the case of ventilated patients, the nebulizer is generally placed in the inspiratory limb, before the Y-connector, and the hygroscopic filter is removed. Notably, if nebulization exceeds 30 minutes, humidification should be added. Likewise, airway size is important for adequate antibiotic delivery. While endotracheal tubes and tracheostomy tubes have some similarities, the tracheostomy tube is more curved and also shorter. Smaller airway diameters lead to increased airway resistance, resulting in greater drug deposition in artificial airways and the tracheobronchial region, where it might not provide the best of effects. Regarding other aspects, mechanically ventilated patients require an average temperature of 37°C and a relative humidity of 95-100% to prevent heat loss. Proper humidification prevents secretion dryness, mucous plugging, and atelectasis. In addition, the filter should be changed after each nebulization treatment[32,34].

The characteristics of ventilator breathing have a significant impact on the efficacy of aerosol delivery. Slower inspiratory flows, prolonged inspiratory times, and tidal volumes > 500 ml correlate with better aerosol delivery. Positive end-expiratory pressure (PEEP) is a ventilator setting as part of the lung protection ventilatory strategy in severe lung diseases. In this context, PEEP affects regional ventilation and perfusion, which could influence the pharmacokinetics of an aerosolized drug. When selecting one antibiotic over another, efficacy, cost, local resistance patterns, drug availability, and drug susceptibility to mechanical processes inherent to artificial ventilation should be considered. The inhaled drug dose is likely to be higher than expected due to concerns about drug losses. However, more studies are needed to guide the dosing of inhaled drugs. Available information has shown that most drug loss with inhalational therapy occurs during the exhalation phase of ventilation. To reduce this loss, nebulizer activation can be synchronized with inspiration; thus, minimizing drug loss[35].

During nebulization with mechanical ventilation, the exhalation filter should be regularly changed to prevent barotrauma. Besides, the filter change should be done with sterile measures to prevent the emission of infectious particles. Adverse effects can occur during the administration of nebulized antibiotics due to ventilator circuit or filter obstruction, leading to hypoxemia, tachycardia, hypertension, hypotension, cough, bronchospasm, pneumothorax, and, in the worst-case scenario, even cardiac arrest. Moreover, pulmonary toxicity is possible if the drug does not meet the requirements for inhalation administration[36].

ICU nurses play a pivotal role in managing invasive mechanical ventilation. Staff working in these units must have continuous education to develop and maintain the knowledge and skills necessary to provide the best quality of care[37].

As stated before, nebulized antibiotics are an alternative for pneumonia caused by multidrug-resistant Gram-negative microorganisms. In this scenario, the most frequently administered intravenous antibiotics are colistin and amikacin. However, generally speaking, they do not have adequate pulmonary penetration to manage multidrug-resistant microorganism located in pulmonary tissue. Nevertheless, studies on nebulized colistin have shown clinical improvement when administered both systemically and by inhalation[38].

Similarly, research results have shown that in patients treated with nebulized amikacin during 7 days, no renal function impairment was observed. In addition, there

was a shorter ICU stay, faster clinical cure, fewer days on mechanical ventilation, and fewer treatment days compared to patients receiving intravenous amikacin[39].

Along these lines, nebulized colistin provided high drug concentrations in lung tissue, while its intravenous counterpart showed undetectable levels in similar samples. Additionally, patients treated with nebulized ceftazidime and amikacin had a rapid and early reduction in bacterial growth, whereas those treated intravenously had a partial and delayed reduction in bacterial growth. Nevertheless, negative outcomes were also reported; although, the incidence was small since only three adverse events related to exhalation filter obstruction were reported[40,41].

Regarding research on nursing considerations when administering nebulized antibiotics, no published evidence is available. Given its relevance, studies should establish protocols or guidelines for nursing staff to assess the impact in clinical outcomes according to the quality of the provided care regarding safe and effective nebulization.

Nurses are responsible for drug administration, and conducting such research is essential to understand effective nebulization. Currently, the lack of available information on nebulized antibiotics from the nursing perspective poses a significant limitation. Furthermore, available studies on nebulized antibiotic therapy are highly heterogeneous and often associated with a high risk of bias, including observational studies and randomized controlled trials. The lacking evidence as well as the lack of standardization regarding this strategy often makes nebulized antibiotics highly questionable. However, this alternative therapy could be potentially advantageous in the management of VAP, making clinical decision-making more effective, as well as providing better overall outcomes.

Conclusions

Nebulized antibiotics could offer a valid strategy for the treatment of VAP caused by multidrug-resistant microorganisms. Nevertheless, more experimental studies are needed to demonstrate their efficacy, especially considering that only few antibiotics are available in formulations specifically for inhalation. Most nebulized medications are intended for intravenous administration, thus rarely possessing optimal properties for other routes of administration. As a result, improvised inhalational preparations could potentially pose greater risks compared to the benefits of specially manufactured inhaled antibiotics. Currently, there is no available information on nebulized antibiotics from the nursing perspective. It is crucial to conduct research on the administration of inhaled antibiotics before, during, and after the procedure. Given the increasing use of inhaled antimicrobials for treating pneumonia caused by multidrug-resistant microorganisms, understanding the implications for nursing practice is vital to achieve the best possible outcomes.

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