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BACTERIAL ETIOLOGY OF RESPIRATORY INFECTIONS ASSOCIATED WITH MECHANICAL VENTILATION AND ITS RELATIONSHIP WITH COVID-19

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ABSTRACT

At the end of 2019 until today, we live with the challenge faced by the Coronavirus pandemic. Added to this, many of the patients affected with this disease end up acquiring another disease called Mechanical Ventilation-Associated Pneumonia (VAP), still within the hospital environment, characterizing a Nosocomial Infection (NI), which makes the treatment for COVID-19 still more challenging. This study aimed to analyze the risk associated with mechanical ventilation and the most prevalent etiological agents in patients with COVID-19, emphasizing the intrinsic and extrinsic risk factors related to this infection. This is an integrative literary review study, descriptive literature and a qualitative approach. For this, a survey of information was carried out in books and scientific articles available on online platforms. The results obtained demonstrate the existence of a relationship between infection by COVID-19 and bacterial infections, with a prevalence that reaches 7% (increasing to 14% if only patients in intensive care are taken into account). These infections are considered one of the most common complications in patients undergoing mechanical ventilation, and their main etiological agents are the microorganisms *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The present article concludes that, although cases of bacterial coinfections are identified in the diagnosis of COVID-19, these are rare in the hospital environment. However, the inappropriate prescription of antibiotics in these patients led to more severe conditions of the disease, especially in cases of mechanical ventilation and ventilator-associated pneumonia.

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INTRODUCTION

The Coronavirus pandemic (SARS COV-2) has brought an immense challenge to society. According to the Ministry of Health, Coronavirus disease-19 (COVID-19) is a disease characterized by an acute flu condition that can be associated with fever, cough, sore throat, runny nose, followed or not by anosmia, ageusia, myalgia, diarrhea and headache. Moreover, the disease may develop with a more severe condition with dyspnea, respiratory distress, characterizing severe acute respiratory syndrome (SARS) (Bardi, 2021). In addition, there is a risk of the patient being affected by a

hospital infection. According to Ordinance No. 2616, of May 12, 1998, Ministry of Health, Hospital Infection (HI) or Nosocomial Infection (NI), is that acquired after the patient's admission and that manifests itself during hospitalization or within 72 hours after discharge, when it can be related to hospitalization or hospital procedures.This infection may be related to poor bed hygiene, cross infection, immune status, among others (Sousa; Ramalho; Camargo, 2020). In Intensive Care Units (ICU), Health Care-Related Infections (HCRI) are mainly associated with the use of invasive procedures (central venous catheters, venous delay probes, mechanical ventilation, among others), use of immunosuppressants;prolonged hospitalization period, previous colonization by resistant microorganisms, indiscriminate and abusive use of antimicrobials and the unit's own environment that already favors the natural selection of microorganisms and, consequently, colonization and/or infection by them, including multidrug-resistant microorganisms (Andrade; Leopold; Haas, 2006; Andrade, 2010). Additionally, mechanically ventilated patients have a high risk of bacterial colonization that can progress to ventilator-associated respiratory infections and contribute to prolong ventilation and ICU stay, increasing health costs. In addition, the detection of specific bacterial pathogens helps guide the treatment and direct the administration of antibiotics early, reducing the severity of the infection (Bassetti, 2012).

The concern about the existence of bacterial co-infections led to the recurrent practice of prescribing antimicrobials empirically for patients hospitalized with Covid-19. Studies have demonstrated the increase in antibiotic consumption in units that house patients with coronavirus (Lansbury *et al.*, 2020).In addition, it is known that the administration of inappropriate antibiotic therapy for infections, usually attributed to multidrug-resistant microorganisms, can further aggravate the patient's condition and prolong his hospitalization period (Arthur, *et al.*,2016; Garnacho Monteiro *et al.*, 2007). Antimicrobial resistance caused mainly by inappropriate empirical administration of antimicrobials has emerged as an important determinant in the clinical evolution of ICU patients (Kollef*et al*., 2000; Kollef, 2001; Niederman, 2001; Zaragoza *et al.*, 2003). Empirical therapy is a medical treatment in which there is basically the use of antibiotics based on the patient's symptomatology, where no prior identification of the etiological agent causing the infection is made (Hoefler*et al.*, 2006).Failure of adequate antimicrobial treatment is associated with negative evolution of patients in critical conditions, since the potential resistance of the etiological agent is often not considered in the selection of initial drugs for empirical therapy (Boyd; Nailor, 2011; Machado, 2018). In this context, hospitalized patients who presented moderate to severe cases of COVID-19 present as risk factors for secondary infection the degree of severity of the disease and the use of corticosteroids. In addition, these patients have high values of C-Reactive Protein (CRP) and neutrophil-lymphocyte ratio (Nasir *et al.*, 2021).In view of this scenario, it is essential to study co-infections in patients hospitalized with COVID-19, since these are related to a worse prognosis and increased mortality. Thus, the present article aimed to analyze the risk associated with mechanical ventilation (MV) and the most prevalent etiological agents in patients with COVID-19, highlighting the intrinsic and extrinsic risk factors related to this infection.

MATERIALS AND METHODS

This study is a bibliographic review, conducted a survey of information related to the object of study through basic literature in Microbiology, such as Tortora, Funke and Case (2010) and Trabulsi and Alterthum(2009). In addition, it was conducted through research in databases and/or platforms such as Scientific Electronic Libary Online (Scielo), Google Scholar, Ministry of Health, PubMed and Latin American and Caribbean Literature on Health Sciences (LILACS),among other databases available, with the descriptors in Portuguese, English, Italian and Portuguese: “COVID-19”, “Hospital infections”, “Bacteria”, “Mechanical Ventilation”, “Pneumonia” and “Antibiotics”. Excel and Word were used to produce graphs and tables. Thus, articles were selected in Portuguese, English, Italian and European Portuguese, in the recognized information sites, books, theses and dissertations published between 2019 and 2021 for the analysis of the study.The selection of articles was made from the titles and abstracts, which were in agreement with the theme, choosing those that provided scientific relevance and that were in agreement with the work. The excluded materials were those that did not have scientific importance and did not contribute to the central objective of the work. Finally, when it was a bibliographic review, no submission was necessary to the Ethics Committee (Figure 1).

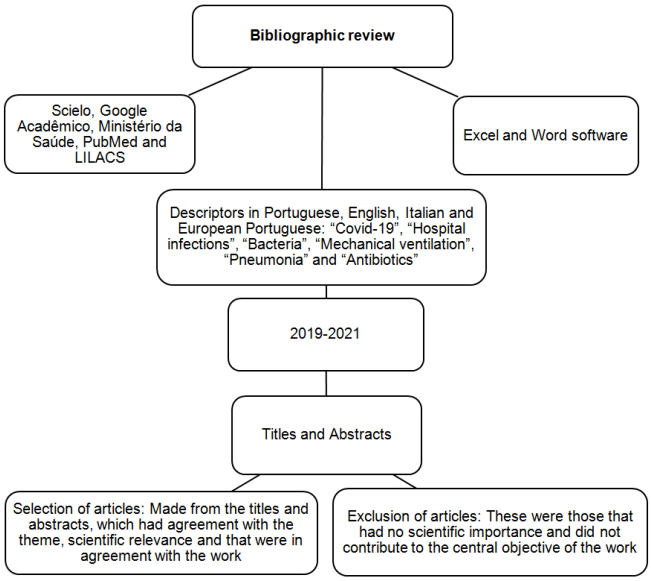

Figure 1. Flowchart describing chronologically the project methodology

RESULTS AND DISCUSSION

Antimicrobial combination therapy first emerged with the most common approach of treatment for severe infection with *Pseudomonas aeruginosa*, after it was demonstrated that co-administration of β-lactam and aminoglycoside agents was associated with decreased mortality in animal models (Christoff *et al*., 2010). According to the author, the application of antimicrobials empirically is used by most ICUs, but estimates of the result are inaccurate and professionals often do not know of the existence of a probable microbial resistance to the medication. Currently, there is little information regarding the role of the speed of the beginning of treatment (first 24h or 48h) of the patient with suspected infection (Nathwani*et al*., 2014; Zimlichman*et al*., 2013; Machado, 2018). The therapeutic approach to the supposed non-fermenting GNB (Gram-Negative Bacilli) infections usually begins with the use of broad-spectrum cephalosporins in combination with some aminoglycoside (Kunz; Brook, 2010). The authors also state that therapy with a carbapenem in combination with an aminoglycoside can be considered for patients who are seriously ill or hospitalized for a prolonged period, especially in ICUs and that this combination provides good coverage for combating species belonging to *Pseudomonas spp*., *Enterobacteriaceae* family and *Acinetobacter spp*. as well as Gram-positive aerobics and all anaerobic bacteria. The diagnosis of nosocomial pneumonia is complex and is currently based on the sum of clinical, radiological and microbiological data, with no gold standard (Zilberberg; Shorr, 2010). The most used criteria are the presence of a new or progressive infiltrate on chest X-ray and the presence of two or three of the following clinical characteristics: temperature >38°C,leukocytosis, purulent respiratory secretion, positive lower respiratory tract secretion culture, and when quantitative culture, a cutoff point of ≥ 106 Colony Forming Units (CFU/ml) for endotracheal aspirate, 104CFU/ml for bronchoalveolar washed and 103CFU/ml for the protected brush, and in semiquantitative cultures, a “moderate” growth of bacteria (Peleg) is observed; Hooper, 2010; Machado, 2018).

The increased incidence of multidrug-resistant Gram-negative bacteria, especially *K. pneumoniae*, *P. aeruginosa* and *A. baumanii* is a global problem, a consequence of the ability of these microorganisms to develop resistance to almost all antimicrobials available for treatment, whether by selecting isolates with mutations in chromosomal genes or by rapid acquisition of resistance plasmid genes and easy dissemination (Gootz, 2010; Hou *et al*., 2015; Porto *et al*., 2013).In Brazil, this problem is even more significant since there is a high density of indiscriminate use of antibiotics, mainly of the class of betalactamics (especially carbapenems) and broad-spectrum cephaloporins (Moreira *et al*.,2013; Giarratano; Green; Nicolau, 2018). *P. aeruginosa* infections are important in the hospital environment, especially in Intensive Care Units (ICU). This pathogen is related to hospital infections, especially Ventilator-Associated Pneumonia (VAP) and Bloodstream Infections (BSI), and is related to outbreaks in ICUs.Moreover, this agent has the ability to develop resistance to several antimicrobials quickly, which can be a problem that implies difficulty in therapeutic management and mortality of patients (Silva, 2021). Viral infections are known to be associated with bacterial infections concomitantly. For this reason, it is common for many professionals to start antimicrobials empirically. Rawson *et al*. (2020) conducted a systematic review and found a prevalence of 8% of bacterial or fungal co-infections in patients diagnosed with Covid-19.In a publication in the Journal of Infection, Lansbury et al. (2020) found a prevalence of 7% of laboratory bacterial co-infection confirmed in patients hospitalized with COVID-19, increasing to 14% when the analysis is only in patients hospitalized in intensive care. Also in this same study, it was reported that the bacteria found most frequently were: *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenza* and *Klebsiella pneumoniae*.In most cases, they were hospital pneumonia.

One of the most common complications in hospitalized patients undergoing mechanical ventilation are bacterial infections. In a study involving 1,419 patients on mechanical ventilation (MV), the six main complications recorded in the one-year period were infections, the most frequent being ventilator-associated pneumonia in 31.0% of patients (Scheinhorn*et al.*, 2007). Approximately 10% of patients requiring mechanical ventilation develop pneumonia, with a mortality rate of 20-50%. The high risk of infections is due to multiple factors, such as prolonged use of invasive elements (tracheostomy cannula, catheters, etc.), prolonged exposure to environments contaminated by virulent and resistant microorganisms, and immunological changes caused by comorbidities and the patient's recent critical illness (Kalb; Lorin, 2002). In addition to these factors, VAP (Ventilator-Associated Pneumonia) caused by Gram-Negative Bacilli (GNB), particularly when related to microorganisms resistant to broad-spectrum cephalosporins and carbapenems, is associated with significant percentages of mortality and morbidity (Gootz, 2010; Hou *et al*., 2015; Porto *et al*., 2013).The etiology of VAP varies in different countries, between ICUs of the same city, between groups of different patients or areas of the same hospital (Monteiro Neto *et al*, 2017; Park, 2005). In addition, GNB organisms, especially *P. aeruginosa*, *A. baumanii* and microorganisms of the enterobacteriaceae family are more frequent isolated in patients submitted to mechanical ventilation (Moreira *et al*., 2013; Porto *et al*., 2013). In Brazil, there was a predominance of non-fermenting GNB with resistance to carbapenems and colistin, currently endemic in many tertiary-level care hospitals (Rossi *et al*, 2017; Silveira *et al*., 2019). In addition to resistance mechanisms, the literature describes several risk factors that may be involved in the development of Ventilator-Associated Pneumonia (VAP), including: immunocompromise, trauma, surgery, presence of comorbidities, severe underlying diseases, invasive procedures, among others (Rossi *et al*, 2017).Several processes are implicated in the pathogenesis of VAP: aspiration of oroamyal secretions resulting from an altered state of consciousness, loss of natural mechanisms of airway protection and direct inoculation of the pathogen at the time of intubation. Colonization of the airways by pathogens detected by bacterial cultures of tracheal aspirate routines may be useful to identify patients at increased risk for the development of VAP (Kalil *et al*, 2016).

Additionally, Machado's study (2018) showed that all patients included in the study presented clinical and microbiological criteria for the development of VAP.We identified 605 cases of pneumonia, and 558 (92.2%) were associated with mechanical ventilation, of which 513 episodes were characterized as monomicrobial, the existence of only one species of microorganism (91.9%) and 45 were of polymicrobial etiology, characterized by the existence of more than one species of microorganism (8.1%) (Table 1).The total mortality of patients who developed VAP was 26.4% and 34.0% developed the disease in the first episode of infection caused by GNB.

Table 1. Description of Pneumonia Cases associated with VAP, microbial modality and Classification of GNB Organisms in the Adult Intensive Care Unit (ICU)

Pneumonia cases	(n)	(%)
VAP	558	92.2
Other causes	47	7.8
Total	605	100
Microbial Modality	(n)	(%)
Monomicrobial	513	91.9
Polymicrobial	45	8.1
Gram negative microorganisms	(n)	(%)
Not Fermenters	500	74.6
Enterobacteriaceae family	170	25.4
Total	670	100

Source: Adapted from Machado, 2018.

Also in the study, 826 microorganisms were isolated by quantitative endotracheal secretion culture of all patients with VAP and, among these, gram-negatives were the most frequent, with 81.1% (n=670/826) of the total microorganisms. Within this group, non-fermenters stood out with a frequency of 74.6% (n= 500/670), followed by microorganisms of the *Enterobacteriaceae* family with 25.4% (n = 170/670) (Table 1). In this study, it was observed regarding the resistance phenotypes in VAP caused by GNB and Gram-positive cocci, 63.3% (n=523/826) of the microorganisms were resistant to antimicrobials. There was an increase in MRSA (Methicillin-resistant *Staphylococcus aureus*) (n=78/142, 54.9%), *Klebsiella*spp, (n=46/55, 83.6%) and *Enterobacter*spp (n=30/42, 71.4%) resistant to cephalosporins broad-spectrum, along with carbapenem-resistant *Acinetobacter baumanni* (n=140/175, 80%) (Table 2).

Table 2. Resistance phenotypes in VAP caused by GNB and Gram-positive cocci in the Adult Intensive Care Unit (ICU)

Resistance phenotypes in VAP	(n)	(%)
MRSA	78	54.9
Klebsiella spp	46	83.6
Enterobacter spp	30	71.4
Acinetobacterbaumanni	140	80

Source: Adapted from Machado, 2018.

Regarding the patients who presented the first episode of VAP in the study addressed, 295 microorganisms were identified. Gram-negatives remained the most frequent group (n =215/295, 72.9%), with a significant participation of non-fermenting GNB (n =146/215, 67.9%). *Staphylococcus aureus* (n =70/80, 87.5%),*A. baumannii* (n =64/215.29.8%), *P. aeruginosa* (n =63/215, 29.3%) and*Enterobacter spp.*(n =24/215, 11.2%) were the most commonly found species. Of these, in total, 155 microorganisms showed antibiotic resistance, mainly *Klebsiella spp*. (n =18/23, 78.3%), followed by *E. coli* (n=2/3, 66.7%) and *A. baumannii* (n =40/64, 62.5%) (Table 3). In relation to patients hospitalized with COVID-19 according to the study by Garcia-Vidal *et al*. (2021), demonstrates a total of 989 consecutive patients with COVID-19, 72 (7.2%) had 88 other infections confirmed microbiologically, 74 bacterial, seven fungal and seven viral. Community-acquired co-infection in the diagnosis of COVID-19 was uncommon (31/989, 3.1%) and mainly caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*.

Table 3. Most frequent bacteria in the first episode of VAP in the Adult Intensive Care Unit

First-episode VAP phenotypes	(n)	(%)
Gram Negative	215	72.9
Non-fermentingGNB	146	67.9
Staphylococcus aureus	70	87.5
Acinetobacterbaumanni	64	29.8
Pseudomonas aeruginosa	63	29.3
Enterobacterspp	24	11.2
Resistancephenotypes in VAP	(n)	(%)
*Klebsiella*spp	18	78.3
Escherichia coli	2	66.7
Acinetobacterbaumanni	40	62.5

A total of 51 bacterial superinfections acquired in hospitals, mainly caused by Pseudomonas aeruginosa and *Escherichia coli*, were diagnosed in 43 patients (4.7%). Overall mortality was 9.8% (97/989). Patients with community-acquired co-infections and hospital-acquired superinfections had worse results. Another point of reflection, are the cases of bacterial coinfections being uncommon the attention of health professionals, in these cases led to the prescription of antibiotic therapy inappropriately. In the review by Lansbury *et al*,(2020), a significant increase in antibiotic consumption was evidenced in units that provide care to patients with COVID-19, especially in Spain.Patients with the disease present risk factors for the development of HCRI, as well as infections by multidrug-resistant microorganisms. Other aggravating factors identified were: presence of previous chronic lung disease, mechanical ventilation, prolonged hospitalization and indiscriminate use of antibiotics without medical prescription. Furthermore, the increase in the number of cases of bacterial infections in patients with COVID-19 alerted to compliance with safety protocols in health units during the pandemic. SARS COV-2 has more serious effects when it affects the lungs and, in many cases, subjecting the patient to mechanical ventilation. MV, in turn, is the main vector of bacteria transmission in hospitals, especially in ICUs.In addition, this article the main pathogens that affect patients hospitalized with Covid-19 submitted to MV are GNB bacteria such as:*Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumanii.* In the hospital context, the adoption of contact precautionary measures is essential to avoid, not only the nosocomial transmission of SARS COV-2, but also of multidrug-resistant microorganisms. Other measures to be taken are hand hygiene, care such as changing gloves for each patient and using an individual bonnet for patients who are in contact precaution for the risk of multidrug-resistant microorganisms.Thus, it is necessary to previously identify the organism that affects the patient in bacterial infections and its resistance profile to then initiate the most appropriate antimicrobial therapy.

Final Thoughts: The emergence of SARS COV-2 presented a great challenge for therapeutic medicine and the health system worldwide, especially with regard to empirical administration of antibiotics in ICU patients with COVID-19. In cases of more severe pulmonary infections caused by the virus, the patient is submitted to mechanical ventilation (MV), increasing the risk of contamination by other pathogens such as bacteria and generating ventilator-associated pneumonia (VAP). In the survey of materials for the construction of this article, it is concluded that although cases of bacterial co-infections are identified in the diagnosis of COVID-19, these are few common in the hospital environment. Additionally, a small number of patients developed superinfections during hospitalization. These findings are different compared to other viral pandemics.With regard to patients hospitalized with coronavirus, such findings may be essential in defining the role of more appropriate antimicrobial therapy and management strategies.

Conflict of interest: The authors state that the research was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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