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MICROBIOLOGICAL PROFILE OF PNEUMONIA ASSOCIATED WITH VENTILATORY SUPPORT IN PATIENTS INTERNED IN THE INTENSIVE CARE UNIT OF A PUBLIC HOSPITAL IN SANTA CATARINA, BRAZIL

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Abstract: Introduction: Pneumonia associated with ventilatory support (VAP), acquired in Intensive Care Units (ICUs), are a relevant cause of risk of death. In addition, antimicrobial resistance of the bacteria involved in these infections is on the rise, making treatment difficult. **Goal**: To evaluate the microbiological profile and bacterial resistance of bronchoalveolar lavage isolates from patients with ventilator-associated pneumonia (VAP) admitted to the Intensive Care Unit (ICU) of a public hospital, Santa Catarina, Brazil. **Methods**: A retrospective, quantitative cross-sectional study of adult patients with VAP admitted to the ICU from 2017 to 2019. Clinical, demographic and microbiological culture results were obtained from electronic medical records. The data were arranged in excel sheets and the results were expressed in absolute numbers and percentages. **Results**: Of the total number of patients investigated, microorganisms grew in 102 (64.5%) individuals, while 56 (35.5%) only used clinical criteria to define VAP. The mean age was 52.7 years, with the majority being male, 67.7%. The mean intubation time was 11.2 days. The most frequent microorganisms were Gram negative bacilli 59.8% and Gram positive cocci 40.1%. Of the most prevalent species, the *Staphylococcus aureus* was observed in 33.3% samples, *Pseudomonas aeruginosa* 23.4% and *Acinetobacter baumannii* 10.7%. In the analysis of the antimicrobial resistance profile, the *Acinetobacter baumannii* showed greater resistance, being 81.9% resistant to imipenem, meropenem, cefepime, ceftazidime, ciprofloxacin; at second place, the *Klebsiella pneumoniae* showed resistance to ampicillin 85.7%, to ampicillin + sulbactam 71.4%, to ceftazidime 66.6%, to gentamicin 50% and to cefepime: 50%. The *Staphylococcus aureus* showed a greater resistance profile to penicillins (83.5%), without MRSA isolates. **Conclusion**: *Acinetobacter baumannii* was the only carbapenemase-producing species, and it is necessary to expand the study to follow the VAP treatment protocols.

Keywords: Pneumonia associated with mechanical ventilation, ICU, Bacterial resistance, multi-resistance.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as hospital-acquired pneumonia that develops within 48 to 72 hours of the start of ventilatory support. VAP is a frequent problem in Intensive Care Units (ICU), associated with a high risk of death, and its prevalence reaches about 5 to 40% of patients with ventilatory support, being more frequent in patients with coexisting comorbidities, mainly Chronic Obstructive Pulmonary Disease (COPD) and neoplasms (ROUZÉ, 2014).

In VAP patients, mortality rates can vary between 20% and 70%, with higher rates when they are related to the involvement of more virulent pathogens or when the initial antibiotic therapy is not appropriate for the causal agent (TORRES, 2017). This disease, in addition to being responsible for increased mortality, data also point to a prolonged stay and use of mechanical ventilation, which leads to a considerable increase in treatment costs (ROUZÉ 2014; COSTA, 2019; WALTRICK, 2015).

Patients with VAP have a broad spectrum of clinical repercussions, such as dyspnea, fever, purulent discharge, and imaging findings, which include alveolar infiltrates and air bronchograms. For a more accurate clinical diagnosis, it is necessary to perform a chest X-ray and culture examination of materials obtained by non-bronchoscopic methods, such as mini-BAL, or bronchoscopic (MARIK, 2014). This way, a diagnosis based on the clinic and complementary exams is important for an adequate and early antimicrobial therapy, and to avoid the

excessive use of antimicrobials (TORRES, 2017).

VAP is caused by several etiological agents, originating from the patient's own microbiota or from the hospital environment. Gram-negative bacilli (GNBs) are the majority, with greater emphasis on the *Pseudomonas aeruginosa*, the *Escherichia coli*, the *Klebsiella pneumoniae* and the *Acinetobacter baumannii*; and among the Gram positive cocci, the *Staphylococcus aureus* (HUANG, 2018; BAILEY, 2015). According to the Report of *European Centre for Disease Prevention and Control*, of 2014, the *Staphylococcus aureus* methicillin-resistant (MRSA) was present in 25% of VAP cases, whereas 3rd-generation cephalosporin-resistant BGNs stood out. *Klebsiella* spp 43,7%, *Enterobacter* spp. 43,5% and *Escherichia coli* 17,3%; but *Pseudomonas aeruginosa* resistant to ceftazidime with 24.2%. Regarding resistance to carbapenems, the species of *Acinetobacter baumannii* 63,5%, *P. aeruginosa* 27,7%, *Klebsiella* spp. 7,7%, *Enterobacte*r spp. 1,5% and *Escherichia coli* 0,9% prevailed.

The etiological agents that cause VAP vary according to the profile of hospital services, the population served and the reason for hospitalization before VAP. These factors corroborate the need for permanent local surveillance. Preventive measures must be guided by an understanding of the pathogenesis of the disease and by local epidemiological data. Thus, it must be noted that Brazilian epidemiological data are scarce, most of which are restricted to a hospital or region, and do not extend to the entire Brazilian territory. Thus, epidemiological studies are important, especially with the approach of evaluating the resistance profile of pathogens for the definition of therapeutic protocols.

In this context, the present study aims to evaluate the microbiological profile and susceptibility to antimicrobials of isolates from bronchoalveolar lavage or bronchial aspirate, from patients with VAP admitted to the ICU, before the COVID-19 pandemic, to assist treatment care and reduce morbidity. of patients during the pandemic.

METHODS

The present quantitative, longitudinal and retrospective study was carried out with data collected from electronic medical records of patients who developed VAP in the ICU, between January 2017 and December 2019, at a trauma referral hospital in the city of Joinville, Brazil. Santa Catarina.

The research was authorized by the Institution and approved by the Research Ethics Committee of UNIVILLE, under protocol 3,971,466.

The study included 158 patients of both genders, older than 15 years, with a suspected diagnosis of VAP after 48 hours on ventilatory support and admitted to the ICU. As ICU cases are not regular cases, the sample consisted of consecutive cases admitted to the ICU with a diagnosis of VAP.

The clinical and demographic data of the patients were obtained from electronic medical records, and the results of the microbiological culture and the profile of susceptibility to antimicrobials in the microbiology exam reports, filed with the Infection Control Service (ICC) of the institution. The data included were age, gender, date of hospital admission, date of admission to the ICU, start date of Mechanical Ventilation Support, criteria adopted in the diagnosis of VAP (clinical or laboratory), clinical material investigated, microbiological profile, susceptibility to antimicrobials and outcome (discharge, transfer or death).

STATISTICAL ANALYSIS

Data were analyzed using descriptive statistics, calculating absolute and relative frequencies. Categorical variables were expressed as absolute numbers and percentages and continuous variables as means and standard deviations.

RESULTS

The study included 158 patients diagnosed with VAP, 102 (64.6%) with confirmation by microbiological culture and 56 (35.4%) diagnosed by clinical and imaging criteria. Men were the majority, 107 (67.7%) and women 51 (32.3%), with a median age of 55 years (mean 52.7 years), and age group between 15 and 86 years. Intubation time before pneumonia acquisition was an average of 11.2 days, with a minimum value of 2 and a maximum value of 73.

The pathogens that prevailed in this study were 61 (57.8%) Gram negative bacilli and 41 (40.2%) Gram positive cocci. Distributed by biological materials, it was found that 79 (77.5%) were from alveolar bronchial lavage and 23 (22.5%) from alveolar bronchial aspirate (ABA); more often for *Staphylococcus aureus* 21 (26,6%) and 13 (56,5%); *Pseudomonas aeruginosa* 20 (25,3%) and 4 (17,4%); *Acinetobacter baumannii* 8 (10,1%) and 3 (13%) and *Klebsiella pneumoniae* 6 (7,6%) and 2 (8.7%), respectively. The distribution of pathogens is shown in Table 01.

In the investigation of the phenotypic profile of resistance of *Staphylococcus aureus* c was found that the greatest resistance was to penicillin with 25 (83.5%) and erythromycin 23 (82.1%) of the tested isolates. Antibiotics, namely: teicoplanin 32 (100%), vancomycin 30 (100%), oxacillin 29 (90.6%), gentamicin 26 (89.6%), amikacin 25 (89.3%), ciprofloxacin 24 (88.8%) were sensitive to the tested isolates. No isolate was MRSA, figure 01.

Among the 61 isolates of Gram negative bacilli, the analysis of susceptibility to antimicrobials was applied to the 03 most prevalent species, such as: *Pseudomonas aeruginosa* (n=24; 39.3%), *Acinetobacter baumannii* (n=11; 18%) and *Klebsiella pneumoniae* (n=8; 1,3%).

Comparing the resistance between the 03 species, the *Acinetobacter baumannii* a showed higher profile, with 81.9% isolates resistant to imipenem, meropenem, cefepime, ceftazidime, ciprofloxacin. As for amikacin and gentamicin, 80% and 36.4% were resistant, respectively. All isolates demonstrated sensitivity to colistin and polymyxin (figure 02).

Among the 24 Pseudomonas aeruginosa isolates, resistance was found in 27.3% to imipenem, 43.5% to ceftazidime, 38.9% to ciprofloxacin, 42% to piperacillin + tazobactam and 30% to amikacin. Only 04 isolates were tested for polymyxin B, and all showed sensitivity (figure 03).

The isolates of *Klebsiella pneumoniae* showed greater resistance to ampicillin (85.7%), ampicillin + sulbactam (71.4%), ceftazidime (66.6%), gentamicin (50%) and cefepime (50%). As for carbapenems, most were sensitive, 100% to meropenem, 85.7% to imipenem; 100% to amikacin, 71.4% to piperacillin + tazobactam and 57.1% to ciprofloxacin. There were no carbapenemase-producing isolates (KPC) (figure 04).

Regarding the outcome of the patients involved in this study, the two groups, that is, with VAP confirmed by microbiological culture (group 1) and VAP only by clinical criteria and images (group 2) had similar frequencies. Death was observed in 44% and 36%; high 53% and 57% and transfer 3% and 7%, respectively.

DISCUSSION

The study aimed to know the microbiological profile, as well as the

Microrganism	n (%)
Staphylococcus aureus	34 (33.3%)
Pseudomonas aeruginosa	24 (23.4%)
Acinetobacter baumannii	11 (10.7%)
Klebsiella pneumoniae	8 (7.8%)
Escherichia coli	5 (4.9%)
Serratia liquefaciens	4 (3,9%)
Proteus mirabilis	3 (2.9%)
Enterobacter aerogenes	3 (2.9%)
Staphylococcus coagulase negativa	3 (2.9%)
Streptococcus alfa hemoliticus	2 (1.96%)
Streptococcus gama hemoliticus	2 (1.96%)
Enterobacter gergoviae	1 (0.98%)
Morganella morganii	1 (0.98%)
Serratia marcescens	1 (0.98%)

Table 1: Distribution of bacterial species isolated in patients with PAV (n=102).

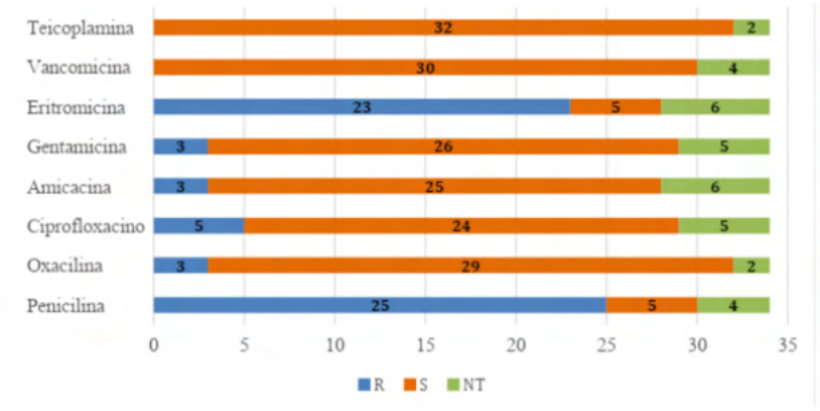

Figure 1: Antimicrobial susceptibility profile of *Staphylococcus aureus* (n=34).

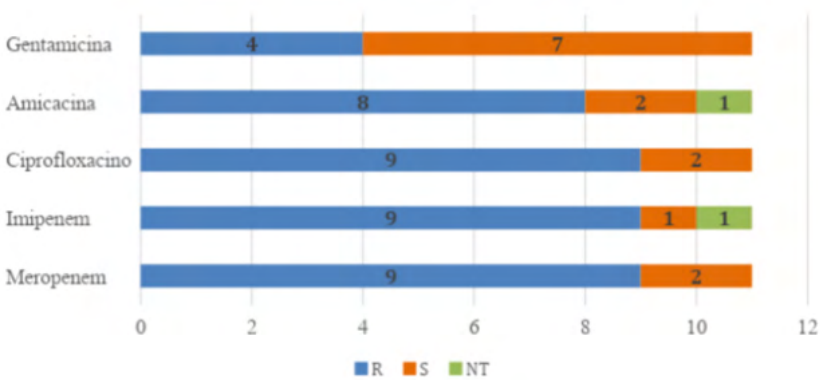

Figure 2: Antimicrobial susceptibility profile of *Acinetobacter baumannii* (n=11).

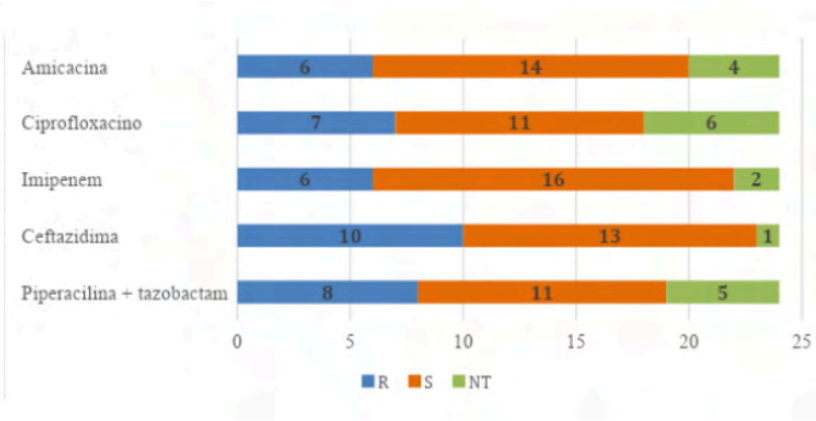

Figure 3: Antimicrobial susceptibility profile of *Pseudomonas aeruginosa* (n=24).

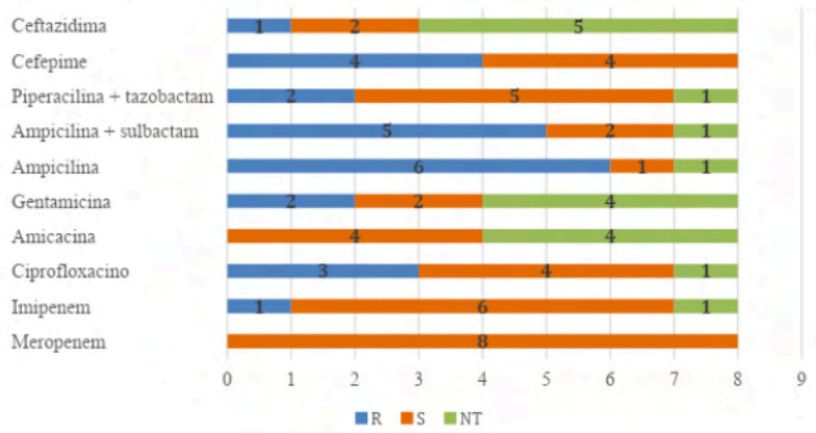

Figure 4: Antimicrobial susceptibility profile of *Klebsiella pneumoniae* (n=08).

susceptibility to antimicrobials involved in cases of pneumonia associated with ventilatory support in patients admitted to the ICU, and its changing trend. In addition, the investigated institution provides a reference service in multiple traumas and stroke.

The incidence of VAP observed in our study was around 13.1/1000 MV days. Similar data was also found by: *European Centre for disease prevention and control* (ECDC), where the PAV rate, in 2019, was between 2.8 and 15.8 per 1000 MV days. In the study "*Hospital-Acquired Pneumonia in a Multipurpose Intensive Care Unit: One-Year Prospective Study*", the data revealed a VAP rate of 69% (COSTA, 2019), similar to our study.

As for the epidemiological profile of the patients studied, the mean age of 52.7 years, with a predominance of males, was also found in the study carried out at the University Hospital of Minas Gerais (MOTA, 2017), from January 2011 to December 2012, 66% were male, and 22 of them were younger than 60 years old.

The study by Chastre J et al. compiled microbiological data from 24 published studies that used a bronchoscopic diagnostic method to confirm 1,689 cases of VAP. Gram negative bacteria represented 58% of the isolates and Gram positive cocci represented 35% (CHASTRE, 2002). A similar study by Fagon JY et al., on the prevalence of specific

pathogens responsible for hospital-acquired pneumonia, including VAP, also showed negative bacteria as most of the isolates (FAGON, 1989). In the study by Charles-Edouard Luyt, in 2018, they reported that of the total of 12,851 VAP bacteria isolated in Europe and the United States, 61.5% and 76.1% were the prevalence rates of Gram negative bacilli, respectively. This shows that these microorganisms are really expected and frequent in patients with VAP (LUYT, 2018). These findings were similar to the present study in which the predominant microorganisms were Gram negative bacilli, with emphasis on the *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae,* corresponding to about 42.1% of the entire sample size, while Gram positive cocci (*Staphylococcus aureus*) were found: 33,3%.

A comparative study, when studying the bacterial profile of patients who were on ventilatory support or had the diagnosis of nosocomial pneumonia in ICUs in Europe and the United States (LUYT, 2018), demonstrated a prevalence of Gram negative bacilli, with a higher frequency for *Pseudomonas aeruginosa* (21%) and Enterobacteriales (31.6-33.8%). On the other hand, Gram positive bacteria were in smaller numbers, with emphasis also on *Staphylococcus aureus* (21.3-30.1%). Of the 11 pathogens isolated, 9 were gram-negative bacilli in both scenarios, and among the gram-positive ones, the *Staphylococcus aureus* had greater epidemiological importance, being the main isolate in the United States and the second most isolated in European countries. The most prevalent pathogens were the same found on both continents, with emphasis on the *Staphylococcus aureus*, *Pseudomonas aeruginosa, Streptococcus pneumoniae*, *Acinetobacter spp, Enterobacteriaceae* and *Escherichia coli*, and are related to both MV and nosocomial pneumonia.

According to the study by Ahmed W et al., on VAP-related microorganisms and their pattern of antibiotic sensitivity:

Acinetobacter baumannii surpassed the other pathogens as the leading cause of VAP (AHMED, 2014). According to the study of Gupta V et al., *Acinetobacter baumannii* and pseudomonas aeruginosa were the species with the highest antimicrobial resistance profile. (GUPTA, 2018).

Antimicrobial resistance has increased among isolates from ICU patients, especially in VAP cases. In the present study, to *Acinetobacter baumannii* was the species with the highest level of resistance to carbapenems - 81.8%, Ciprofloxacin - 81.1%. Colistin was found susceptible among all isolates.

Another most frequent pathogen in this study was *Pseudomonas aeruginosa* with a resistance to ceftazidime 43.5%, to piperacillin + tazobactam 42%, to ciprofloxacin 38.9%, amicanchin 30% and carbapenems 27.3%.

However, resistance to carbapenems has been observed in species of the order Enterobacterales and in non-fermenters, such as *P. aeruginosa* (TOLEMAN, 2002). Resistance to carbapenems may occur due to low penetration of active substances, that is, mutations in genes that synthesize porin-type membrane proteins and/or efflux pumps, in addition to the production of carbapenemase enzymes, the latter being a mechanism of high relevance, due to the exponential diversity of these enzymes, particularly the metalo-β-lactamases (MβL) (JÁCOME, 2012). However, in our study, we did not observe isolated *Klebsiella pneumoniae* carbapenemase (KPC). Data not in agreement with the literature, where this species has a high profile of resistance to beta-lactams and carbapenems.

Among the Gram positive cocci, the *Staphylococcus aureus* prevailed in this study, however, no isolates were found expressing

resistance to oxacillin, known as: *Methicillin Resistant Staphylococcus aureus* (MRSA). The highest resistance was found for penicillin 73.5% and erythromycin 82.1%. Studies indicate a high prevalence of these pathogens in patients hospitalized in ICUs, with rates between 25% (MARIK, 1995; HUANG, 2018) and 14.8% (DÍAS, 2010). Currently, the coding mechanism of the blaZ gene, located in the plasmid, which promotes penicillin inactivation through hydrolyzing the beta-lactam ring, is widely discussed (TAKAYAMA, 2018).

It is believed that the low resistance profile of enterobacterales and *Pseudomonas aeruginosa,* is related to the profile of the hospital, where most patients were young, with mild trauma and little time on ventilatory support.

As for the outcome of the patients included in this study, 54.4% were discharged from hospital, 41.1% died and 4.4% were transferred to other health institutions. Research developed in the city of Chapecó, Santa Catarina, between 2014 - 2015, among patients diagnosed with VAP, the death rate reached 44% (SILVA, 2017). In VAP episodes, the overall mortality rate varies between 20% and 60%, reflecting the severity of the underlying disease of these patients, organ failure, the specificities of the population studied and the etiological agent involved, where 30% of mortality is attributed directly to VAP, as described by Brazil's national surveillance agency in 2017.

The study had some limitations, as the present study was a retrospective study, not allowing inferences on the methodology applied at the time of diagnosis of VAPs, and these results were based on a filtered population of patients with trauma and stroke, not being applicable to the population general. The lack of standardization of the antibiotics tested and the limitation of newer drugs must be included in further studies to better determine the antimicrobial susceptibility profile in the studied ICU.

CONCLUSION

In this study, it was possible to conclude that VAP is a nosocomial infection of great relevance in the population studied, showing the presence of *Acinetobacter baumannii* multidrug, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* with less resistance. Therefore, with knowledge of the most common organism isolated and its antibiotic resistance pattern, the institution under study can extend the study period, including the period of the COVID-19 pandemic, as the prescription of antimicrobials was expanded in the treatment of pulmonary infections, and mainly in cases of VAP. Also, we emphasize the importance of implementing the Patient Safety Center (NSP), which contains indicators of practices that prove the reduction of VAPs.

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