

Prevalence of bacterial infections and antimicrobial resistance profile in hospitalized patients with COVID-19

Prevalência de infecções bacterianas e perfil de resistência aos antimicrobianos em pacientes internados com COVID-19

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ABSTRACT

Background and Objectives: bacterial resistance is an important public health problem worldwide and is related to the indiscriminate use of antimicrobials, limiting the available therapeutic options. The COVID-19 pandemic aggravated this scenario, since the lack of a standardized therapy led to a considerable increase in the prescription of these drugs. Therefore, we proposed to investigate the prevalence of bacterial infections and the profile of antimicrobial resistance in patients diagnosed with COVID-19 as well as to point out possible risk factors. **Methods:** a retrospective study based on the analysis of medical records of patients hospitalized with COVID-19 over the age of 18. Information such as age, gender, length of stay, hospitalization unit, bacterial species and resistance profile and previous use of antimicrobials by patients diagnosed with COVID-19 were collected and analyzed using Excel[®] 2016. **Results:** of the 268 patients with COVID-19, 162 had suspected bacterial infections, and 26 patients (9.7%) were confirmed from positive cultures. Furthermore, around 80% of these patients underwent empirical treatment with antimicrobials, the majority of whom were male and admitted to the Intensive Care Unit. A total of 32 bacterial isolates were recovered, of which 59.4% were resistant to at least one class of antimicrobials, with 21.8% being multidrug resistant. **Conclusion:** despite the low percentage found of patients with COVID-19 who had bacterial infections and of these 21.8% were by multidrug-resistant bacteria, the reinforcement in infection prevention policies and the adequate management in the release of antimicrobials is necessary to reduce the hospital dissemination rates of such bacteria.

Keywords: COVID-19; Bacterial Infections; Drug Resistance, Microbial; Cross Infection.

RESUMO

Justificativa e Objetivos: a resistência bacteriana é um importante problema de saúde pública mundial relacionado ao uso indiscriminado de antimicrobianos, limitando as opções terapêuticas disponíveis. A pandemia de COVID-19 agravou esse cenário, uma vez que a falta de uma terapia padronizada resultou no aumento considerável na prescrição desses fármacos. Diante disso, propôs-se investigar a prevalência de infecções bacterianas e o perfil de resistência aos antimicrobianos em pacientes diagnosticados com COVID-19, bem como apontar possíveis fatores de risco. **Métodos:** estudo retrospectivo baseado na análise de prontuários de pacientes internados com COVID-19 com idade superior a 18 anos. Informações como idade, gênero, tempo de internação, unidade de internação, espécie bacteriana e perfil de resistência e uso prévio de antimicrobianos pelos pacientes diagnosticados com COVID-19 foram coletadas e analisadas pelo *software* Excel® 2016. **Resultados:** dos 268 pacientes com COVID-19, 162 apresentaram suspeitas de infecções bacterianas, sendo 26 pacientes (9,7%) confirmados a partir de culturas positivas. Ainda, cerca de 80% desses pacientes realizaram tratamento empírico com antimicrobianos, sendo a maioria do sexo masculino e internados em Unidade de Terapia Intensiva. Foram recuperados um total de 32 isolados bacterianos, dos quais 59,4% apresentaram resistência a pelo menos uma classe de antimicrobianos, sendo 21,8% multidroga resistente. **Conclusão:** apesar do baixo percentual encontrado de pacientes com COVID-19 que apresentaram infecções bacterianas e, desses, 21,8% serem causados por bactérias multirresistentes, o reforço nas políticas de prevenção de infecções e o adequado gerenciamento na liberação de antimicrobianos se fazem necessários para a redução das taxas de disseminação hospitalar de tais bactérias.

Descritores: COVID-19; Infecções Bacterianas; Resistência Microbiana a Antibióticos; Infecção Hospitalar.

RESUMEN

Justificación y Objetivos: la resistencia bacteriana es un importante problema de salud pública en todo el mundo y está relacionada con el uso indiscriminado de antimicrobianos, lo que limita las opciones terapéuticas disponibles. La pandemia por COVID-19 agravó este escenario, ya que la falta de una terapia estandarizada llevó a un aumento considerable en la prescripción de estos fármacos. Por ello, nos propusimos investigar la prevalencia de infecciones bacterianas y el perfil de resistencia antimicrobiana en pacientes diagnosticados de COVID-19, así como señalar posibles factores de riesgo. **Métodos:** estudio retrospectivo basado en el análisis de historias clínicas de pacientes hospitalizados con COVID-19 mayores de 18 años. Información como edad, sexo, duración de la estadía, unidad de hospitalización, especies bacterianas y perfil de resistencia y uso previo de antimicrobianos por parte de pacientes diagnosticados con COVID-19 fueron recopiladas y analizadas mediante el *software* Excel® 2016. **Resultados:** de los 268 pacientes con COVID-19, 162 tenían sospecha de infección bacteriana, con 26 pacientes (9,7%) confirmada a partir de cultivos positivos. Además, alrededor del 80% de estos pacientes recibieron tratamiento empírico con antimicrobianos, la mayoría de los cuales eran hombres e ingresaron en la Unidad de Cuidados Intensivos. Se recuperaron un total de 32 aislados bacterianos, de los cuales el 59,4% eran resistentes a al menos una clase de antimicrobianos y el 21,8% eran resistentes a múltiples fármacos. **Conclusión:** a pesar del bajo porcentaje encontrado de pacientes con COVID-19 que presentaron infecciones bacterianas, y de éstas cerca del 21,8% fueron por bacterias multirresistentes, es necesario reforzar las políticas de prevención de infecciones y una gestión adecuada en la liberación de antimicrobianos para reducir las tasas de diseminación hospitalaria de dichas bacterias.

Descriptores: COVID-19; Infecciones Bacterianas; Farmacorresistencia Microbiana; Infección Hospitalaria.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, was declared in March 2020 by the World Health Organization (WHO). During the second half of that same year, the virus infected around 43 million people, with around 2 million dying worldwide during this period. The global mortality rate showed a significant increase from March 11, 2020 to the end of May 2022, and more than 530 million of the world's population were affected, with around 6 million individuals dying. In Brazil, by October 2023, more than 37 million confirmed cases and approximately 706,531 deaths had been recorded, resulting in a fatality rate of 1.9%.^{1,2}

Although there is still no standardized drug therapy

or prophylaxis to be used in patients confirmed with COVID-19, there have constantly been prescriptions for drug "kits" including antiparasitics and antimicrobials, such as azithromycin, among others.^{3,4} This approach, in addition to not having substantial scientific evidence regarding benefits for patients, can contribute to the selection of resistant bacteria. Furthermore, the use of antimicrobials has also been considered as a preventive treatment for secondary bacterial infections in patients with COVID-19, which needs to be assessed in each case.⁵

Critically ill patients require intensive care and, often, a prolonged period of hospitalization, which can lead to the emergence of Healthcare-Associated Infections (HAIs). In the case of patients with COVID-19, such infections represent one of the complications caused

mainly by bacteria that have antimicrobial resistance genes.^{5,6} Still, few data regarding the prevalence of bacterial infections in patients with COVID-19 are found, and to date, it has been observed that rates can vary from 1 to 10% among patients with COVID admitted to hospitals.⁷

Antimicrobial resistance is recognized as a global health issue, impacting the success of HAI treatment, as around 2,000 people die every day worldwide due to complications caused by these bacteria. Furthermore, the WHO estimates that the number of annual deaths due to bacterial resistance will increase to around 10 million by 2050.⁸ Given this scenario, the present work proposed to investigate the prevalence of bacterial infections and the antimicrobial resistance profile in patients diagnosed with COVID-19 as well as point out possible risk factors that may be associated.

METHODS

This is a retrospective observational study, based on analysis of medical records of adult patients over 18 years old, who were hospitalized with COVID-19 from May 2020 to October 2021 and who presented secondary bacterial infections during the hospitalization period.

The research was carried out in a tertiary hospital located in Vitória, Espírito Santo. It is a hospital with a highly complex surgical profile specializing in neurosurgery, vascular and orthopedics. During the pandemic period, it did not act as a reference for COVID-19, but provided care for patients with COVID, having a separate Intensive Care Unit (ICU) for this purpose. Data analysis was carried out by collecting information from the medical records of hospitalized patients who were over 18 years old, with a diagnosis of SARS-CoV-2 confirmed by molecular biology (PCR – SARS-CoV-2 positive) and who during the hospitalization period, they presented a bacterial infection confirmed by positive culture samples after being diagnosed with COVID. Patients who already had a bacterial infection before the diagnosis of COVID-19, as well as those who, upon suspicion of infection, had negative cultures, were excluded.

In the analysis, information such as age, gender, length of stay, hospitalization unit, diagnosed bacterial infection, isolated bacteria, antimicrobial resistance profile and previous use of antimicrobials of patients diagnosed with COVID-19 were collected. The microbiology sector of the hospital's laboratory uses manual methodology and automation. The sector uses as a reference for criteria for interpreting cultures and releasing infection diagnostic reports as well as for carrying out antimicrobial susceptibility testing, the criteria established by BrCast 2020 (Brazilian Committee on Antimicrobial Susceptibility)⁹ and the Brazilian National Health Regulatory Agency (ANVISA - Agência Nacional de Vigilância Sanitária) clinical microbiology manuals.¹⁰ Tracheal aspirate cultures with counts equal to or greater than 10⁶CFU/mL were considered positive, and in the case of blood cultures with growth of coagulase-negative *Staphylococcus* spp., those released with growth of an isolate of the same

species in at least two samples.

The collected data were analyzed descriptively and organized in a Microsoft Excel® 2016 spreadsheet. The analyzes were represented by frequency, percentage and means. The research project was previously approved in February 2022 by the Research Ethics Committee of Centro Universitário Multivix, under Opinion 5.263.680 (CAAE (Certificado de Apresentação para Apreciação Ética - Certificate of Presentation for Ethical Consideration) 51597321.4.0000.5066). All stages of research were developed in accordance with required ethical principles (Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health).

RESULTS

During the period assessed, 846 patients presented clinical respiratory symptoms suspicious of SARS-CoV-2 infection, undergoing molecular testing for laboratory diagnosis. Of these, 268 (31.68%) tested positive for the virus, 145 (54.1%) men and 123 (45.9%) women. Considering the group of patients with a confirmed diagnosis of COVID-19, 162 (19.15%) had culture tests requested after the diagnosis of COVID-19 based on a suspected bacterial infection, according to the medical record. Only 26 (9.7%) of patients with COVID-19 were positive for requested bacterial cultures. Of the 26 patients, 11 (42.3%) were admitted to care units (neurosurgery, stroke and vascular) and 15 (57.7%) were in ICUs. It is worth noting that the study hospital was not a reference for receiving patients with COVID-19, however, during the pandemic period, there was an increase in the number of ICU beds to accommodate patients who were unable to find places at the reference institution.

Regarding gender, of the 26 patients, the majority were men (61.5%) and were admitted to ICUs. The profile of the population participating in the study is shown in table 1.

Table 1. Epidemiological profile of patients diagnosed with COVID-19.

Gender (n/%)	Age group (years)	Mean age	Mean hospitalization	ICU admission
Male (16/61.5%)	48 - 85	58.6	17.5 days	62.50%
Female (10/38.5%)	39 - 41	62	14.2 days	50%

Of the 26 selected patients, 29 biological samples were collected, from which 32 bacterial species were isolated. More than 50% of the samples collected were representative of bloodstream infections and urinary tract infections, and 17% were isolated from respiratory samples.

Regarding the isolates, in the total cultures, there was a predominance of gram-negative bacteria (65.6%), with around 43% of the total isolates belonging to the enterobacteria group. Graph 1 shows the distribution of bacterial isolates identified in different biological materials from patients.

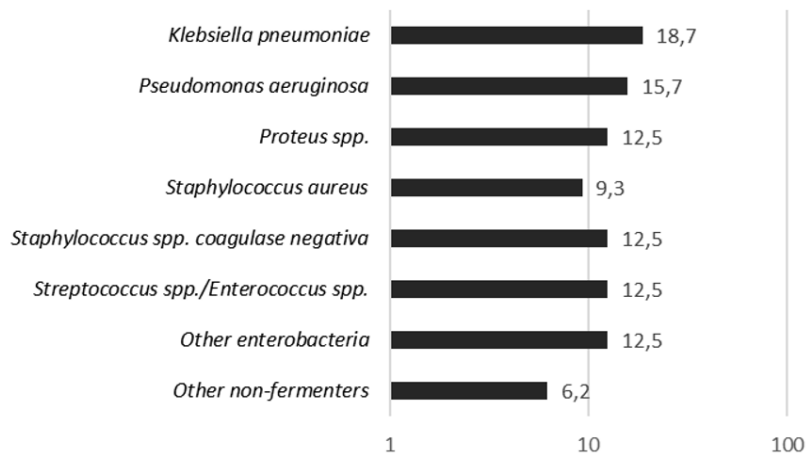


Table 1. Distribution in % of bacterial species identified from biological samples from patients with COVID-19 who presented an infectious condition.

Table 2. Percentage of antimicrobial resistance of the most common gram-negative isolates.

ATB*	<i>Pseudomonas spp.</i> n = 05	<i>K. pneumoniae</i> n = 06
AMI	2 (40%)	0 (0%)
CAZ	5 (100%)	1 (16.67%)
CIP	2 (40%)	1 (16.67%)
CPM	2 (40%)	1 (16.67%)
CRO	NT	1 (16.67%)
ERT	NT	1 (16.67%)
GEN	0 (0%)	1 (16.67%)
MER	2 (40%)	1 (16.67%)
PPT	5 (100%)	1 (16.67%)
SUT	0 (0%)	0
IMI	3 (60%)	1 (16.67%)

*Antimicrobials: AMI - amikacin; AMX - amoxicillin-clavulanate; CAZ - ceftazidime; CFL - cephalothin; CIP - ciprofloxacin; CPM - cefepime; CRO - ceftriaxone; ERT - ertapenem; GEN - gentamicin; MER - meropenem; PPT - piperacillin/tazobactam; SUT - sulfamethoxazole/trimethoprim; NT - not tested; n - number of bacterial isolates; % - percentage of resistance.
 Source: author.

When correlating species by biological material, there was a predominance of *Klebsiella pneumoniae* (37.50%) in the samples received. In blood cultures, growth was observed mainly of *Staphylococcus aureus* (27.3%), coagulase-negative *Staphylococcus spp.* (27.3%) and *Klebsiella pneumoniae* (27.3). On the other hand, in tracheal secretion samples, there was a predominance of gram-negatives, with non-fermenters (*Acinetobacter spp.*, *Stenotrophomonas spp.* and *Pseudomonas aeruginosa*) making up a total of 60% of respiratory isolates.

Regarding the resistance profile, of the 32 isolates, 13 (40%) were sensitive to all antimicrobials tested and 7 (21.8%) were resistant to at least one representative in 3 or more classes of antibiotics, being classified as multidrug resistant (MDR). It was observed that, among gram-negative bacteria, 23.8% were producers of ex-

tended spectrum beta-lactamase (ESBL) and 19% were resistant to carbapenems with phenotypically confirmed carbapenemase production, namely: 1 *K. pneumoniae*, 2 *P. aeruginosa* AND 1 *A. baumannii*. Among gram-positive bacteria, 57.1% of *Staphylococcus spp.* were resistant to oxacillin (methicillin-resistant *Staphylococcus spp.* - MR-SA/MRS). Tables 2 and 3 show the resistance profile of the most frequent species isolated in the cultures of the patients assessed.

Table 3. Percentage of antimicrobial resistance of the most common gram-positive isolates.

ATB*	Coagulase-negative <i>Staphylococcus spp.</i> n = 04	<i>S. aureus</i> n = 03
CIP	2 (50%)	2 (66.7%)
GEN	2 (50%)	1 (33.4%)
SUT	2 (50%)	0
OXA	2 (50%)	2 (66.7%)
CLI	1 (25%)	1 (33.4%)
ERY	4 (100%)	3 (100%)
LIN	0	0
RIF	1 (25%)	0

*Antimicrobials: CIP - ciprofloxacin; GEN - gentamicin; OXA - oxacillin; LIN - linezolid; ERY - erythromycin; CLI - clindamycin; RIF - rifampicin; SUT - sulfamethoxazole/trimethoprim; n - number of bacterial isolates; % - percentage of resistance.
 Source: author.

It was observed that 22 (84.6%) of patients received preventive treatment with antimicrobials during hospitalization, but before requesting bacterial culture tests. It is worth mentioning that ten of these patients (45.4%) were infected with resistant bacteria. Regarding the drugs used in empirical treatment, 13 (50%) received piperacillin-tazobactam, ten (38.4%), vancomycin, and four (15.4%), clarithromycin.

DISCUSSION

Critically ill patients hospitalized with COVID-19 present an important risk of developing bacterial infections of various microbiological types involving bacteria with different resistance profiles.^{11,12} In the present study, a higher rate of bacterial infections was observed in men admitted to ICUs. According to the Pan American Health Organization (PAHO), one of the justifications for men being more prone to such infections than women would be that, in general, the immune response developed against the virus in women tends to be more effective and adaptive to the virus.¹³ Furthermore, men tend to be less cautious about taking care to prevent virus infection.^{14,15} Moreover, it is known that patients in ICUs, as they are more constantly subjected to invasive procedures, also present a greater risk of infections associated with healthcare.¹⁶

Our results corroborate other similar works. In a retrospective study carried out in China, a prevalence of 6.8% of bacterial infection was identified in patients with COVID-19, and of those affected, 66.7% were men.¹⁷ In another similar study carried out in Italy, a prevalence of bacterial infections in male patients diagnosed with COVID-19 was also found to be 71.8%.¹⁸

Different authors found a wide spectrum of hospital infections in patients with COVID-19, the main ones being ventilator-associated pneumonia (VAP), bloodstream infections and urinary infections.^{12,14} In the present study, bloodstream and urinary tract infections were the most frequent. Different factors may contribute to such secondary infections in patients infected with the SARS-CoV-2 virus. Immune compromise resulting from COVID, associated with admission to ICUs, as well as invasive procedures in these patients, such as the need for a bladder catheter, can facilitate bacterial interaction and infection development.^{1,18,20}

The prevalence of infections caused by gram-negative bacteria is common, since the main bacteria associated with infection in the hospital environment belong to the *Enterobacteriales* family or the group of non-fermenting gram-negative bacilli. The most prevalent bacteria in the present study (*K. pneumoniae* and *P. aeruginosa*) are frequently found in the hospital environment and have the capacity to adapt to different environments, colonizing the patients' microbiota, or contaminating surfaces, and can also be transmitted by contaminated hands.²⁰

The predominance of infections by gram-negative bacteria originating from different sites was also found in other studies.^{19,21,22} However, divergences were observed in these percentages of distribution by biological site, when comparing our results with other authors. A study carried out in India found a predominance of *K. pneumoniae* isolates (44% of isolates) mainly in the respiratory tract.²³ On the other hand, a study carried out in New York found a predominance of *S. aureus* in 70% of isolates from the bloodstream and respiratory secretions in patients infected with SARS-CoV-2.²⁴ Another work carried out in Wuhan on patients with COVID-19 who

acquired secondary bacterial infections identified that, of the 159 strains isolated, 85.5% were gram-negative bacteria, with emphasis on *A. baumannii* and *K. pneumoniae*, more present in the respiratory tract and in the blood.²³

For *P. aeruginosa* isolates from the five strains, three (60%) showed phenotypic resistance to carbapenems, while one isolate (16.7%) of *K. pneumoniae* was multiresistant, with sensitivity only to sulfamethoxazole/trimethopim and amikacin. Our results differ from those found by Li *et al.* (2020), who found 42.9% of *P. aeruginosa* species resistant to carbapenems and 76.6% of *K. pneumoniae* isolates resistant.¹⁵ Furthermore, in a cohort study carried out on COVID-19 patients with secondary infections, resistance to carbapenems was found in 94.5% of *K. pneumoniae* isolates (n=256) isolated mainly from respiratory secretions.²⁵

As for *Staphylococcus* spp. isolates (n=07), the majority were isolated from blood cultures, four (57.1%) showed resistance to oxacillin (MRSA), and, of these, two isolates were *S. aureus*. Comparable results were found in similar work in China, where around 50% of *Staphylococcus* spp. isolates were MRSA.²⁴ On the other hand, in the most serious scenario of the pandemic, in the city of Wuhan, it was observed that methicillin resistance was present in 100% of *S. aureus* isolates from patients with COVID-19.¹⁷

It was observed that 84.6% of patients assessed were previously using antimicrobials, i.e., they used these antimicrobials without the diagnosis of bacterial infection confirmed by culture. The practice of prescribing antibiotics for individuals with COVID-19 proved to be quite common during the pandemic in several countries, despite the lack of proof of their effectiveness against the virus. For instance, from March to October 2020 alone, around 80% of COVID-19 patients hospitalized worldwide received at least one antibiotic. However, the literature shows that in around 15% of cases antibiotic therapy was actually necessary, once they had a confirmed diagnosis of true bacterial infection. Several studies have already demonstrated that the selective pressures of such drugs can also contribute to the selection of bacteria resistant to existing treatments.^{8,26,27}

A hospital in Napoli, Italy, when assessing 32 hospitalized patients diagnosed with SARS-CoV-2 and bacterial infections, observed that 78% of these patients had previously received antimicrobials, with piperacillin/tazobactam administered to 37.5%.¹⁸ Meanwhile, a study identified that 97% of patients hospitalized for COVID-19 received empiric antibiotic therapy upon admission, of which 46% had bacterial infection due to carbapenem-resistant enterobacteria.²⁸

In the present study, 45.4% of patients were infected with resistant bacteria. In correlation with the number of bacterial isolates, 21.8% of them were MDR. In Brazil, in 2019, the *Instituto Oswaldo Cruz* laboratory received more than 1,000 isolates of resistant bacteria from public service laboratories in several states in the country in the pre-pandemic period. In the following two years, the number of samples tripled.²¹ These facts reinforce that antibiotic resistance is irreversible, as it develops in a

hospital environment, where there are several favorable factors for bacteria to acquire this profile.

Among the limitations of this study, there was a lack of information records in some patients' medical records as well as the presence of patients diagnosed with COVID-19 only through the rapid test, reducing the sample size, which also limited a better assessment of risk factors. However, being a descriptive analysis, data comparison was possible and could contribute to other studies on the topic covered.

Secondary bacterial infections in patients with COVID-19 represent a challenge for public health, and the present study highlights the reality of the high use of antimicrobials in these patients (80%). The literature is clear in establishing a relationship between the indiscriminate use of antimicrobials and antimicrobial resistance, which has seen a considerable increase during the pandemic. The prevalence of bacterial infections found, although low, is significant, as it mainly affects vulnerable patients. The fact that 21.8% of isolated bacteria are multi-resistant shows the importance of maintaining prevention policies and programs as well as the appropriate use of antimicrobials in hospitals, which are essential measures to reduce the spread and control of such infections.

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Evelyn Faria Zanni, Ana Helena Croce, Thayglerson Augusto Almeida Paixão: contributed to manuscript conception, data collection, and writing. **Jhully Pimentel:** contributed to article planning and design, data collection, analysis and discussion of results and manuscript writing. **Thaís Dias Lemos Kaiser:** contributed to article planning and design, analysis and discussion of results, manuscript writing, review and correction.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.