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Bacterial infections in patients with COVID-19 admitted to an adult ICU: incidence and pharmaceutical performance

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Abstract

Objective: The present study aimed to determine the incidence of bacterial infection in patients infected with SARS-COV-2 admitted to intensive care units (ICUs) of an oncological hospital in southern Brazil and to demonstrate the role of the pharmacist in the management of antimicrobials. **Methods:** In this descriptive and retrospective observational study, all patients with COVID-19 confirmed by polymerase chain reaction (PCR) examination, admitted to adult ICUs at Erasto Gaertner Hospital from May 2020 to August 2021 were included, and demographic and clinical data were evaluated through medical records, in addition to the number and classification of pharmaceutical measures. **Results:** Of 192 patients hospitalized with COVID-19 in the ICU, 104 (54%) had an oncological diagnosis, 62 (60%) with solid cancer and 42 (40%) with hematological diagnosis. Regarding the length of hospital stay, the patients were hospitalized for an average of 9.5 days (SD:6.4), treated with invasive procedures. Of these, 44 (23%) had ventilator-associated pneumonia (VAP) and 32 (17%) patients developed a bloodstream infection (BSI). The most prevalent bacteria were Acinetobacter baumannii with a multiresistant profile and methicillin-sensitive Staphylococcus aureus. Sixty pharmaceutical measures were taken to manage the use of antimicrobials, the most prevalent being: addition, discontinuity, de-escalation, calculation and dose adjustment. With regard to clinical outcome, 147 (77%) of patients hospitalized with COVID-19 died. As for the co-infected patients, 36 (82%) of the patients with VAP and 28 (88%) with ICS died. **Conclusions:** The results obtained were consistent with the literature, in which the rates of co-infection and use of antimicrobials were high. In addition, pharmaceutical interventions demonstrate the importance of this professional in patient care and in the multidisciplinary team regarding the rational use of antimicrobials.

Keywords: COVID-19, antimicrobial, ICU, infection, pharmacist.

Infecções bacterianas em pacientes com COVID-19 internados em UTI adulto: incidência e atuação farmacêutica

Resumo

Objetivo: O presente estudo teve como objetivo investigar a incidência de infecções por bactérias em pacientes infectados pelo SARS-COV-2 internados em unidades de terapia intensiva (UTIs) de um hospital oncológico do Sul do Brasil e descrever a atuação do farmacêutico no manejo de antimicrobianos. **Métodos:** Neste estudo observacional descritivo, com coleta de dados retrospectivos, foram incluídos todos os pacientes com COVID-19, confirmada através de exame de reação em cadeia da polimerase (PCR), internados em UTIs adulto no Hospital Erasto Gaertner no período de maio de 2020 a agosto de 2021. Foram analisados os dados demográficos e clínicos coletados em prontuário. Também foram relacionados o número e a classificação das intervenções farmacêuticas realizadas no período. **Resultados:** De 192 pacientes internados com COVID-19 na UTI, 104 (54%) apresentavam diagnóstico oncológico, sendo 62 (60%) diagnosticados com câncer sólido e 42 (40%) hematológicos. O tempo de internamento observado foi, em média, igual a 9,5 dias (DP:6,4), sendo que a maior parte dos pacientes demandou procedimentos invasivos. Destes, 44 (23%) apresentaram pneumonia associada a ventilação (PAV) e 32 (17%) pacientes desenvolveram infecção de corrente sanguínea (ICS). As bactérias mais prevalentes foram *Acinetobacter baumannii* com perfil multirresistente e *Staphylococcus aureus* sensível à meticilina. Foram realizadas 60 intervenções farmacêuticas no gerenciamento do uso de antimicrobianos, sendo as mais prevalentes: adição, descontinuidade, descalonamento, cálculo e ajuste de dose. No que diz respeito ao desfecho clínico, 147 (77%) dos pacientes internados com COVID-19 foram a óbito, sendo que parte destes apresentou coinfecções como PAV (n=36) ou ICS (n=28). **Conclusões:** Os resultados obtidos foram condizentes com a literatura, em que as taxas de coinfecção e uso de antimicrobianos foram altas. Além disso, as intervenções farmacêuticas descritas reforçam a importância deste profissional na assistência ao paciente e na equipe multidisciplinar frente ao uso racional de antimicrobianos.

Palavras-chave: COVID-19, antimicrobianos, UTI, infecção, farmacêutico.

Introduction

The pandemic caused by the SARS-COV-2 virus is the largest of our generation, leaving millions of individuals infected and millions of deaths worldwide[1]. Infected people who have Severe Acute Respiratory Syndrome (SARS) frequently require care in Intensive Care Units (ICUs), including ventilatory support and other invasive measures for survival[2].

However, ICUs are considered epicenters of infections, especially those associated with healthcare (HAIs), by superbacteria or multi-drug resistant (MDR) bacteria. MDR bacteria can survive the action of a previously active antimicrobial agent due to mechanisms of acquired resistance through phenotypic changes[3-6]. In the ICU context, HAIs are of concern and present a higher mortality rate[3-5]. Ventilation-Associated Pneumonia (VAP) and Bloodstream Infections (BSIs) are among the most prevalent HAIs that can progress to fatal outcomes[4,7,8].

Simultaneously with this scenario, there was an unjustifiable increase in the consumption of antimicrobial agents during COVID-19 treatments. Some reasons for this increase were as follows: absence of rapid SARS-COV-2 infection diagnosis, experimental treatment of the disease with antimicrobials, empirical treatment of co-infections, and prolonged treatment and/or use of broad-spectrum antimicrobials. Thus, the selective pressure exerted by MDRs tends to increase, leading to a limitation of our therapeutic arsenal[1,9,10].

On the other hand, cancer patients are more vulnerable to infections, including SARS-CoV-2, associated with the development of severe symptoms, given their immunocompromised state, myelosuppression, use of invasive devices and increased exposure to health services[11]. This clinical condition represents a challenge for rational antimicrobial use, mainly due to the higher mortality rate when compared to the general population[12].

As a way of coping, it is indispensable to implement Antimicrobial Stewardship Programs to promote their proper use. The program should consist of a multidisciplinary team, in which pharmacists contribute to obtaining better results in the patients' clinic and in reducing the selection of MDR strains[13-15].

This study aimed at investigating the incidence of bacterial infections in patients with SARS-COV-2 admitted to the ICU of a hospital specialized in Oncology from southern Brazil and to describe the pharmacists' role in the management of antimicrobials in this population.

Methods

An observational study was conducted in the Intensive Care Unit (ICU) of a reference hospital specialized in Oncology (Erasto Gaertner) located in the state of Paraná.

The patients included were all those over 18 years of age, diagnosed with COVID-19 by polymerase chain reaction (PCR), with notification by the Hospital Infection Control Commission (*Comissão de Controle de Infecção Hospitalar*, CCIH), admitted to the ICU for adults from May 2020 to August 2021. Retrospective data collection was carried out from November 2021 to July 2022.

The cases of patients diagnosed with COVID-19 and who developed healthcare-associated infections during hospitalization due to the use of invasive devices were considered as co-infections: Central Venous Catheter (CVC) and Invasive Mechanical Ventilation (IMV). The suspected patients underwent microbiological tests to identify the infectious agent and, together with the clinical symptomatology, establish a diagnosis of VAP and/or BSI by a microbiological agent sensitive to antimicrobials or MDRs.

Co-infection by MDR bacteria was considered to be cases with results of microbiological cultures whose microorganism identified showed growth capacity against the action of a previously sensitive antimicrobial agent according to the literature.

The patients with a suspected clinical co-infection, but without diagnostic confirmation based on the microbiological culture result, were not classified as co-infected.

Demographic and clinical data were collected from these patients' physical and electronic medical records.

The variables analyzed were the following: age, gender, pre-existing comorbidities, presence or absence of solid or hematological cancer and disease activity status, chemotherapy/radiotherapy treatment within 30 days from the COVID-19 diagnosis, blood count result to verify presence of neutropenia at admission, hospitalization time, need and use time of invasive devices, results of microbiological cultures to confirm co-infection, antimicrobial use time and clinical outcome.

The pharmaceutical interventions for the population under study, carried out under the institutional antimicrobial stewardship program, were also identified and described. In the hospital researched, the Antimicrobial Stewardship Program (ASP) actions were already implemented to manage rational use of this class, with the active participation of clinical pharmacists along with infectologists and intensivists. Carried out according to the adapted PRAT (*Problemas Relacionados a Terapêutica Antimicrobiana*) (Antimicrobial-Related Problems) tool, the interventions were recorded and collected in the hospital management system[16].

Data compilation and analysis were carried out in a Microsoft Office Excel® spreadsheet.

The study was approved by the Committee of Ethics in research with Human Beings of the Erasto Gaertner Hospital – *Liga Paranaense de Combate ao Câncer* – under CAAE No. 53098321.5.0000.0098.

Results

A total of 192 patients with COVID-19 were admitted to the intensive care unit of the Erasto Gaertner Hospital during the study period (Table 1).

Of these, 104 (54%) had cancer diagnoses, 62 (60%) were diagnosed with solid tumors and 42 (40%) with hematological cancer.

Forty-four patients (23%) had Ventilator-Associated Pneumonia (VAP), of which 14 (32%) were oncology patients with a diagnosis of hematologic (n=9) and solid (n=5) cancer. Of these 14 cancer patients, 11 had active disease and 8 were undergoing treatment during the period. Referring to HAIs, in addition to the 44 (23%) patients who developed VAP, 32 (17%) patients developed BSIs.

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Table 1. Characteristics and evolution of the COVID-19 patients admitted to the intensive care unit

Characteristics	
Age in years old, mean (SD)	60 (14)
Gender, N (%)	
Female	85 (44)
Male	107 (56)
Comorbidities, N (%)	
Cancer	104 (54)
Hypertension	93 (48)
Diabetes	64 (33)
Obesity	44 (23)
Dyslipidemia	19 (10)
COPD	9 (5)
Asthma	6 (3)
Cancer population, N (%)	
Solid cancer	62 (32)
Hematological cancer	42 (22)
Patients with active disease	77 (74)
Patients undergoing antineoplastic treatment	43 (41)
Patients with neutropenia (neutrophils ≤ 500 mm3)	22 (21)
Evolution	
Antimicrobial use, N (%)	
During hospitalization	160 (83)
Prior to COVID-19 diagnosis	56 (29)
Corticosteroid use, N (%)	174 (91)
ICU hospitalization time in days, mean (SD)	10 (6)
IMV use time in days, mean (SD)	6 (7)
CVC use time in days, mean (SD)	6 (7)
Patients with neutropenia, N (%)	22 (11)
Population with VAP, N (%)	44 (23)
Not cancer patients	30 (68)
Solid cancer	5 (12)
Hematological cancer	9 (20)
Population with BSIs, N (%)	32 (17)
Not cancer patients	16 (50)
Solid cancer	10(31)
Hematological cancer	6(19)
Clinical outcome of the population with VAP, N (%)	
Discharge	8 (18)
Death	36 (82)
Clinical outcome of the population with BSI, N (%)	
Discharge	4 (12)
Death	28 (88)
Clinical outcome of the study population, N (%)	
Discharge	45 (23)
Death	147 (77)

CVC: Central Venous Catheter; COPD: Chronic Obstructive Pulmonary Disease; BSIs: Bloodstream Infections; VAP: Ventilation-Associated Pneumonia; IMV: Invasive Mechanical Ventilation Source: Data collected at the Erasto Gaertner Hospital, 2021|2022

Regarding hospitalization time, the patients with infections associated with COVID-19 stayed a mean of13 days (SD: 8.05) admitted to the ICU, undergoing invasive procedures, such as Central Venous Catheter (CVC) insertion and Invasive Mechanical Ventilation (IMV), where the mean time was 6.5 (SD: 7.1) for mechanical ventilation and 6.4 (SD: 6.8) for central access.

The microbiological agents identified in laboratory culture results are described in Table 2.

Table 2. Agents isolated in microbiological cultures from COVID-19 patients admitted to the intensive care unit

Type of infection	N	MDR agent	N
Microorganisms isolated in tracheal aspirate cultures			
Acinetobacter baumannii	14	MR	14
Staphylococcus aureus	13	-	-
Enterococcus faecalis	7	-	-
Pseudomonas aeruginosa	7	MR	1
Klebsiella pneumoniae	3	ESBL	1
Proteus mirabilis	2	-	-
Escherichia coli	1	ESBL	1
Microorganisms isolated in blood cultures			
Staphylococcus aureus	11	MRSA	1
Staphylococcus coagulase negativa	10	-	-
Enterococcus faecalis	4	-	-
Acinetobacter baumannii	3	MR	3
Pseudomonas aeruginosa	2	-	-
Escherichia coli	2	ESBL	1
Candida albicans	2	-	-
Klebsiella pneumoniae	1	ESBL	1
Proteus mirabilis	1	-	-

ESBL: Extended spectrum beta lactamase; MR: Multi-resistant; MSSA: Methicillin-sensitive *Staphylococcus aureus.*Source: Data collected at the Erasto Gaertner Hospital, 2021|2022

The most prevalent VAP-causing bacteria were *Acinetobacter baumannii* with a multi-drug resistant profile and methicillin-sensitive *Staphylococcus aureus* (MSSA). Other agents with antimicrobial resistance identified in the tracheal aspirate cultures were MDR *Pseudomonas aeruginosa*, ESBL (Extended-Spectrum-Beta-Lactamase) *Klebsiella pneumoniae* and ESBL *Escherichia coli*. In the blood culture samples, MSSA, coagulase-negative *Staphylococcus* (CNS), and MDR *Enterococcus faecalis* and *Acinetobacter baumannii* were identified.

Regarding the clinical outcomes, 147 (77%) of the patients hospitalized with COVID-19 evolved to death during ICU hospitalization. Regarding the co-infected patients, the number of deaths was 36 (82%) in the VAP cases and 28 (88%) in the BSI cases.

During follow-up of these patients, 60 interventions were performed, described Table 3. Most of them were related to the management of antimicrobials in cases of co-infections by MDR bacteria in patients with COVID-19. Frequent use of broad-spectrum antimicrobials such as third-generation cephalosporins and macrolides was observed.

Table 3. Pharmaceutical interventions in COVID-19 patients co-infected by multi-drug resistant bacteria admitted to the ICU.

Interventions	N=60 (%)
Addition	15 (25)
Discontinuity	6 (10)
Escalation	6 (10)
Dose adjustment by renal function	6 (10)
Dose calculation	6 (10)
Laboratory monitoring	5 (8)
Dosage	5 (8)
De-escalation	4 (7)
Substitution	3 (5)
Treatment time	3 (5)
Infusion time	1 (2)

Source: Data collected at the Erasto Gaertner Hospital, 2021|2022

A representative number of patients (29%) had previously used antimicrobials empirically, coming from outpatient emergency care units. During admission in this hospital, it was possible to discontinue antimicrobial use for twelve patients who did not present significant evidence of co-infection.

Discussion

This study showed a significant number of bacterial co-infections in patients with COVID-19 admitted to the ICU, especially invasive mechanical ventilation-associated pneumonia (23%). These findings were similar to other studies conducted in ICU environments, considering, however, that this rate can vary from 14% to 40% between different centers[17-19].

Most of the patients monitored in this study (73%) required invasive mechanical ventilation and presented a mean hospitalization time of 6.5 days. Of them, 32% developed VAP. Our results are consistent with a study conducted in China that identified VAP in 10 (31%) patients undergoing IMV[20].

The bacteria that were most frequently identified in this study were MDR *Acinetobacter baumannii*, MSSA, *Enterococcus faecalis* and *Pseudomonas aeruginosa*. Our findings are consistent with the literature, which identified with greater frequency *Staphylococcus aureus* and other agents such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*[17,19,21].

Although antimicrobial use for the treatment of COVID-19 is ineffective, their use has been expanded worldwide in view of the challenges in eliminating the suspicion of associated bacterial infections, based on traditional markers (vital signs, leukocyte count, C-reactive protein and imaging tests), employed to direct clinical decisions regarding the use of this class[10,22].

In addition to that, it should be noted that the scarce number of health professionals during the pandemic height, and the lack of expertise of the teams regarding aerosol generation and dissemination of the infection, possibly led to a reduction in the number of patients submitted to microbiological investigation[10].

Antimicrobial use in this population was observed in 160 (83%) cases, which was also consistent with other studies where the rate of antimicrobials varied between 70% and 95%[19-21,23].

Empirical antimicrobial use corroborates the selection of resistant strains, in addition to other consequences such as toxicity and infection by *Clostridioides difficile*[22]. In this sense, it is fundamental to implement stewardship programs that promote rational antimicrobial use through practices that instigate microbiological research, prior to initiating the therapy, and that institute therapy reviews and interruptions based on clinical evidence[10].

Of the co-infected patients, 30 (40%) were oncological, representing a major challenge in decision-making regarding antimicrobial therapy, in view of the greater susceptibility to infections for several reasons, such as: immunodeficiency caused by the disease or by chemotherapy/radiotherapy treatment; myelosuppression; use of invasive devices; and increased exposure to health services[24].

Although the incidence of co-infection is higher in these patients when compared to the general population, in the multicenter study conducted by Gudiol (2021) with 684 onco-hematological patients with COVID-19, it was found that the main risk factors for the development of infections were neutropenia and ICU admission. Thus, it was suggested that antimicrobial use in these cases should be targeted and not exclusively based on the cancer diagnosis[25].

In view of this scenario, it is indispensable to implement stewardship programs aimed at optimizing antimicrobial use in order to obtain better results in the patients' clinical conditions, with a reduction in adverse events and in the selection of MDR strains[14]. During the COVID-19 pandemic, stewardship was intended to support the optimal selection of empirical treatments with antimicrobials and, mainly, to support discontinuation of this treatment in confirmed SARS-COV-2 infection cases. Another aggravating factor is the scarcity of antimicrobials, which is one of the main reasons for their use to be directed to the therapy of patients with confirmed bacterial infections[10].

Thus, pharmacists play a vital role in the management of antimicrobials and contribute effectively to the program[13,15]. The literature indicates that the main interventions are as follows: releasing antimicrobials according to available resource and need; monitoring the spectrum of action and treatment time; verifying culture results and laboratory tests; requesting plasma concentration tests; providing guidance on administration and collection of the tests; optimizing doses; and discontinuing the antibiotic therapy[13]. In this study, the 60 pharmaceutical interventions described were made possible by the pharmacists' role in the ASP, within the ICU. It is believed that their active participation in the bedside visit and the bond with the intensive care physician, infectologist and microbiologist were fundamental for the management of rational antimicrobial use in the hospitals under study.

Our results exemplified the pharmacists' clinical practice in the COVID-19 context with the multidisciplinary team, in view of preserving our therapeutic arsenal and the patients' clinical conditions[15].

Our study presents some important limitations that should be pointed out. We considered as co-infected patients only those with positive culture results (blood cultures or tracheal aspirate) and, therefore, suspected cases or those when there was no time for microbiological research were excluded. Some microorganisms identified can be colonizing and not causing infections. However, the severity of these patients' clinical conditions, with altered ICU parameters, led to instituting the antimicrobial therapy. Possibly, there was underreporting of confirmed patients with COVID-19 and bacterial infections, considering the critical scenario. In addition to being a retrospective study, it was limited to a single center, and may be restricted to local and unrepresentative epidemiology, requiring further studies with the cancer population during the fight against COVID-19 to verify the co-infection rates.

Conclusion

High incidence of co-infections was identified in this study, consistent with the literature in a population that included cancer patients. Microorganisms that had multi-drug resistance to antimicrobials such as *Acinetobacter baumannii* were frequently observed in the patients included in this study, which limited the therapeutic arsenal used and demanded greater support and care from the multiprofessional team.

Rational antimicrobial use was optimized in the fight against COVID-19, considering the pharmacists' expertise in the ICU context. Conducting pharmaceutical interventions reinforces the importance of stewardship programs, mainly in the face of extreme situations such as a pandemic. Our findings suggested that bedside pharmacists plated a relevant role in the management of this class, contributing to the patients' clinical conditions.

The cancer population has particularities within this context and more studies correlated to the topic are required to better support clinical decision-making.

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Collaborators

DF, KA, KO and MC: Conception and design or data analysis and interpretation; Writing of the article or relevant critical review of the intellectual content.

Declaration of conflict of interests

The authors declare that there are no conflicts of interests in relation to this article.

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