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Bacterial Resistance in Primary Bloodstream Infections in the COVID-19 Pandemic: What has Changed at a Reference Hospital in Northeastern Brazil?

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Abstract: The increased use of central venous catheters due to the severity of COVID-19 cases and the difficulty in implementing preventive Healthcare-Associated Infection measures contributed to worsening an already challenging scenario of bacterial resistance. Characterizing the impact of these significant health crises on the bacterial resistance profile is necessary to strengthen antimicrobial control protocols in an effort to decrease morbidity. Our main goal was to investigate changes in the bacterial resistance profile in patients with Primary Bloodstream Infections (PBSIs) receiving care at the intensive care unit of a reference hospital in Ceará (northeastern Brazil) during the COVID-19 pandemic. PBSI registries from the hospital infection control service, dating from 2018-2021, and medical records were reviewed. A 5% significance level and a 95% confidence interval were adopted in all inferential procedures. Ninety-four bacterial isolates from blood cultures were studied (29 from the pre-pandemic period and 65 from the pandemic period). *Pseudomonas aeruginosa* was the most frequently identified bacterium in the pre-pandemic period (20.68%), while *Klebsiella pneumoniae* was most commonly found during the pandemic (24.61%). The mean antibiotic resistance per bacterium was 4.8 (SD = 3.4) in the pre-pandemic period, increasing to 7 (SD = 4.1) during the pandemic. Penicillins (96%, n = 28) and second-generation cephalosporins (57.1%, n = 28), the most frequent antibiotic classes with resistance in the pre-pandemic era, gave way to carbapenems (115.5%, n = 65) and third-generation cephalosporins (86.1%, n = 65) during the pandemic period. No statistical difference was observed in the number of central venous catheter insertions (p = 0.96). However, more deaths were recorded during the pandemic period (p = 0.014). The antimicrobial resistance profiles increased during the pandemic, including resistance to more selectively used antibacterials.

Keywords: Bloodstream Infection, COVID-19, Healthcare-Associated Infections (HCAIs), Bacterial Resistance to Antibiotics, SARS-CoV-2

Introduction

In December 2019, the World Health Organization (WHO) received alerts of a novel Coronavirus that was identified in humans with pneumonia in the city of Wuhan, China (Sohrabi *et al*., 2020). This new viral strain was subsequently isolated and named severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of the 2019 coronavirus disease (COVID-19) (Hao *et al*., 2022).

The first confirmed case of COVID-19 in Brazil was registered on February 26, 2020, in the state of São Paulo.

A few weeks later, on March 20th, the Brazilian Ministry of Health declared community transmission of the coronavirus in the country. Brazil was severely affected by the COVID-19 pandemic, with nearly 700,000 deaths from the disease by early 2023 (Cribari-Neto, 2023). Until May 31, 2020, most of the confirmed cases and deaths were reported in the states of São Paulo and Rio de Janeiro, in the Southeast region, while Ceará, in northeastern Brazil, recorded 48,489 cases and 3,010 deaths (Souza *et al*. 2020).

As SARS-CoV-2 continued to spread, further genetic modifications occurred, leading to the emergence of variants such as Alpha, Beta, Delta, Gamma, and Omicron (Carabelli, 2023). In Brazil, three distinct waves were observed: the first, caused by the alpha variant, lasted from February 23 to July 25, 2020, during which 7,677 weekly deaths were reported. The second wave (gamma) was longer and more lethal, occurring from November 8, 2020, to April 10, 2021, resulting in triple the number of deaths (21,141) in one week. The third wave was the shortest, extending from December 26, 2021, to May 21, 2022, during which period a total of 6,246 deaths were registered (Moura *et al*., 2022). These successive waves further strained the limited resources in healthcare facilities across the country. In these scenarios, opportunistic infections caused by multidrug-resistant bacteria, with significant clinical impacts, began to play a crucial role in morbidity, especially in Intensive Care Units (ICUs) (García-Meniño *et al*., 2021).

The lengthening of hospital stays, the prolonged use of life-sustaining invasive devices, reduced staff, the empirical use of broad-spectrum antimicrobials, and the challenges in implementing infection prevention and control measures were among the key factors influencing the growth of resistant agents (Blot, 2022).

According to the WHO, as of 2050, more than 10 million people a year will be victims and at risk of death from superbugs. These numbers could be even higher due to the abusive and indiscriminate use of antibacterials that were rampant during the COVID-19 pandemic (Malik and Mundra, 2022). This resistance is most often caused by genetic alterations in pathogens, which change their structure and functionality. Exposure to antimicrobials (antibiotics, antifungals, antivirals, antimalarials, or anthelmintics) favors the selection of resistant, Multidrug-Resistant (MDR), or pan-resistant organisms. As a result, infections persist and become a source of potential risk for spreading to other individuals (Jian, 2021).

The use of antibiotics in patients with SARS-CoV-2 exceeded the incidence of secondary infections and coinfections during the COVID-19 pandemic. While 7-8% of hospitalized patients in general and 14% of ICU patients had some type of secondary infection (sepsis, nosocomial pneumonia), 72% received broad-spectrum antibiotics (Rossato *et al*., 2020). The reported incidence of secondary infections ranged from 10-15%, while the rate of antibiotic use in the hospital environment was between 94-100% (Lansbury *et al*., 2020).

Among the most common problems faced in healthcare is Primary Bloodstream Infections (PBSIs), where approximately 60% of hospital environment bacteremias are related to some intravascular device. The use of Central Venous Catheters (CVCs), especially short-stay catheters, is among the most prevalent risk factors for PBSI. In the United States, around 50% of patients admitted to ICUs require the insertion of at least one CVC (Rupp and Majorant, 2016). In a retrospective study that reviewed adult hospitalizations from March to October 2020, COVID-19 positivity was associated with a higher risk of laboratory-confirmed bloodstream infections and increased odds of in-hospital death (Shukla *et al*. 2021). In another study, COVID-19 patients with hospital-acquired blood stream infections had an elevated risk of mortality in a prospective observational multicontinental cohort study conducted between August 2019 and June 2021 (Buetti *et al*., 2022).

The determining risk factors for Healthcare-Associated Infections (HAIs) depend on the medical care environment, the patient's condition, and the level of knowledge healthcare professionals have on the subject (Khan *et al*., 2017).

The increase in bacterial resistance observed during the COVID-19 pandemic has persisted. To control their spread to susceptible patients, namely those with frailties, effective performance of the Hospital Infection Control Service (HICS) is essential. In this context, understanding changes in the microbiota is crucial for surveillance, for better designing strategies to control spread, to strengthen antimicrobial stewardship protocols, and to ensure the appropriate initiation of antimicrobial regimens to enhance patient survival. This study has the potential to contribute to understanding the role of the COVID-19 pandemic in bacterial resistance in the PBSI scenario in one of the most affected countries by COVID-19. The aim of this study was to investigate changes in the bacterial profile and antimicrobial resistance among adult patients with PBSIs receiving care at the ICUs of a private hospital in Fortaleza, Ceará, Brazil, a reference center for medical care in such cases.

Materials and Methods

Study Design

This cross-sectional analytical study compared the pre-COVID-19 pandemic period (2018 and 2019) and the

pandemic period (2020 and 2021) to identify differences in the bacterial and antimicrobial resistance profiles of patients with PBSI receiving care at the ICU of a large private hospital located in Fortaleza, the capital of the state of Ceará, Brazil. HAI notifications from the HICS were reviewed, as well as laboratory blood culture results, followed by a review of the electronic medical records of the identified cases.

Study Location

Fortaleza, the capital of the state of Ceará, has a population of 2,428,708 inhabitants, making it the fourth most populous municipality in Brazil. The UNIMED regional hospital is a private referral hospital that has 338 beds and is capable of performing highly complex procedures. Categorized as a large tertiary hospital, it has ICU beds, an urgent and emergency service, an imaging center, and a clinical pathology laboratory. To cope with the pandemic, the hospital expanded its number of beds (increased the hospital's capacity to 454 beds, with 179 allocated to adult ICU care), constructed a field hospital in its parking lot, restructured the flow of patients and employees, and invested in equipment and materials to enhance care during that period.

Study Sample and Inclusion Criteria

The study included all adult patients (>18 years of age) of either sex who were admitted to the ICU between 2018 and 2021 and diagnosed with PBSIs caused by bacteria.

The definition of PBSI followed the Brazilian national surveillance criteria (Brasil, 2017), which are in accordance with the Centers for Disease Control and Prevention criteria (CDC, 2024). They define PBSI as the isolation of one or more organisms from the bloodstream that are not related to any other site of infection, with additional established criteria. Therefore, PBSI was considered when a patient had one or more positive blood cultures, and the pathogen was not associated with any other infection site, along with at least one of the following signs or symptoms: Fever (>38°C), oliguria (urinary volume <20 mL/h), tremors, or hypotension (systolic pressure ≤90 mmHg). For cultures with common skin contaminants (e.g., diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative *Staphylococcus*, *Micrococcus*), two or more blood cultures from different puncture sites within a maximum interval of 48 h were required.

During the pandemic period (2020 and 2021), patients were required to have been diagnosed with COVID-19, confirmed by RT-PCR testing for SARS-CoV-2.

Patients whose hospital records were unavailable for investigation were excluded from the study.

Data Collection and Study Variables

The manual HAI notification forms from the HICS were reviewed to identify cases of PBSI, and the manual laboratory records documenting positive blood cultures were also assessed; other clinical data were collected through a semi-structured questionnaire included in the patient's electronic records. Sociodemographic and clinical variables, including age, sex, comorbidities, site of infection, isolated bacteria, susceptibility profile of the cultured organism, duration of invasive device usage, type and class of the prescribed antibiotics, length of hospital stay, and the outcome (discharge or death) were all investigated.

Data Analysis

The statistical analyses were conducted using Stata 11.2 statistical software (StataCorp LLC, TX, USA), Epi Info™ 7 (version 7.2.4.0) (CDC, USA), and a StatCalc statistical calculator.

Descriptive univariate analyses (absolute and relative frequencies) were carried out for qualitative variables. As for analytical variables, Pearson's chi-square test was used, and Prevalence Ratios (PR), along with their Confidence Intervals (CI), were calculated. Some variables were created and categorized to proceed with the chi-square test, such as age (under or over 60), presence or absence of comorbidities, and length of stay in the ICU (less or more than 30 days). Epi Info™ 7 (version 7.2.4.0) software was used for this analysis.

In order to select the appropriate test for our study, a normality distribution test was conducted using a histogram, and the most suitable was found to be Student's parametric t-test. A significance level of 5% and a 95% CI were used for all inferential procedures.

Ethical Aspects

This study was approved by the ethics committee of the Federal University of Ceará under process No. 5.549.371 and adhered to the ethical principles outlined in the Declaration of Helsinki of 1975, revised in 2000, for research involving human beings. Additionally, a letter of consent was obtained from the executive director of the UNIMED Regional Hospital for the study procedures.

Results

A total of 94 patients were identified: 29 patients in the pre-pandemic period (2018-2019) and 65 in the pandemic period (2020-2021). Male patients were more frequent in both the pre-pandemic period (51.7%) and during the pandemic (66.1%), as shown in Table 1. Additionally, there was a statistically significant difference in the mean age of patients between the two periods (63 *vs*. 71 years old; $p = 0.0136$).

There was no statistical difference in the mean lengths of hospital stay between the two periods ($p = 0.1350$), nor were they different when compared based on a stay of over or under 30 days (Table 1).

The number of deaths in both periods was elevated (Table 1), although it was significantly higher (p = 0.028) during the pandemic (n = 65; 78.5%).

No difference was observed regarding the presence and number of comorbidities between the two periods (Table 2). Obesity showed a significant increase in the latter period compared to the former (p = <0.001), while cardiovascular diseases decreased during the pandemic period (p = <0.001). In addition, no association was found between the number of comorbidities and death (p = 0.483).

Overall, 97.87% of patients had at least one CVC insertion, with a maximum of four insertions per patient. No statistical difference (p = 0.96) was observed in the number of CVC insertions during the pre-pandemic period (mean: 1.96; Standard Deviation [SD]: 1.09) compared to the pandemic period (mean: 2.13; SD: 0.97). The mean length of CVC stay was 38.13 days (SD: 33.98) in the first period and 33.83 days (SD: 20.51) in the second. The jugular vein (48.28%) was the most used pathway in the pre-pandemic period, while subclavian access (60%) predominated during the pandemic.

Table 3 shows the 94 bacterial isolates identified during the study, with the most frequent being *Klebsiella pneumoniae* (20.21%), coagulase-negative *Staphylococcus* (13.83%), and *Pseudomonas aeruginosa* (11.70%). In the pre-pandemic period, the most frequent organism was *Pseudomonas aeruginosa* (20.68%), while during the pandemic, it was *Klebsiella pneumoniae* (24.61%).

Table 1: Sociodemographic and clinical characteristics of patients with primary bloodstream infections admitted to the intensive care unit in the pre-COVID-19 pandemic period (2018-2019) and during the pandemic (2020-2021) at a reference hospital in Fortaleza, Ceará, Brazil

	2018-2019		2020-2021				
Characteristics	n (%)	$\bar{x}$	n (%)	$\bar{x}$	p-value	PR	95% CI
Sex							
Male	15 (51.7)	-	43 (66.1)	-	0.009	1.220	0.80-1.60
Female	14 (48.3)		22 (33.8)				
Age							
<60 years	6 (20.7)	71.89	27 (41.5)	63.20	0.002	0.761	0.59-0.98
≥60 years	23 (79.3)		38 (58.4)				
Length of stay							
≤30 days	9 (31.0)	58.93	26 (40.0)	42.09	0.210	0.880	0.68-1.16
>30 days	20 (69.0)		39 (60.0)				
Length of ICU stay							
≤30 days	12 (41.3)	54.51	29 (44.6)	37.07	0.389	0.960	0.73-1.25
>30 days	17 (58.7)		36 (55.4)				
Outcome							
Death	17 (58.7)	-	51 (78.5)	-	0.028	1.390	0.95-2.03
Discharge	12 (41.3)		14 (21.5)				

Captions: $\bar{x}$ = mean; PR = Prevalence Ratio; 95% CI = 95% Confidence Interval

Table 2: Comorbidities in patients with primary bloodstream infections admitted to the intensive care unit in the pre-COVID-19 pandemic period (2018-2019) and during the pandemic (2020-2021) at a reference hospital in Fortaleza, Ceará, Brazil

	2018-2019		2020-2021				
	N = 29	%	n = 65	%	p-value	PR	95% CI
Total patients with comorbidities	25	86.2	55	84.6	0.434	0.96	0.66-1.38
Comorbidities							
SAH	19	65.5	37	56.9	0.22	0.89	0.68-1.17
DM	6	20.7	21	32.3	0.13	1.18	0.90-1.15
Cardiovascular diseases	14	48.3	7	10.8	<0.001	0.41	0.22-0.77
Respiratory diseases	2	6.9	4	6.2	0.43	0.96	0.53-1.72
Liver diseases	2	6.9	0	0.0	-	-	-
Neoplasms	1	3.4	2	3.1	-	-	-
Immune diseases	1	0.0	0	0.0	-	-	-
Renal insufficiency	1	6.9	2	3.1	-	-	-
Neurological diseases	0	0.0	5	7.7	0.075	1.48	1.28-1.71

PR = Prevalence Ratio; 95% CI = 95% Confidence Interval; SAH: Systemic Arterial Hipertension; DM: Diabetes Mellitus

Table 3: Bacteria isolated from patients with primary bloodstream infections admitted to the intensive care unit in the pre-COVID-19 pandemic period (2018-2019) and during the pandemic (2020-2021) at a reference hospital in Fortaleza, Ceará, Brazil

Bacterial isolates	2018-2021 n (%)	2018-2019 n (%)	2020-2021 n (%)
Total isolates	94 (100.00)	29 (100.00)	65 (100.00)
Isolated species			
Klebsiella pneumoniae	19 (20.21)	3 (10.34)	16 (24.61)
Coagulase-negative *Staphylococcus*	13 (13.83)	2 (6.90)	11 (16.92)
Pseudomonas aeruginosa	11 (11.70)	6 (20.68)	5 (07.69)
Staphylococcus epidermidis	6 (6.39)	3 (10.34)	3 (04.60)
Staphylococcus haemolyticus	6 (6.39)	3 (10.34)	3 (04.60)
Serratia marcescens	5 (5.31)	1 (3.45)	4 (06.15)
Enterococcus faecalis	4 (4.26)	1 (3.45)	3 (04.60)
Staphylococcus hominis	4 (4.26)	1 (3.45)	3 (04.60)
Acinetobacter baumannii	4 (4.26)	0 (0.00)	4 (06.15)
Enterococcus faecium	3 (3.20)	1 (3.45)	2 (03.10)
Acineto lwoffii	2 (2.13)	2 (6.90)	0 (00.00)
Burkholderia cepacia	2 (2.13)	1 (3.45)	1 (01.54)
Enterobacter cloacae	2 (2.13)	1 (3.45)	1 (01.54)
Staphylococcus cohnii	2 (2.13)	0 (0.00)	2 (03.10)
Stenotrophomonas maltophilia	2 (2.13)	0 (0.00)	2 (03.10)
Acinetobacter junii	1 (1.06)	0 (0.00)	1 (01.54)
Achromodacter xylosoxidans	1 (1.06)	0 (0.00)	1 (01.54)
Enterobacter aerogenes	1 (1.06)	0 (0.00)	1 (01.54)
Escherichia coli	1 (1.06)	1 (3.45)	0 (00.00)
Listeria monocytogenes	1 (1.06)	1 (3.45)	0 (00.00)
Morganella morganii	1 (1.06)	0 (0.00)	1 (01.54)
Staphylococcus aureus	1 (1.06)	1 (3.45)	0 (00.00)
Staphylococcus caprae	1 (1.06)	0 (0.00)	1 (01.54)
Streptococcus agalactiae	1 (1.06)	1 (3.45)	0 (00.00)

Gram-negative bacteria (n = 94; 55.32%) were the most frequently isolated bacteria. Considering the pre-pandemic period (15/94), *Pseudomonas aeruginosa* (40.0%), *Klebsiella pneumoniae* (20.00%), *Acinetobacter lwoffii* (13.36%), *Burkholderia cepacia* (6.66%), *Enterobacter cloacae* (6.66%), *Escherichia coli* (6.66%), and *Serratia marcescens* (6.66%) were the most frequently found. Meanwhile, during the pandemic (37/94), the most frequent isolates were *Klebsiella pneumoniae* (43.24*%)*, *Pseudomonas aeruginosa* (13.51%), *Acinetobacter baumannii* (10.82%), *Serratia marcescens* (10.82%), *Stenotrophomonas maltophilia* (5.41%), *Acinetobacter junii* (2.70%), *Achromodacter xylosoxidans* (2.70%), *Burkholderia cepacia* (2.70%), *Enterobacter cloacae* (2.70%), *Enterobacter aerogenes* (2.70%), and *Morganella morganii* (2.70%).

Gram-positive bacteria accounted for 44.68% (n = 94) of the isolated bacteria. When comparing the two periods, the most frequent in the pre-pandemic period (n = 14) were *Staphylococcus epidermidis* (21.43%), *Staphylococcus haemolyticus* (21.43%), and other coagulase-negative staphylococci (14.30%). During the pandemic (n = 28), the most frequent were coagulase-negative staphylococci (39.29%), followed by *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Enterococcus faecalis*, and *Staphylococcus hominis*, each accounting for 10.71%.

Regarding the resistance data, the most frequent antimicrobial resistance detected in the pre-pandemic period was related to cefoxitin (n = 28; 39.3%), ampicillin (n = 28; 35.7%), and ceftriaxone (n = 28; 35.7%), whereas during the pandemic period, it was related to imipinem with cilastatin (n = 65; 46.2%), ciprofloxacin (n = 65; 44.6%), ampicillin with sulbactam and meropenem (n = 65; 43.1%, each).

Among the 94 bacterial isolates, 94.68% showed resistance to at least one antibiotic, with a mean resistance to 6.3 drugs (SD = 4; 95% CI: 5.4-7.1). A significant difference in the bacterial resistance profile (p = 0.01) was found between the two periods. In the first period, the mean resistance was to 4.8 antibiotics (SD = 3.4), while in the second period, it was to 7 (SD = 4.1).

The resistance profiles of the isolated bacteria are shown in Table 4. Although the number of isolates was small, thus limiting the statistical analysis, it is important to note that *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* showed an increase in the percentage of isolates resistant to carbapenems during the pandemic.

Coagulase-negative *Staphylococcus* grouped those bacteria for which speciation was not performed. The two isolates obtained in the pre-pandemic period already showed significant resistance; however, it is noteworthy that there was an increment in resistance to cefoxitin and ceftazidime with avibactam (Table 4) during the pandemic period (11 strains).

Staphylococcus epidermidis and *Staphylococcus haemolyticus* had only three isolates studied each, which showed variations in the percentage of resistance to the tested antimicrobials when comparing the two periods (Table 4).

When analyzed by antimicrobial class, in the pre-pandemic period, penicillins (n = 28; 96%), second-generation cephalosporins (n = 28; 57.1%), and penicillins with beta-lactamase inhibitors (n = 28; 46.4%) showed a higher frequency of resistance. During the pandemic, new classes were included among the more resistant bacteria, which, in decreasing order of frequency, were: Carbapenems (n = 65; 115.5%), third-generation cephalosporins (n = 65; 86.1%), and penicillins with beta-lactamase inhibitors (n = 65; 78.5%) (Table 5). The percentage above one hundred corresponds to the use of the drug of the same pharmacological class more than once for the same patient.

A total of 93 bacterial isolates (n = 93) were included in the analysis shown in Table (5), as there was no resistance test conducted for the bacterium *Listeria monocytogenes*.

Table 4: Resistance profiles of the most frequent bacteria in the pre-COVID-19 pandemic period (2018-2019) and during the pandemic (2020-2021) in patients with primary bloodstream infections admitted to the intensive care unit in Fortaleza, Ceará, Brazil

	K. pneumoniae		Coagulase-negative *Staphylococcus**		*P. aeruginosa*		*S. epidermidis*		*S. haemolyticus*	
Bacterias antimicrobials	2018-2019 % (n = 3)	2020-2021 % (n=16)	2018-2019 % (n = 2)	2020-2021 % (n = 11)	2018-2019 % (n = 6)	2020-2021 % (n = 5)	2018-2019 % (n = 3)	2020-2021 % (n = 3)	2018-2019 % (n = 3)	2020-2021 % (n=3)
Amikacin	0	37.5	0	0.0	0.0	20	0.0	0.0	0	0.0
Amoxicillin + Clavulanate	0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0
Ampicillin	100	100.0	100	72.2	50.0	0	0.0	0.0	0	0.0
Ampicillin + sulbactam	100	100.0	100	0.0	33.3	0	0.0	0.0	0	0.0
Benzylpenicillin	0	0.0	50	0.0	0.0	0	100.0	66.6	100	0.0
Cefepime	100	87.5	50	0.0	0.0	40	0.0	0.0	0	0.0
Cefoxitin	100	25.0	0	90.9	83.3	60	0.0	0.0	0	0.0
Ceftazidime	100	68.7	0	0.0	0.0	40	0.0	0.0	0	0.0
Ceftazidime + avibactam	0	37.5	0	45.4	0.0	20	0.0	0.0	0	0.0
Ceftriaxone	100	100.0	0	0.0	83.3	60	66.6	0.0	0	0.0
Cefuroxime	100	100.0	0	0.0	16.6	0	0.0	0.0	0	0.0
Ciprofloxacin	100	87.5	0	0.0	0.0	40	66.6	0.0	0	0.0
Clindamycin	0	0.0	0	0.0	0.0	0	66.6	100.0	100	100.0
Erythromycin	0	0.0	0	0.0	0.0	0	66.6	33.3	100	0.0
Ertapenem	100	75.0	0	0.0	0.0	0	0.0	0.0	0	0.0
Gentamicin	50	43.7	100	81.8	0.0	0	33.3	33.3	100	100.0
Imipenem	50	81.2	0	27.2	16.6	80	0.0	0.0	0	0.0
Levofloxacin	0	0.0	0	0.0	0.0	0	0.0	33.3	0	100.0
Linezolide	0	0.0	50	0.0	0.0	0	33.3	33.3	0	0.0
Meropenem	50	81.2	0	0.0	33.3	60	0.0	0.0	0	0.0
Moxifloxacin	0	0.0	100	0.0	0.0	0	66.6	0.0	0	0.0
Nitrofurantoin	0	0.0	50	9.0	0.0	0	0.0	0.0	0	0.0
Norfloxacin	0	0.0	0	0.0	0.0	0	33.3	0.0	0	0.0
Oxacillin	0	0.0	0	0.0	0.0	0	100.0	100.0	100	100.0
Piperacillin + tazobactam	100	81.2	0	0.0	0.0	60	0.0	0.0	0	0.0
Rifampicin	0	0.0	0	0.0	0.0	0	0.0	0.0	100	66.6
Sulfamethoxazole + Trimethoprim	0	0.0	0	0.0	0.0	0	100.0	33.3	100	100.0

*Bacteria grouped as coagulase-negative *Staphylococcus* without species identification

Table 5: Bacterial resistance profiles based on the class of antimicrobial drugs used in patients with primary bloodstream infections admitted to the intensive care unit in the pre-COVID-19 pandemic period (2018-2019) and during the pandemic (2020-2021) in Fortaleza, Ceará, Brazil

Class	2018-2019	% (n = 28)	2020-2021	% (n = 65)	Total	% (n = 93)
Aminoglycosides	8	28.6	44	68.0	52	55.9
Carbapenems	10	35.7	75	115.5	85	91.4
Cephalosporin 2nd generation	16	57.1	33	51.0	49	52.7
Cephalosporin 3rd generation	14	50.0	56	86.1	70	75.3
Cephalosporin 4th generation	4	14.2	21	32.3	25	26.9
Glycylcyclines	0	0.0	2	3.0	2	2.2
Lincosamides	9	32.1	20	30.8	29	31.2
Macrolides	7	25.0	5	7.7	12	12.9
Nitroimidazoles	2	7.1	1	1.5	3	3.2
Oxazolidinones	1	3.6	1	1.5	2	2.2
Penicillin + Beta-lactamase inhibitor	13	46.4	51	78.5	64	68.8
Penicillins	27	96.4	49	75.4	76	81.7
Quinolones	12	43.0	49	75.4	61	65.6
Rifamycins	5	18.0	8	12.3	13	14.0
Sulphonamides	8	28.6	10	15.4	18	19.4

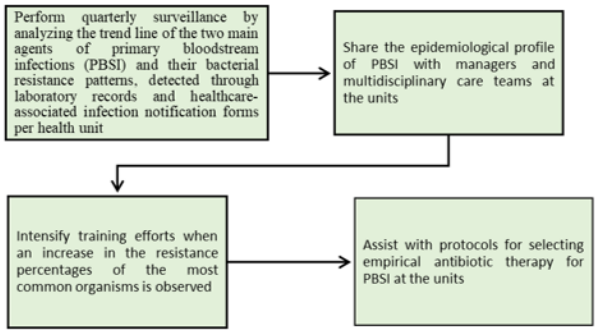

Fig. 1: Diagram to monitor organism resistance in healthcare institutions by the Hospital Infection Control Service (HICS)

There was no significant difference in number of deaths between Gram-positive and Gram-negative bacteria (p = 0.533; PR = 1.08 [95% CI: 0.84 - 1.3]). Based on the results obtained in this study, which demonstrated the impact on the resistance profile, we created a diagram to monitor organism resistance in healthcare institutions by the HICS (Fig. 1).

Discussion

The SARS-CoV-2 pandemic worsened and accelerated the already growing antimicrobial resistance of bacteria occurring worldwide. Brazil, the seventh most populous country in the world, with 203,080,756 inhabitants, was highly affected by COVID-19. Living with significant inequities among its five regions, with a wealthy South/Southeast and a poorer North/Northeast, the pandemic impacted the country in many ways, affecting both the public and private healthcare systems.

This study aimed to demonstrate how a well-equipped hospital with access to newer-generation antibiotics, even in a resource-limited area like Fortaleza, the capital of Ceará state, in northeastern Brazil, was impacted by the pandemic in terms of bacterial resistance to antimicrobials. To achieve this, we compared the bacterial and antimicrobial resistance profiles of PBSIs during the pre-pandemic and pandemic periods in patients in the ICU of a private reference hospital that handled the majority of COVID-19 cases admitted to a non-public service in Fortaleza. We focused on a specific topic PBSI to obtain more straightforward results, as it primarily reflects skin and hand colonization and is strongly related to improper manipulation of venous access. This situation better characterizes the difficulties in following established protocols for preventing hospital infections during the pandemic.

In the present study, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the most frequently isolated bacteria during the pre-pandemic and pandemic years, respectively; with an increase in resistance to carbapenems for both organisms during the COVID-19 period. It was also observed that, in the pre-pandemic period, penicillins, followed by second-generation cephalosporins, were the most commonly prescribed classes of drugs, while during the pandemic, there was a predominant use of classes with a broader spectrum, such as carbapenems and third-generation cephalosporins, which topped the ranking of drugs used.

Another study conducted in Fortaleza analyzed the impact of COVID-19 on the microbiological resistance profile, this time in an emergency department and ICUs of a private tertiary hospital and found an increase in the use of broad-spectrum cephalosporins, as well as a higher level of resistance in Gram-negative bacteria (*P. aeruginosa* and *K. pneumoniae*) to carbapenems and polymyxins during this period (Mesquita *et al.*, 2022).

Corroborating our findings, a study carried out in France compared the periods from January-April 2019 and January-April 2020 and observed an increase in bloodstream infections and antimicrobial resistance during the first wave of COVID-19. This increase in infection rates was due to organisms resistant to third-generation cephalosporins (ceftriaxone, ceftazidime, and cefotaxime) through mechanisms such as Extended Spectrum Beta-Lactamase (ESBL) production and overproduction of cephalosporinases, especially in *Klebsiella*, *Enterobacter*, and *Pseudomonas* species (Amarsy *et al*., 2022). Similarly, a study conducted from July 2020 to December 2021 in an ICU of a COVID-19 referral center in India analyzed the clinical profile of bloodstream infections and found that most of the isolated agents were Gram-negative (82.8%; n = 64), with *Acinetobacter baumannii* and *Klebsiella pneumoniae* being the most frequent (Palanisamy *et al*., 2021).

When bacterial infections are caused by Gram-negative bacilli, carbapenems are often used and with potent activity against this class of drugs. Although carbapenemases are more frequently isolated in non-fermenting Gram-negative bacteria (*Pseudomonas aeruginosas* and *Acinetobacter baumannii*), they have been increasingly reported in members of the *Enterobacteriaceae* family (Jabalameli *et al.*, 2018). The WHO has listed Gram-negative bacteria as a priority concerning antibiotic-resistant pathogens, which require special attention in hospitals, nursing homes, and patients in use of ventilators and intravenous catheters. These agents include *Acinetobacter*, *Pseudomonas*, and various *Enterobacteriaceae* (*Klebsiella* sp., *E. coli*), which can cause serious and often fatal infections, such as PBSIs and pneumonia (Mancuso *et al*., 2021).

In a study carried out in the ICUs of a university hospital in southeastern Brazil during the pre-pandemic period, involving patients diagnosed with PBSI using CVCs, Gram-negative bacteria accounted for 48.5% of the organisms isolated, followed by 33.3% Gram-positive bacteria. However, unlike our findings, the most common agent was *Acinetobacter baumannii*, followed by

Staphylococcus aureus and *Staphylococcus epidermidis* (Dias *et al.*, 2022). In that same study, 100% of coagulase-negative *Staphylococcus* and 25% of *Staphylococcus aureus* strains were resistant to oxacillin. In the current study, coagulase-negative *Staphylococcus* showed greater resistance to oxacillin in both periods.

Considering the same study from southeastern Brazil, *Enterobacteriaceae* (*Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia marcescens*) exhibited 62.5% resistance to broad-spectrum cephalosporins and 25% to carbapenems, which is much lower than our results. Among non-fermenters (*Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Acinetobacter baumannii*), the resistance to carbapenems was 75% (Dias *et al.*, 2022).

In general, the mean length of stay in hospitals and ICUs was longer than 30 days for most patients, even when comparing the pre-pandemic period to the pandemic period. It is well known that long periods of hospitalization associated with the insertion of invasive devices are risk factors for HAIs, especially in the ICU setting (Khor *et al.*, 2020).

A detailed anamnesis in patients with comorbidities is required to reduce the chances of adverse outcomes, especially in the COVID-19 scenario (Rente *et al.*, 2020). Patients with heart disease, as well as those affected by other chronic diseases, even at younger ages, often had severe COVID-19 and unfavorable outcomes, resulting in sequelae or death (Polido *et al.*, 2022). According to our findings, the majority of patients had at least one comorbidity. When the data was analyzed by period, obesity was most striking during the pandemic, while cardiovascular diseases decreased in the same period.

Similar to a Spanish study performed by Pérez-Granda *et al.* (2022), the length of stay with the CVC in our research was shorter in patients hospitalized with COVID-19. The choice of the initial access route also varied, with the jugular vein being the most commonly used during the pandemic, while the subclavian vein was preferred in the pre-pandemic period. As mentioned by others, this was likely related to the prone position adopted by many COVID-19 patients (Pérez-Granda *et al.*, 2022).

The mean age of patients hospitalized during the pandemic was lower when compared to patients in the pre-pandemic period ($p = 0.003$). In a study involving patients admitted to ICUs due to COVID-19 in the state of São Paulo in 2020 and 2021, 52.9% were male and their mean age was 64.3 years (Takenaka *et al.*, 2022), comparable to the findings in our study.

In the current study, a significantly higher number of deaths occurred during the pandemic period; however, this difference was not significant when considering bacteria as Gram-negative or Gram-positive. Elevated mortality during the pandemic was also found in other settings. At a university hospital in Campo Grande (midwestern Brazil), 172 patients admitted due to COVID-19 were selected to assess clinical outcomes, and the majority (56%) died (Deitos *et al.*, 2022). A combination of appropriate hygiene measures and the rational use of antimicrobial agents should be implemented to minimize the risks of catastrophic outcomes in the face of another sudden crisis similar in magnitude to COVID-19 (Amarsy *et al.*, 2022).

Conversely, a study carried out at a university hospital in Poland with critically ill patients with COVID-19 and bacterial bloodstream infections found that these infections did not significantly influence patient mortality. The deaths of those patients may be more strongly associated with the severity of their COVID-19, their age, and the presence of comorbidities (Bartoszewicz *et al.*, 2023)· However, a retrospective study conducted in Miami, Florida, USA, using data obtained from >10,000 patients hospitalized after SARS-CoV-2 testing, found that COVID-19 positivity increased the odds of developing a laboratory-confirmed bloodstream infection by 3.88-fold, and was associated with increased odds of hospital death. The authors discussed that this finding may be related to COVID-19 itself or other variables, such as changes in supplementary nursing care or in infection control practices (Shukla *et al*., 2021).

The limitations highlighted in this study were primarily due to its retrospective nature, relying on information obtained from medical records that are often incomplete. In spite of this, relevant information was gathered, albeit requiring cautious interpretation, mainly based on the number of isolates obtained. Although the number of isolates herein was small, the potential morbidity of these species points to a concerning scenario if uncontrolled dissemination occurs, emphasizing the essential nature of rational antimicrobial use to control the progressive rise in resistance. Nevertheless, our findings should be considered, and the study should continue, this time in a prospective manner to adhere to the recommendations outlined in Fig. (1).

It is noteworthy that the increase in bacterial resistance during the COVID-19 pandemic had multifactorial causes, but the high rate of antimicrobial agent usage in those years, despite the relatively low rates of co-infections or secondary infections, likely played an important role (Markovskaya *et al*., 2022). The impact of COVID-19 on bacterial resistance has been spreading worldwide, and the inappropriate Brazilian pandemic response, which led to elevated numbers of severe hospital admissions, resulted in difficulties obtaining protective supplies and providing adequate patient care. An optimized prescription guide, in accordance with the principles of good antimicrobial management, combined with quality diagnosis, surveillance, and strict infection control measures, can preclude the occurrence of more resistant organisms and prevent these agents from causing death in future health crises.

Conclusion

A significant difference in the bacterial resistance profile was found between the two periods, characterized by an increase in the number of antibiotics with bacterial resistance during the pandemic, as well as an increase in bacterial resistance to newer classes of antibiotics with more restricted use. This highlights the importance of strengthening antimicrobial control and the role of the HICS in the hospital, sending a clear message to hospital managers.

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Author's Contributions

Jonathan Da Silva Xavier: Made considerable contributions to conception and design, acquisition of data, analysis and interpretation of data. Contributed in drafting the article and reviewing it critically for significant intellectual content.

Jorge Luiz Nobre Rodrigues: Made considerable contributions to conception and design of the study, and in the acquisition, analysis and interpretation of data.

Caroline Mary Gurgel Dias Florêncio and Samuel Arruda Rodrigues Pereira: Made considerable contributions to analysis and interpretation of data.

Evelyne Santana Girão: Made considerable contributions to conception and design of the study, acquisition, analysis and interpretation of data. Contributed to reviewing the article critically for significant intellectual content.

Licia Borges Pontes: Made considerable contributions to acquisition of data.

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Pablo Eliack Linhares De Holanda: Made considerable contributions to conception and design of the study and acquisition of data.

Terezinha Do Menino Jesus Silva Leitão: Made considerable contributions to conception, and design of the study, as well as in drafting the article and reviewing it critically. Gave final approval of the version to be submitted and any revised version.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all other authors have read and approved the manuscript and that no ethical issues are involved.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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