Infection and Drug Resistance

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ORIGINAL RESEARCH

Characterization of the Pathogen Distribution and Drug Resistance in Bloodstream Infections During COVID-19 Pandemic in a Tertiary Hospital in Eastern China: Comparison with the Pre-Pandemic Period

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Purpose: To explore the characteristics of the pathogen distribution and drug resistance in bloodstream infections (BSIs) during the COVID-19 pandemic in a tertiary hospital in eastern China, and to compare them with those before the pandemic.

Patients and Methods: Non-repetitive strain data of BSIs were retrospectively obtained before the COVID-19 pandemic (Pre-Pandemic, n=2698) and during the COVID-19 pandemic (Pandemic, n=2922), the distribution of pathogens and drug resistance were compared between the two groups.

Results: The main pathogens of BSIs were Gram-negative bacteria (57.91%), followed by Gram-positive bacteria (32.58%), fungi and anaerobic bacteria accounting for 5.48% and 3.39%, respectively. *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* were the top 3 isolates. The proportion of *Serratia marcescens, Enterobacter aerogenes, Enterococcus faecium, Enterococcus faecalis* and *Candida tropicalis* were significantly increased, while those of *Pseudomonas aeruginosa, Streptococcus sanguinis* and *Streptococcus pneumoniae* were significantly decreased when compared to the Pre-Pandemic ($P<0.05$). Carbapenem-resistant *Enterobacterales* (CRE) significantly elevated during the Pandemic (17.4% vs 14.4%, $P=0.041$); the detection of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) significantly ascended (39.0% vs 24.4%, $P=0.016$); and the proportion of carbapenem-resistant *Acinetobacter baumannii* (CRAB) maintained stable (78.8%). Gram-positive bacteria had the lowest resistance to linezolid, vancomycin and tigecycline, which remained a stable trend with the Pre-Pandemic (<5.0%). The isolate rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) were 38.9% and 1.0%, respectively. *Staphylococcus aureus* showed a decrease in the isolation rate of vancomycin minimum inhibitory concentration (MIC) ≤ 0.5 μg/mL ($\chi 2=7.676$, $P=0.006$) and an increase with vancomycin MIC=1 μg/mL ($\chi 2=9.008$, $P=0.003$).

Conclusion: The pathogen distribution and drug resistance of BSIs during the COVID-19 pandemic were transformed from Pre-Pandemic and accompanied by increasing bacterial resistance. Clinical management of antibiotic application and infection control should be strengthened.

Keywords: COVID-19 pandemic, bloodstream infection, pathogen distribution, antibiotic resistance

Introduction

Bloodstream infections (BSIs) are frequent life-threatening infectious diseases clinically, the incidence of which is approximately 113–204 per 100,000 population, similar to that of stroke or venous thrombosis.[1] The disease has a mortality rate of 18%-35%[2] and may contribute to prolonged hospitalizations and severe complications, imposing a heavy burden on patients and healthcare systems.[3,4] Due to the widespread application of modern invasive diagnostic and therapeutic technologies and the inappropriate use of antibiotics, the incidence rate of BSIs has been increasing.[5]

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Antibiotic therapy is an effective method for BSIs, and timely control of BSIs is crucial for patients' prognosis. Blood culture is currently the gold standard for diagnosing BSIs.[6] Clinicians typically choose broad-spectrum antibiotics empirically based on the blood culture results and then adjust the type and dosage of antibiotics according to antimicrobial susceptibility testing in vitro.[7] The distribution of pathogen and drug resistance in patients with BSIs has general heterogeneity. Therefore, understanding the distribution of pathogenic bacteria and drug resistance characteristics of BSIs in different periods, regions, and even populations is essential for empirical therapy and antibiotic management.

Coronavirus disease 2019 (COVID-19) is an aggressive respiratory infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is fairly easy to propagate via various transmission routes, such as respiratory, droplet, and contact, etc. It has been reported that COVID-19 patients are prone to occur secondary bacterial infections, especially in those with immune dysfunction, and secondary BSI is a serious type of infection, which often have a more severe clinical course, leading to critical social risks.[8,9] Since the first patient was found in December 2019 in Wuhan, China, the world entered the COVID-19 pandemic era, and public health security was severely impacted.[10] In such a special period, a variety of coercive measures had been implemented, including maintaining good hand hygiene, wearing masks, avoiding crowd gatherings, strengthening environmental disinfection, setting up isolation wards, and building Fangcang shelter hospitals.[11,12] These forceful measures caused significant changes in the hospital care settings and patient population.[13] The lack of awareness of COVID-19 in the early stage led to the absence of antimicrobial stewardship interventions in response to such respiratory infection and the overprescription of antibiotics. In addition, healthcare environments also became overcrowding due to the rapid spread of COVID-19.[3] All these changes may contribute to the pathogen distribution and antimicrobial resistance transition of BSIs.[13]

In this background, correct recognition of the pathogen distribution and drug resistance patterns of BSIs during the Pandemic had guiding implications for the early appropriate choice of antibiotics and the reduction of mortality in clinical practice.

Material and Methods

Patient Cohort

This retrospective study was conducted at the First Affiliated Hospital of Nanjing Medical University, a 4300-bed tertiary-care grade A hospital in the eastern section of China. The National Health Commission (NHC) issued that China officially started to manage COVID-19 as a Class-B infectious disease on January 08, 2023, representing that China entered a new phase of COVID-19 response (https://english.www.gov.cn/statecouncil/ministries/202301/09/content_WS63bb82bcc6d0a757729e5483.html). Data of the patients from January 2017 to December 2019 (Pre-Pandemic) and January 2020 to December 2022 (Pandemic) was obtained from the electronic medical records system, including age, gender, department source, and bloodstream infection pathogens. This study obtained informed consent from all participants prior to the commencement and was approved by the Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2024-SR-114).

BSI Definition and Study Inclusion Criteria

A patient was deemed to be BSI if any blood culture conducted was non-contaminant bacterial or fungal growth.[14] Contaminant bacteria commonly referred to potential skin-colonizing contaminants, including coagulase-negative staphylococcus, *Propionibacterium acnes, Micrococcus species, Aerococcus species, Corynebacterium species, Clostridium perfringens*, and *Bacillus species* (except for *Bacillus anthracis*).[15] The blood culture from one venous puncture point is regarded as one set and one patient may submit one or more sets of blood cultures. When the number of bottles for detecting bacteria above is 1/per set, it is reviewed as contamination.[14] The inclusion criteria were as follows: **a**. patients who were older than 18 years old; **b**. all patients had clear pathogenic microorganisms in their blood and had complete in vitro antimicrobial susceptibility testing results; **c**. patients from all departments of our institute were enrolled, including the outpatient department, emergency department, intensive care unit (ICU), medicine department and surgical department; **d**. repeated isolates from the same patient were only included in the results of the first isolation.

Microbiological Identification and Antimicrobial Susceptibility Testing

Microbiological identification was conducted via VITEK 2 Compact system (Bio-Merieux SA, Marcy l 'etoile, France) and VITEK MS (Bio-Merieux SA, Marcy l 'etoile, France). Antimicrobial susceptibility testing of bacteria was performed by using VITEK 2 Compact, *Streptococcus* spp. susceptibility was determined by Kirby-Bauer disk-diffusion or E-test assay. All standardized antimicrobial susceptibility testing methodologies and results based on minimum inhibitory concentration (MIC) and antibacterial circle diameter were determined according to the latest Clinical and Laboratory Standards Institute (CLSI) guidelines of each year. The quality control strains were *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

Statistical Analysis

All statistical analyses were performed on SPSS version 26.0 software (IBM, Armonk, NY, United States). Continuous variables were shown as median with quartile ranges [*M (P25, P75)*] for non-normal distribution and mean ± standard deviation for normal distribution after being verified with the Kolmogorov–Smirnov test. Comparisons between the two groups were analyzed by the Mann–Whitney *U*-test. Categorical variables were presented as percentages (%) and comparisons between the two groups were performed by the $\chi 2$ test. Results were considered statistically significant at two-sided *P*-values <0.05. Heat maps were conducted through GraphPad Prism version 10.0 software (GraphPad, SanDiego, CA, United States), and the higher the isolate rates, the darker the color of the small squares.

Results

Demographic and Clinical Characteristics of Patients

A total of 2922 pathogenic microorganisms during the Pandemic of COVID-19 and 2698 pathogenic microorganisms during the Pre-Pandemic were enrolled in our study. During the Pandemic, the age of patients was 62 (52, 71) years old, 1823 (67.19%) patients were male and 890 (32.81%) were female, the patients were mainly from the ICU, emergency department, and general surgical ward. Compared to the Pre-Pandemic period, the median age of patients during the Pandemic remained unchanged (62 years), while the median age of females elevated (63 years vs 60 years, P=0.010), and the proportion of males increased (67.19% vs 62.64%, $\chi 2$=11.932, P=0.001).

Distribution of Pathogenic Microorganisms in BSIs

The distribution of the top 20 pathogens with the highest isolation rates of BSIs and the top 10 departments of patients' sources before and during the pandemic years were shown in Figure 1. Pathogens were ranked in descending order from up to down of the vertical coordinate, and departments were ranked in descending order starting with ICU from left to right of horizontal ordinate. Table 1 showed the details of the distribution of pathogenic bacteria during the two periods. During the Pandemic, the main pathogens of BSIs in patients were Gram-negative bacteria (57.91%), followed by Gram-positive bacteria (32.58%), fungi and anaerobic bacteria were less, accounting for 5.48% and 3.39%, respectively. *Escherichia coli, Klebsiella pneumoniae*, and *Staphylococcus aureus* were the top 3 isolates, the same as that in Pre-Pandemic. The isolation rate of *Enterococcus faecium* increased from seventh in the Pre-Pandemic to fourth position of the Pandemic, and *Pseudomonas aeruginosa* decreased from fifth to eighth (P<0.05). Furthermore, *Serratia marcescens, Enterobacter aerogenes, Enterococcus faecalis* and *Candida tropicalis* isolation rates were prominently increased, and those of *Streptococcus sanguinis* and *Streptococcus pneumoniae* decreased during the Pandemic (P<0.05). The distribution of pathogens in different ages, genders, and departments varied. We noticed that both in Pre-Pandemic and Pandemic, *Klebsiella pneumoniae* had the largest number of isolates in the ICU, while *Brucella* spp. was the highest isolate of outpatients.

Resistance Transition of Gram-Negative BSI Pathogens

We analyzed the antimicrobial susceptibility testing results in vitro of 2922 infected strains during the Pandemic, which were compared with 2698 infected strains in the Pre-Pandemic. As shown in Table 2, *Escherichia coli* had the lowest

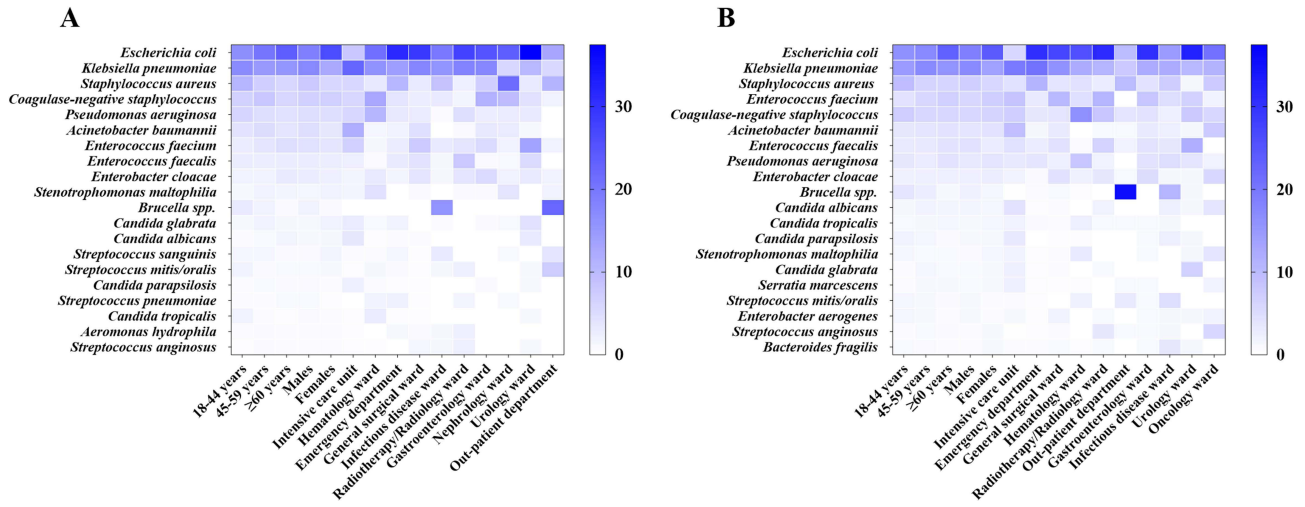

Figure 1 Distribution of the top 20 pathogenic microorganisms and the top 10 departments of patients' sources of BSIs. (**A**) Pre-Pandemic; (**B**) Pandemic.
Notes: Pre-Pandemic, January 01, 2017-December 31, 2019; Pandemic, January 01, 2020-December 31, 2022.

resistance to carbapenems (imipenem and meropenem), aminoglycoside (amikacin), *β*-lactam/*β*-lactamase inhibitor (piperacillin/tazobactam) and cephalosporin (cefotetan) with the resistance rates less than 6.2% and had the highest resistance to penicillin (ampicillin and piperacillin) and cephalosporins (cefuroxime, cefazolin, and ceftriaxone) with the

Table 1 Top 23 Bacterial Isolates from BSI Patients Collected in the Pre- and Pandemic Periods (n, %)

Pathogens	Pre-Pandemic (N=2698)	Pandemic (N=2922)	$\chi 2$	*P*-value
Gram-negative bacteria	1631 (60.45)	1692 (57.91)		
Escherichia coli	578 (21.42)	596 (20.40)	0.894	0.344
Klebsiella pneumoniae	423 (15.68)	470 (16.08)	0.174	0.677
Pseudomonas aeruginosa	131 (4.86)	105 (3.59)	5.554	0.018
Acinetobacter baumannii	116 (4.30)	113 (3.87)	0.671	0.413
Enterobacter cloacae	68 (2.52)	69 (2.36)	0.149	0.699
Stenotrophomonas maltophilia	42 (1.56)	31 (1.06)	2.690	0.101
Brucella spp.	40 (1.48)	56 (1.92)	1.573	0.210
Aeromonas hydrophila	18 (0.67)	12 (0.41)	1.738	0.187
Serratia marcescens	15 (0.56)	30 (0.99)	3.913	0.048
Enterobacter aerogenes	12 (0.44)	26 (0.89)	4.137	0.042
Gram-positive bacteria	837 (31.02)	952 (32.58)		
Staphylococcus aureus	191 (7.08)	193 (6.61)	0.496	0.481
Coagulase-negative staphylococcus	180 (6.67)	176 (6.02)	0.994	0.319
Enterococcus faecium	115 (4.26)	178 (6.09)	9.499	0.002
Enterococcus faecalis	72 (2.67)	108 (3.70)	4.777	0.029

(*Continued*)

Table 1 (Continued).

Pathogens	Pre-Pandemic (N=2698)	Pandemic (N=2922)	$\chi 2$	*P*-value
Streptococcus sanguinis	29 (1.07)	13 (0.44)	7.505	0.006
Streptococcus mitis/oralis	28 (1.04)	29 (0.99)	0.029	0.865
Streptococcus pneumoniae	21 (0.78)	7 (0.24)	8.214	0.004
Streptococcus anginosus	17 (0.63)	23 (0.79)	0.490	0.484
Fungus	134 (4.97)	160 (5.48)		
Candida glabrata	37 (1.37)	30 (1.03)	1.415	0.234
Candida albicans	31 (1.15)	45 (1.54)	1.608	0.205
Candida parapsilosis	22 (0.82)	33 (1.13)	1.427	0.232
Candida tropicalis	19 (0.70)	37 (1.27)	4.492	0.034
Anaerobic bacteria	93 (3.45)	99 (3.39)		
Bacteroides fragilis	15 (0.56)	22 (0.75)	0.832	0.362

Notes: Pre-Pandemic, January 01, 2017-December 31, 2019; Pandemic, January 01, 2020-December 31, 2022.

Table 2 Antimicrobial Resistance Transition of the Main Gram-Negative Bacteria (%)

Antibiotics	*Escherichia coli*		*Klebsiella Pneumoniae*		*Pseudomonas Aeruginosa*		*Acinetobacter Baumannii*	
	Pre-Pandemic (n=578)	Pandemic (n=596)	Pre-Pandemic (n=423)	Pandemic (n=470)	Pre-Pandemic (n=131)	Pandemic (n=105)	Pre-Pandemic (n=116)	Pandemic (n=113)
Ampicillin	86.6	87.3	/	/	-	-	-	-
Ampicillin/ sulbactam	61.2	56.1	58.7	57.2	-	-	72.2	76.8
Piperacillin	70.8	65.2 *	57.3	56.1	13.0	13.3	-	-
Piperacillin/ tazobactam	5.2	3.4	36.3	39.6	8.4	11.4	72.4	74.8
Cefuroxime	70.6	71.6	58.9	57.9	-	-	-	-
Cefazolin	70.9	71.8	58.2	57.8	-	-	-	-
Ceftriaxone	69.7	71.3	57.4	57.4	-	-	72.2	79.1
Ceftazidime	35.8	35.4	45.6	47.2	13.0	15.2	73.3	78.8
Cefepime	27.9	27.2	42.9	42.0	13.0	13.9	75.0	79.3
Aztreonam	49.8	47.0	50.5	48.9	-	-	-	-
Cefotetan	4.5	6.2	32.4	36.0	-	-	-	-
Cefoperazone/ sulbactam	19.4	23.3	44.9	45.6	14.9	23.9	64.7	78.5 *
Imipenem	2.2	2.5	34.4	37.2	19.4	31.7 *	76.7	78.8
Meropenem	2.1	2.2	33.6	38.5	18.3	35.6 **	76.7	78.8
Gentamicin	40.0	33.2 *	41.8	35.1 *	5.3	7.6	67.0	72.7

(*Continued*)

Table 2 (Continued).

Antibiotics	*Escherichia coli*		*Klebsiella Pneumoniae*		*Pseudomonas Aeruginosa*		*Acinetobacter Baumannii*	
	Pre-Pandemic (n=578)	Pandemic (n=596)	Pre-Pandemic (n=423)	Pandemic (n=470)	Pre-Pandemic (n=131)	Pandemic (n=105)	Pre-Pandemic (n=116)	Pandemic (n=113)
Tobramycin	16.9	16.1	35.0	33.0	5.3	6.7	62.9	73.9
Levofloxacin	58.0	55.0	42.1	44.6	6.1	11.4	62.9	73.4
Ciprofloxacin	60.5	56.6	44.8	46.3	6.9	11.4	75.0	79.3
Amikacin	2.6	2.9	25.5	21.8	4.6	4.8	-	-
Sulfamethoxazole/ trimethoprim	52.2	52.3	41.1	38.3	-	-	70.4	76.1

Notes: Pre-Pandemic, January 01, 2017-December 31, 2019; Pandemic, January 01, 2020-December 31, 2022; /, natural drug resistance; -, without detection. *P<0.05, **P<0.01.

resistance rates more than 65.2%. Compared to the Pre-Pandemic, the resistance rate of *Escherichia coli* to piperacillin and gentamicin significantly decreased (both P-values <0.05). *Klebsiella pneumoniae* had the lowest resistance to aminoglycosides (gentamicin, tobramycin, and amikacin) and carbapenems (imipenem and meropenem) with resistance rates less than 38.5%, and had the highest resistance to cephalosporins (cefuroxime, cefazolin, and ceftriaxone), β-lactam /β-lactamase inhibitor (ampicillin/sulbactam) and penicillin (piperacillin), with the resistance rates more than 56.1%. The resistance rate of *Klebsiella pneumoniae* to gentamicin significantly declined compared to that in Pre-Pandemic (P<0.05). *Pseudomonas aeruginosa* showed the highest resistance rate to carbapenems (imipenem and meropenem) (around 35%) and a prominent increase was observed in the pandemic epoch (P<0.05). For other antibiotics, *Pseudomonas aeruginosa* exhibited lower resistance rates (≤23.9%). *Acinetobacter baumannii* displayed multiple resistance with antibiotic resistance rates higher than 72.7%, including a significant elevation in resistance to cefoperazone/sulbactam compared to that in the Pre-Pandemic (P<0.05).

Resistance Transition of Gram-Positive BSI Pathogens

Staphylococcus spp. had the lowest resistance to linezolid, rifampicin, vancomycin, and tigecycline which remained a stable trend before and during the Pandemic (Table 3). For *Staphylococcus aureus*, the bacterium also had a low resistance to other antibiotics (≤43.0%), except for penicillin, whose drug resistance rate was as high as 92.2%. The resistance rate of Coagulase-negative staphylococcus (CoNS) to oxacillin was 81.1%, twofold as *Staphylococcus aureus*.

Table 3 Antimicrobial Resistance Transition of the Main Gram-Positive Bacteria (%)

Antibiotics	*Staphylococcus Aureus*		*Coagulase-Negative Staphylococcus*		*Enterococcus Faecium*		*Enterococcus Faecalis*	
	Pre-Pandemic (n=191)	Pandemic (n=193)	Pre-Pandemic (n=180)	Pandemic (n=176)	Pre-Pandemic (n=115)	Pandemic (n=178)	Pre-Pandemic (n=72)	Pandemic (n=108)
Levofloxacin	33.5	26.4	52.6	62.1	87.7	88.2	25.0	34.3
Sulfamethoxazole/ trimethoprim	7.9	5.7	48.2	44.5	-	-	-	-
Clindamycin	51.3	39.4 *	50.0	42.7	-	-	-	-
Erythromycin	56.5	43.0 **	74.6	71.3	81.6	86.5	51.4	43.5
Linezolid	0.0	0.0	0.8	3.0	0.9	1.1	3.1	5.0
Penicillin	90.5	92.2	95.8	94.6	90.9	91.5	8.5	7.4
Oxacillin	39.3	38.9	78.5	81.1	-	-	-	-

(*Continued*)

Table 3 (Continued).

Antibiotics	*Staphylococcus Aureus*		*Coagulase-Negative Staphylococcus*		*Enterococcus Faecium*		*Enterococcus Faecalis*	
	Pre-Pandemic (n=191)	Pandemic (n=193)	Pre-Pandemic (n=180)	Pandemic (n=176)	Pre-Pandemic (n=115)	Pandemic (n=178)	Pre-Pandemic (n=72)	Pandemic (n=108)
Gentamicin	11.6	6.7	15.8	16.3	-	-	-	-
Rifampicin	1.6	2.1	6.2	8.9	-	-	-	-
Ciprofloxacin	33.7	22.3 *	52.1	56.8	88.2	88.1	28.2	36.1
Moxifloxacin	27.9	18.7	31.9	38.5	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.0	0.9	1.1	0.0	0.9
Quinuputin/ dafoputin	28.4	23.3	28.4	21.8	1.8	0.6	77.5	50.9***
Tigecycline	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tetracycline	30.0	20.2 *	23.7	15.6*	29.6	32.2	61.7	60.2
High-level streptomycin	-	-	-	-	37.6	30.4	28.2	20.0
High-level gentamicin	-	-	-	-	39.5	33.9	27.8	22.3
Ampicillin	-	-	-	-	88.4	88.8	1.4	0.0

Notes: Pre-Pandemic, January 01, 2017-December 31, 2019; Pandemic, January 01, 2020-December 31, 2022; -, without detection. *P<0.05, **P<0.01, ***P<0.001.

In addition, CoNS also had high resistance rates to penicillin, erythromycin, levofloxacin, and ciprofloxacin of more than 56.8%. Compared to the Pre-Pandemic, there was a significant decrease in the resistance rates of *Staphylococcus aureus* to clindamycin, ciprofloxacin, tetracycline, and erythromycin (P<0.05), whatever CoNS only showed a decrease in tetracycline resistance rate (P<0.05). *Enterococcus* manifested low resistance to vancomycin, linezolid, and tigecycline. *Enterococcus faecium* expressed ultra-high resistance to antibiotics including penicillin, ampicillin, levofloxacin, ciprofloxacin, and erythromycin (≥86.5%), to which *Enterococcus faecalis* had low resistance (≤43.5%). There was no statistically significant change in the drug resistance of *Enterococcus faecium*, while the resistance of *Enterococcus faecalis* to quinuputin/dafoputin was significantly decreased in the Pandemic (P<0.001).

Distribution of Drug-Resistant Strains

We analyzed the distribution of drug-resistant bacteria causing BSIs including carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) during the Pandemic, which were showed in Table 4. The detection rates of CRE, CRAB, CRPA, MRSA, and VRE were 17.4%, 78.8%, 39.0%, 38.9%, and 1.0%, respectively, and no PRSP was detected during the Pandemic. Notably, the detection rates of CRE and CRPA were significantly higher in the Pandemic compared to the Pre-Pandemic.

MIC Creep of Staphylococcus Spp

Considering no vancomycin-resistant *Staphylococcus* spp. has been identified yet, to comprehend the variation of vancomycin MIC values of this genus, we analyzed the vancomycin MIC creep of *Staphylococcus* spp., as shown in Figure 2. All the strains were susceptible to vancomycin in our study according to the latest CLSI breakpoint. However, we found that there was a decrease in the isolation rate of vancomycin MIC ≤ 0.5 μg/mL ($\chi 2$=7.676, P=0.006) and an increase with vancomycin MIC=1 μg/mL ($\chi 2$=9.008, P=0.003) of *Staphylococcus aureus* in the Pandemic. The vancomycin MIC value of CoNS during the pandemic did not show significant change compared to the Pre-Pandemic.

Table 4 Distribution of the Drug-Resistant Strains

	Pre-Pandemic (N, n, %)	Pandemic (N, n, %)	$\chi 2$	*P*-value
CRE	1192, 172 (14.4)	1284, 224 (17.4)	4.185	0.041
CRAB	116, 90 (77.6)	113, 89 (78.8)	0.046	0.830
CRPA	131, 32 (24.4)	105, 41 (39.0)	5.831	0.016
MRSA	191, 75 (39.3)	193, 75 (38.9)	0.007	0.935
VRE	199, 1, (0.5)	301, 3, (1.0)	0.896	0.624
PRSP	21, 0 (0.0)	7, 0 (0.0)	-	-

Notes: Pre-Pandemic, January 01, 2017-December 31, 2019; Pandemic, January 01, 2020-December 31, 2022.
Abbreviations: CRE, carbapenem-resistant *Enterobacterales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*.

Discussion

Bacteria are common concurrent pathogens of viral respiratory infections and important causes of morbidity and mortality. A recent meta-analysis showed that about 15.5% of COVID-19 patients reported secondary bacterial infections.[8] Among which BSIs have always been a highly concerning infectious issue globally, and the pandemic of COVID-19 caused a more serious situation.[16] Research from Sweden manifested that the incidence rate of hospital-onset BSIs during the COVID-19 pandemic was higher compared to the period before, and the mortality risk associated with hospital-onset BSIs was also greater.[17] Timely acquisition of the latest epidemiological and antibiotic resistance information on BSI is of great significance for patients' management.

In our study, Gram-negative bacteria were primary pathogens of BSIs with a proportion of around 60% in the two periods, consistent with published reports,[18–20] among which *Escherichia coli* and *Klebsiella pneumoniae* were the most common. Gram-positive bacteria in our investigation accounted for around 30% during both two periods, and *Staphylococcus aureus* maintained the top. Although CoNS are common contaminants of blood cultures, we found that after the elimination of contamination, CoNS ranked second in BSIs caused by Gram-positive coccus. Several clinical practices considered CoNS a highly risky pathogen, especially for neonates and immunocompromised patients.[21] Therefore, when CoNS is isolated clinically in blood cultures, its potential as a causative agent should be taken into consideration. Previous clinical reports showed that *Candida* species was the major pathogen of fungal BSIs,[18,22] and our research result confirmed the opinion with a slightly lower isolation rate (5.48% vs 7%). Our study expressed that before the Pandemic, *Candida glabrata* was the main species of fungal BSIs, relegating *Candida albicans* to second place, which was consistent with the conclusion of *Aldardeer*

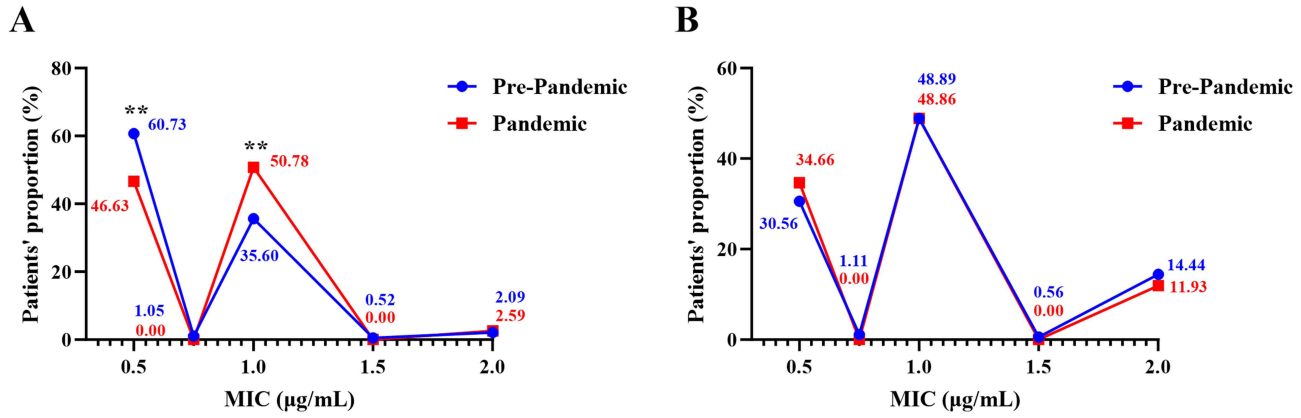

Figure 2 MIC creep of *Staphylococcus* spp. during the pre-pandemic and pandemic periods. (**A**) *Staphylococcus aureus*; (**B**) Coagulase-negative staphylococcus.
Notes: Pre-Pandemic, January 01, 2017-December 31, 2019; Pandemic, January 01, 2020-December 31, 2022. **P<0.01.

NF et al.[23] However, *Candida albicans* became the top-ranked species in the Pandemic. Additionally, the isolation rate of anaerobic bacteria from blood was 3.39% during the Pandemic according to our data, and *Bacteroides fragilis* was the most frequently isolated strain, which was similar to other reports.[24]

Although *Escherichia coli* was the most common pathogenic microorganism causing BSIs, we interestingly found that *Klebsiella pneumoniae* in ICU and *Brucella* spp. in the outpatient department were observed leading the ranking of BSIs, and the COVID-19 pandemic seemed to have no impact on such distribution. A recent report on the epidemiology of hospital-acquired BSI in Europe also revealed the salient role of *Klebsiella pneumoniae* in ICU patients, followed by *Escherichia coli*.[25] Furthermore, the infectious disease ward was another high-occurrence area for *Brucella* spp. BSIs. This might relate to patients entering the outpatient department for diagnosis and treatment due to unexplained fever or being empirically dispersed directly to the infectious disease department by the nurses' station.

Compared to the Pre-Pandemic, the isolate rate of *Pseudomonas aeruginosa* significantly decreased during the Pandemic in our study. *Pseudomonas aeruginosa* is the main source of hospital infections or opportunistic infections because of its omnipresent distribution in the environment,[26] the decrease in isolation rate of *Pseudomonas aeruginosa* in our institution may be attributed to systematic preventive and infection control measures in patients, healthcare workers, medical equipment and healthcare environments that guided by relevant policies during the Pandemic.[27] We also found that *Enterococcus faecium* and *Enterococcus faecalis* displayed significant increases in isolation rates during the Pandemic and *Enterococcus faecium* turned into the fourth pathogen of BSIs following *Staphylococcus aureus*. The SENTRY Drug Resistance Surveillance Program, which covers more than 200 medical centers in 45 countries, showed a trend of increasing isolation rates of *Enterococcus* spp. in BSIs annually.[28] Such data warned us to pay adequate attention to BSIs derived from *Enterococcus* spp.

The excess usage of antimicrobial agents was serious during the Pandemic and the transition in antibiotic resistance seemed to be predictable.[17] A survey from *Yang X* et al reported that during the hospitalization of patients with COVID-19 infection, their administration rate of antibiotics was up to 94%-100%, which was much higher than the secondary bacterial or fungal infection incidence (10%-15%).[29] It was reported in 2019 that BSIs accounted for more than 70% of antimicrobial resistance-associated deaths.[30] In this study, *Enterobacteriales*, especially *Escherichia coli and Klebsiella pneumoniae*, were sensitive to aminoglycoside and carbapenem antibiotics, cefotetan, and piperacillin/tazobactam before and during the pandemic periods, which were consistent with other investigations.[31,32] However, the proportion of CRE significantly increased during the Pandemic, rising from 14.4% to 17.4%, and the carbapenem resistance of *Klebsiella pneumoniae* was up to approximately 38%, much more severe than that of *Escherichia coli* (2%). *Acinetobacter baumannii* had been incrementally reported as an important hospital pathogen that had prominent drug resistance.[33] Our data showed that *Acinetobacter baumannii* had a high prevalence of antibiotic resistance of more than 72.7%, showing multi-drug resistance, and with a high percentage of CRAB of 78.8% which was similar to *Diekema DJ*'s report.[28] *Pseudomonas aeruginosa* owned the highest resistance to imipenem and meropenem and deteriorated obviously during the Pandemic in our institution, the proportion of CRPA raised to 39.0%, whose increased tendency was in line with the result of a Chinese multicenter retrospective study that CRPA isolation rate in BSIs increased dramatically from 17% in 2012 to 60% in 2020.[34] Unlike CRE and CRAB, which generally exhibit multi-drug resistance, partial CRPA manifests considerable sensitivity to other antibiotics except for carbapenems. This may contribute to the fact that their underlying different resistance mechanisms to carbapenems. CRE and CRAB arise mainly from carbapenemase-producing strains, such as KPC, DNM, and OXA48, etc.,[35,36] whereas that of *Pseudomonas aeruginosa* is more complex, including efflux pumps, reduction or deletion of porin OprD, and over-expression of the cephalosporinase AmpC.[34]

In our study, the isolation rates of MRSA remained stable at around 39%, which was comparable to that among several other provinces in China.[37] *Staphylococcus aureus* from blood culture did not occur any vancomycin, linezolid, or tigecycline-resistant strains during these two periods, which was consistent with the conclusion that general Gram-positive bacteria were sensitive to the above three antibiotics.[38] There were no vancomycin and tigecycline-resistant strains in CoNS, and the resistance rates to linezolid and rifampicin were relatively low. *Enterococcus* exhibited no resistance to tigecycline and fairly low resistance to linezolid in the present study. Thus, clinicians could choose the aforementioned antibiotics in response to severe BSIs caused by common Gram-positive bacteria. It was worth

noticing that although there was no resistance to vancomycin was found in *Staphylococcus aureus*, its isolation rate with vancomycin MIC≤0.5 μg/mL significantly decreased and that of MIC=1 μg/mL increased during the Pandemic, which indicated vancomycin MIC creep of the causative agent. Our findings were similar to the results of *Takumi Fujimori* et al from Japan aimed at vancomycin MIC creep progress of MRSA.[39] The latent molecular mechanism of such MIC creep involved reduced drug permeability due to the cell wall thickening, which could arise from repeated exposure to antibiotics.[39] Therefore, the selection of antibiotics must be cautious to avoid reduced drug sensitivity. However, it was identified that vancomycin MIC declined both in MRSA and methicillin-sensitive *Staphylococcus aureus* in another study from China.[40] Patient demographics, regionality and the year data were detected might partially explain the contradictions.[40] Creep regarding the MIC of *Staphylococcus aureus* to vancomycin still requires continuous monitoring.

Conclusion

This study indicated that the pathogen distribution of BSIs altered during the COVID-19 pandemic, and antibiotic resistance increased. The increasing problem of carbapenem resistance, represented by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and the creep of the MIC value of *Staphylococcus aureus* to vancomycin in the upward trend of resistance should be emphasized. However, whether the discovery of such results is associated with the increased administration of carbapenems or glycopeptides in clinical targeted medication is uncertain. Therefore, to guide clinicians in the proper antibiotic selection and prevent the emergence of drug-resistant strains, more efforts and data are needed to investigate the epidemiology and drug resistance of pathogens causing BSI, and we will continue this research.

Data Sharing Statement

All the findings are available from the corresponding author upon request. All relevant data have been included in the manuscript.

Ethics Statement

This study obtained informed consent from all participants prior to the commencement and was reviewed and approved by the Ethics Committee of Jiangsu Province Hospital (No. 2024-SR-114).

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Disclosure

The authors report no conflicts of interest in this work.

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