

Distribution and Antibiotic Resistance Analysis of Blood Culture Pathogens in a Tertiary Care Hospital in China in the Past Four Years

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Purpose: This study aimed to investigate the antibiotic resistance patterns and clinical distribution of blood culture-positive isolates at Suining Central Hospital between 2018 and 2021. The findings of this study can provide a basis for ensuring rational and effective use of antibiotic therapy in clinical settings.

Methods: This retrospective study analyzed the data of 3660 non-repeating strains that tested positive for clinical blood culture, collected from the microbiology laboratory of Suining Central Hospital between January 2018 and December 2021. The identification of bacterial species and their antibiotic resistance patterns were analyzed.

Results: The study found that 76.7% of the bacterial strains identified were Gram-negative bacteria, while 23.3% were Gram-positive bacteria. *Escherichia coli* (44.8%), *Klebsiella* spp. (19.2%), *Staphylococcus aureus* (9.2%), *Enterococcus* spp. (5.3%), and *Enterobacter* spp. were the top five bacterial ratios observed. These bacteria were detected most frequently in the Digestion Center, intensive care unit (ICU), Neurology Center, Urology Department, and Hematology Department. Among the *Staphylococcus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *coagulase-negative staphylococci* (MRCNS) were detected at rates of 39.3% and 71.8%, respectively. However, no vancomycin- or linezolid-resistant staphylococci were identified. *Enterococcus faecalis* showed higher susceptibility to most antibiotic than *Enterococcus faecium*, except for tetracycline. The resistance rates of *E. coli* and *Klebsiella* spp. to meropenem and imipenem were low, but the resistance rates for other antibiotic were above 40%.

Conclusion: The results of this study show a rising incidence of bacterial antibiotic resistance in positive blood culture specimens at Suining Central Hospital. Clinicians should carefully consider the importance of blood culture antibiotic susceptibility testing to ensure effective treatment. The Department of Microbiology at Suining Central Hospital should regularly analyze the distribution of pathogenic bacteria and antibiotic resistance in blood cultures to ensure the most effective treatment possible.

Keywords: blood stream infection, antibiotic resistance, antibacterial drugs

Introduction

Bloodstream infection (BSI) is a serious and potentially life-threatening systemic infectious disease caused by pathogenic microorganisms invading the bloodstream and releasing toxins and metabolites that can lead to infection, poisoning, and a systemic inflammatory response.¹ Although molecular approaches have been explored for pathogen diagnosis, blood culture (BC) remains the gold standard tool for identifying BSI and sepsis.² It provides an accurate and reliable basis for clinical diagnosis and rational antibiotic administration.³ The pathogenic spectrum and pattern of antibiotic resistance of BSI vary among affected regions due to distinct epidemiological and geographic factors.^{4,5} Monitoring data from Dalian, China, from 2015 to 2019 showed that Gram-positive cocci were the most prevalent BSI pathogens in blood cultures.⁶ In contrast, antibiotic resistance surveillance data from Korea and Europe revealed that *E. coli* and *S. aureus* were the most

common pathogens of, BSI.^{7,8} According to studies, incorrect empiric antibiotic therapy is an independent risk factor for increased mortality, particularly in individuals with *S. aureus* or *Enterobacter* spp. In addition relevant studies have shown that bloodstream infections are associated with various risk factors, such as advanced age, comorbidities, previous infections, neutropenia, long-term use of immunosuppressive medications, and the presence of indwelling venous catheters.^{9,10} Therefore, to provide clinicians with a reference for rational antibiotic use in treating BSI, this retrospective study aimed to examine the main pathogenic species and resistance patterns in blood cultures of inpatients at Suining Central Hospital between 2018 and 2021. In summary, bloodstream infection is severe, and blood culture remains the most reliable diagnostic tool. Antimicrobial resistance patterns vary across regions, highlighting the need for region-specific surveillance and treatment guidelines. This study investigates the pathogenic species and resistance patterns of BSI in Suining Central Hospital, aiming to guide the rational use of antibiotics in the treatment of BSI.

Materials and Methods

Data Collection

This retrospective study aimed to analyze blood cultures conducted between January 1, 2018, and December 31, 2021, at Suining Central Hospital in China. The dataset was obtained from the esteemed microbiology department, encompassing crucial information such as the date of blood culture, outcomes, AST results, patient demographics (age and sex), and the respective ward. To ensure the elimination of any potential bias arising from duplicate isolates, our analysis solely focused on the initial pathogen isolated from each patient and exclude positive outcomes from blood cultures containing single vials of coagulase-negative *staphylococci* and treating it as contamination.

Pathogen Identification and Antimicrobial Susceptibility Test

Blood samples were collected from patients using commercially available media bottles (bioMérieux, France) in accordance with established protocols. For adult patients, a combination of both aerobic and anaerobic bottles was utilized, whereas children were subjected to blood culture using exclusively aerobic bottles. The volumes of the blood samples collected were approximately 8–10 mL and 2–5 mL per bottle for adults and children, respectively. These samples were subsequently processed for blood culture analysis utilizing the BACT/ALERT 3D system (bioMérieux, France). The incubation cycle is five days. Positive blood samples were subjected to meticulous microscopic examination and subsequently subcultured on appropriate media. The suspected pathogens were then identified utilizing conventional biochemical tests, and an automatic identification instrument (Vitek-2 Compact system, bioMérieux, France). Ensuring accurate detection and characterization.^{11,12} Bacterial identification and antibiotic sensitivity identification were performed using a fully automated Vitek 2 compact. Instrument from Mérieux, France, with reagents for GN and GP identification cards matched with GN13 and GP67 antimicrobial susceptibility testing cards, Antimicrobial drug susceptibility testing (AST) was conducted in accordance with the guidelines outlined by the Clinical and Laboratory Standards Institute (CLSI). The testing methods employed included the disk diffusion method, gradient diffusion method, and Vitek-2 Compact system. Antimicrobial susceptibility test discs and ETEST test strips were procured from Wenzhou Kangtai Biotechnology Co. in accordance with the manufacturer's instructions. To control the quality of results, all laboratory activities were strictly conducted in accordance with ISO 15189.¹³ Antibiotic sensitivity testing followed the method recommended by the American Clinical and Laboratory Standardization Institute (CLSI) in 2021. The quality control strains used included *E. coli* ATCC25922, *S. aureus* ATCC25923 (for paper method) and ATCC29213 (for Minimum Inhibitory Concentration (MIC) method), *Pseudomonas aeruginosa* ATCC27853, *E. faecalis* ATCC29212, *Streptococcus pneumoniae* ATCC49619, and *Haemophilus influenzae* ATCC49247.

Statistical Analysis

The antibiotic sensitivity test results were interpreted according to the CLSI 2021⁹ guidelines. Analysis of the data was performed using WHONET 5.6 software and version standards. The chi-square test was performed to compare the differences in the proportion of positive blood cultures among the sex, age, and hospital ward groups. Furthermore, to evaluate the significance of the annual trend, the Mann-Kendall trend test was employed on the linear trend. This

statistical analysis allowed for a robust assessment of the temporal patterns observed in the data. Statistical analysis was performed using SPSS Statistics 28.0 (IBM Corp, NY, USA) and R software version 4.2.3.

Results

Blood Culture

A total of 29,283 blood culture tests were conducted from 2018 to 2021, with 3660 tests (12.5%) yielding positive results. Among these positive blood culture results, males accounted for 47.0% (1721/3660) and females accounted for 53.0% (1939/3660). The blood culture positivity rate was found to be significantly higher in individuals aged 60 years and above, with a rate of 60.7% (2223/3660) ($P < 0.05$), compared to those in the age groups of 0–17 years, where the rate was 3.4% (125/3660), and 18–59 years, where the rate was 35.8% (1312/3660). Patients' general information is presented in [Table 1](#). This stark disparity in blood culture positivity rates across different age groups highlights the increased susceptibility and potential severity of infections among elderly individuals. The top five departments in this study were found to be Digestion Center, ICU, Neurology Center, Urology Department, and Hematology Department. The positive rate of blood culture of Digestion Center was significantly higher than that of other hospital wards ($P < 0.05$). Please refer to [Figure 1](#) Distribution of clinical departments with positive blood culture bacteria, 2018–2021.

Distribution of Bacteria

From 2018 to 2021, our hospital collected a total of 3660 clinical, non-repeated strains that yielded positive blood cultures. Among these, 76.7% (2807 strains) were identified as Gram-negative, while the remaining 23.3% (853 strains) were Gram-positive. The most frequently isolated strains during this period were *E. coli* (44.8%), *Klebsiella* spp. (19.2%), *S. aureus* (9.2%), *Enterococcus* spp. (5.3%), and *Enterobacter* spp. (3.4%). Please refer to [Table 2](#) for a detailed breakdown of the major species distribution.

Antibiotic Resistance Characteristics of Gram-Positive Bacteria

In the period spanning from 2018 to 2021, a comprehensive survey of blood culture-positive isolated specimens yielded a total of 336 *S. aureus* and 117 coagulase-negative *Staphylococcus* (CoNS) strains. The detection rates of MRSA and MRCNS were 39.3% and 71.8%, respectively. Notably, there were no isolated *Staphylococci* strains that exhibited resistance to either vancomycin or linezolid, a finding that is presented in [Table 3](#). This dataset represents a valuable resource for future investigations into antibacterial treatment modalities.

Enterococci spp. were isolated from blood culture-positive specimens during the period spanning 2018 to 2021. A total of 195 *Enterococcus* spp. were identified, with 79 (40.5%) and 93 (47.7%) being *E. faecalis* and *E. faecium*, respectively. *E. faecalis* exhibited higher rates of resistance to antibiotics, with the exception of tetracycline, compared to other *Enterococcus* spp. Notably, vancomycin-resistant *E. faecium* strains were identified (all confirmed by E-test strips), while no enterococci resistant to linezolid were detected in the isolates. Antibiotic sensitivity data is presented in [Table 4](#).

Table 1 Baseline Data of Patients

Items	n	Ratio (%)
Gender		
Male	1721	47.0
Female	1939	53.0
Age		
0–17year	125	3.4
18–59year	1312	35.8
≥60 year	2223	60.7

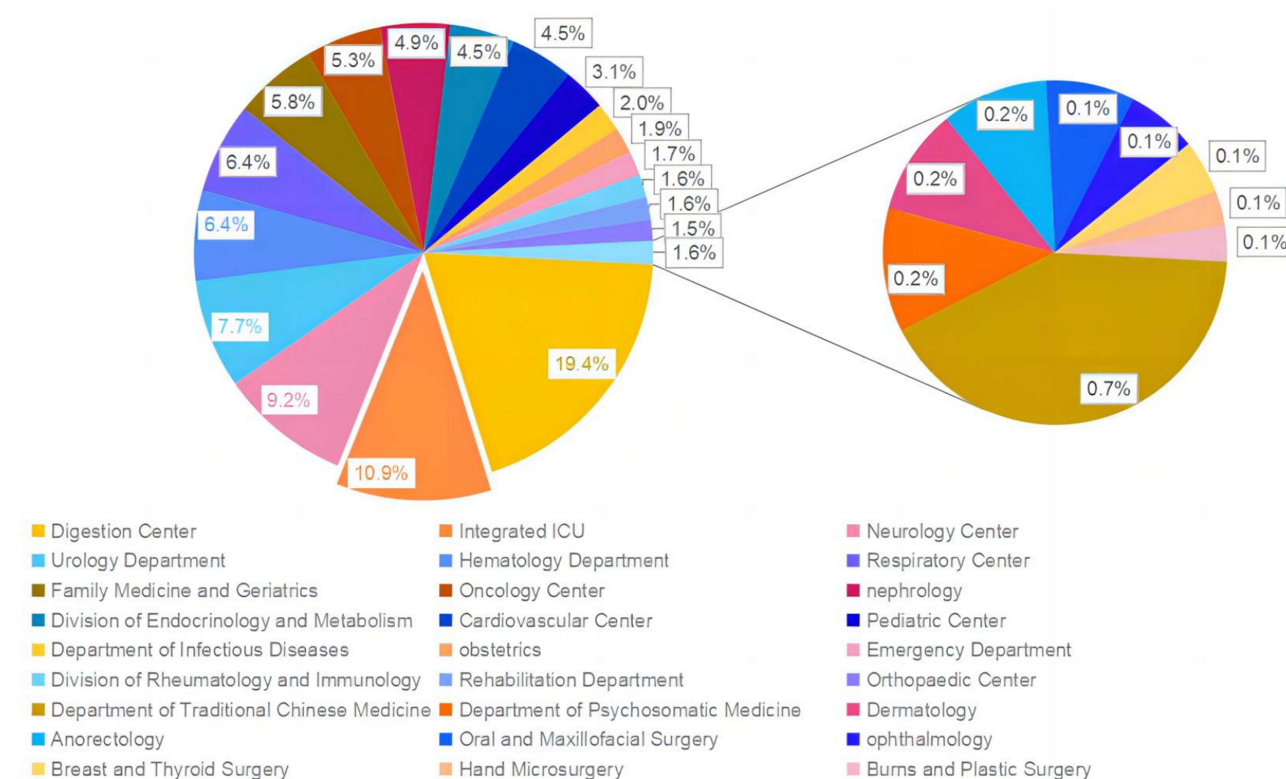


Figure 1 Distribution of clinical departments with positive blood culture bacteria, 2018–2021.

Antibiotic Resistance Characteristics of Gram-Negative Bacteria

In common gram-negative bacilli, high detection rates of extended-spectrum β -lactamase (ESBL) were observed for *E. coli* (47.5%, 779/1641) and *Klebsiella pneumoniae* (14.8%, 104/703). Notably, ESBL-producing strains exhibited

Table 2 Distribution of Clinically Isolated Bacteria, 2018–2021

Organisms	Number of Isolates	Proportion (%)
<i>Escherichia coli</i>	1641	44.8%
<i>Klebsiella spp.</i>	703	19.2%
<i>Staphylococcus aureus</i>	336	9.2%
<i>Enterococcus spp.</i>	195	5.3%
<i>Enterobacter spp.</i>	124	3.4%
<i>Coagulase-negative Staphylococcus</i>	117	3.2%
<i>S. viridans</i>	95	2.6%
<i>Pseudomonas aeruginosa</i>	91	2.5%
<i>Acinetobacter spp.</i>	73	2.0%
<i>Streptococcus pneumoniae</i>	49	1.3%
<i>Serratia spp.</i>	36	1.0%
β -hemolytic <i>Streptococcus</i>	33	0.9%
<i>Proteus spp.</i>	23	0.6%
<i>Citrobacter spp.</i>	20	0.5%
<i>Burkholderia spp.</i>	8	0.2%
<i>Stenotrophomonas maltophilia</i>	7	0.2%
<i>Morganella spp.</i>	6	0.2%
<i>Haemophilus influenzae</i>	4	0.1%
Other	99	2.7%
Total	3660	100%

Table 3 Rates (%) of *Staphylococcus* spp Resistance to Antimicrobial Agents from 2018 to 2021

Organisms Antibiotics	MRSA	MSSA	MRCNS	MSCNS
	(N=132) R	(N=204) R	(N=84) R	(N=33) R
Penicillin G	100	89.2	100	77.8
Oxacillin	100	0	100	0
Gentamicin	9.1	8.8	14.3	0
Levofloxacin	6.1	8.3	53.6	16.7
Clindamycin	43.9	13.7	33.3	23.3
Erythromycin	66.7	45.6	79.8	70
Linezolid	0	0	0	0
Vancomycin	0	0	0	0
Tigecycline	0	0	0	0
Trimethoprim-sulfamethoxazole	6.8	11.8	57.8	28.6
Rifampin	6.1	1	7.2	0
Tetracycline	31.8	21.1	21.4	16.7

Abbreviations: MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRCNS, Methicillin-resistant coagulase-negative *Staphylococcus*; MSCNS, Methicillin-sensitive coagulase-negative *Staphylococcus*; N, number; R, drug resistance rate (%).

Table 4 Rates (%) of *Enterococcus* spp. Resistance to Antimicrobial Agents from 2018 to 2021

Organisms Antibiotics	<i>E. faecalis</i> (n=79)	<i>E. faecium</i> (n=93)
	R	R
Penicillin G	0	96.8
Ampicillin	0	94.6
Gentamicin-high	0	0
Streptomycin-high	0	0
Levofloxacin	15.6	86
Erythromycin	55.8	89.2
Linezolid	0	0
Vancomycin	0	5.4
Tetracycline	74.7	59.8
Tigecycline	0	0

higher resistance rates to most antimicrobial treatments compared to non-ESBL producing strains. However, it is noteworthy that *E. coli* demonstrated low resistance rates to meropenem (0.2%) and imipenem (0.4%), respectively. Similar trends were observed for *Klebsiella* spp., with resistance rates to meropenem and imipenem at 2.4% and 3.0%, respectively. These specific antibiotic sensitivity findings are presented in Table 5.

Discussion

Bloodstream infection (BSI) is a grave systemic infectious malady typified by the infiltration of deleterious microorganisms, including bacteria and fungi, into the bloodstream.¹⁴ Annually, a staggering 31 million cases of sepsis are reported globally.¹⁵ During the designated study period, a noteworthy 3660 cases (equivalent to 12.5%) of blood cultures exhibited positive results. A considerable 60.7% of these blood stream infections (BSIs) were observed in patients aged ≥ 60 years, demonstrating a notably higher culture positivity rate within this age bracket compared to other groups. These findings substantiate prior study outcomes and lend further credence to the observations made.^{16–18} Gram-negative bacteria (76.7%) were the dominant isolated pathogen group compared to gram-positive bacteria (23.3%). This result is consistent with those reported by reputable organizations in China such as the China Antimicrobial Drug Surveillance Network (CHINET),¹⁹

Table 5 Rates (%) of Common Gram-Negative Bacilli. Resistance to Antimicrobial Agents from 2018 to 2021

Antibiotics	Organisms	<i>E. coli</i>	<i>Klebsiella spp</i>	<i>Enterobacter spp</i>	<i>Acinetobacter spp</i>	<i>P. aeruginosa</i>
		(n=1641) R	(n=703) R	(n=124) R	(n=73) R	(n=91) R
Ampicillin		86.7	100	100	NA	NA
Ampicillin-sulbactam		56.5	28.4	100	61.8	NA
Amoxicillin-clavulanate		10.5	19.5	100	NA	NA
Cefoperazone-sulbactam		1.2	5.6	6	7.7	0
Piperacillin-tazobactam		1.2	4.7	5.6	43.1	6.6
Cefazolin		55	26.8	100	NA	NA
Cefuroxime		52.2	24.6	100	NA	NA
Ceftazidime		19.1	12.1	35.5	58.9	6.6
Ceftriaxone		48.3	18.9	37.1	NA	NA
Cefepime		11.3	6.3	4.8	57.5	6.6
Cefotetan		1	2.8	100	NA	NA
Aztreonam		28.5	15.9	33.1	NA	16.7
Meropenem		0.2	2.4	6.7	56.2	5.5
Imipenem		0.4	3	4.8	57.5	4.4
Amikacin		0.9	3.1	0.2	36.8	0
Gentamicin		33.7	11.5	9.7	54.2	2.2
Ciprofloxacin		37.9	10.1	6.5	58.3	8.8
Levofloxacin		36.9	7.9	6.7	56.3	7.8
Trimethoprim-sulfamethoxazole		50.2	21	12.1	34.3	NA

Abbreviation: NA, not available.

Vietnam Antimicrobial Resistance Network (VINARES),²⁰ and Korea Global AMR Surveillance System (Kor-GLASS)^{21,22} However, this study diverges from the findings of numerous studies conducted in various regions, including Europe and Africa, as well as within our own country. These studies consistently identified Gram-positive bacteria as the prevailing culprits responsible for BSI.^{5,23,24} According to the findings of this investigation, *E. coli* (44.8%) emerged as the predominant causative agent, followed closely by *K. pneumoniae* (17.5%, 639/3660) and *S. aureus* (9.2%). This discovery aligns with previous reports from diverse countries and regions.^{20,22} However, this stands in stark contrast to investigations conducted in Italy and certain hospitals in Africa, where Coagulase-Negative *Staphylococci* (CoNS) and *Salmonella* have been consistently identified as the prevailing culprits responsible for bloodstream infections (BSIs).^{24,25} The reasons for these differing results may be multifaceted and could arise from dissimilar amounts of specimen collections, disparities in geographical locations, and distinctive community lifestyles. Among all the Gram-negative organisms identified, *E. coli* ranked foremost with a notable detection rate of broad-spectrum-lactamase ESBLs at an impressive 47.5%, surpassing the rate reported in Vietnam, which stood at 45%.²⁶ Relevant studies show that patients who were infected with ESBL-producing Enterobacteriaceae should be firstly treated with carbapenems.²⁷ The preponderance of *E. coli* as the primary causative agent for bloodstream infections (BSIs) is a worldwide phenomenon.²⁸ The incidence of carbapenem resistance in this study was found to be less than 1%, which is notably lower than the 3.5% reported in Vietnam. Furthermore, the VINARES report from 2016–2017 revealed that *E. coli* strains isolated from blood and cerebrospinal fluid samples exhibited a carbapenem resistance rate of 8%, surpassing the resistance rate observed in this study.^{16,20} In addition, a comprehensive analysis (focusing on bloodstream infections (BSIs)) conducted from 2017 to 2019 showed that *E. coli* resistance to carbapenems ranged from 0.1% to 0.2%, which is consistent with the results of the present study, consistently low rates of *E. coli* resistance to carbapenems.²² Meanwhile, the resistance rates for piperacillin/tazobactam and cefoperazone/sulbactam remain at a low level, which indicates that these antibacterial medications containing enzyme inhibitors could still be viable treatment options for *E. coli*-caused bloodstream infections. *K. pneumoniae*, a member of the Enterobacteriaceae family, is another common causative agent for bloodstream infections, following only *E. coli* in

terms of its frequency. However, the detection rate of broad-spectrum extended-spectrum beta-lactamases (ESBLs) was found to be relatively low at 14.8%, which stands in stark contrast to the higher percentage of 72% documented in India.²⁹ Within the scope of our investigation, it was determined that the resistance rate of *K. pneumoniae* to carbapenem antibiotics persisted at approximately 3%. In contrast, several studies conducted in China have reported a considerably higher resistance rate of 26.5% for *K. pneumoniae* towards carbapenem antibiotics, thus highlighting a notable discrepancy when compared to our study findings.³⁰ However, it should be noted that while the resistance rate of *K. pneumoniae* towards carbapenems remains low, there has been a gradual increase in the detection rate of Carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) over the years. The key mechanisms underlying carbapenem resistance in enterobacteria include the production of carbapenemases, deficits in outer membrane protein expression, elevated expression levels of efflux pumps, and altered target locations of antimicrobial antibiotic action. Antimicrobial resistance in non-fermentable, Gram-negative bacilli (such as *Acinetobacter baumannii*) presents a serious challenge. Bacteremia caused by *A. baumannii* is a prevailing cause of mortality amongst patients, with the associated mortality rate ranging from 32.5% to 63.5%.^{31,32} Research highlights that *A. baumannii* is predominantly multidrug-resistant, challenging to manage and spreads rapidly - causing bloodstream infections in critically unwell patients with potentially grave consequences. Alarming findings emerged from our investigation of *A. baumannii*, indicating that over 55% of the isolates exhibited resistance to carbapenem antimicrobials. This resistance rate closely aligns with the 56.5% reported by Wang et al,³² underscoring the consistent and concerning trend of carbapenem resistance in *Acinetobacter baumannii* strains,³² furthermore, it is noteworthy that the rate of carbapenem resistance observed in our investigation of *A. baumannii* bloodstream infections (BSIs) was comparatively lower than that reported in BSI studies conducted in other geographical regions.^{16,20,22} In contrast, *P. aeruginosa* exhibits a lower resistance rate than *A. baumannii*, with carbapenem resistance at only approximately 5%. Data obtained from a comprehensive study conducted at a tertiary care hospital in Beijing unveiled a concerning resistance rate of 27.8% among *P. aeruginosa* strains towards carbapenem antibiotics. This rate starkly contrasts with our study data, which demonstrates a significantly lower resistance rate.³⁰ Apart from carbapenemase synthesis, *P. aeruginosa* strategy of resistance includes high bacterial antibiotic efflux pump expression, bacteriophage biofilm formation, and alterations to extracellular membrane permeability. The antibiotic resistance rates of common Gram-positive bacteria were investigated, indicating a MRSA detection rate of 39.3% - higher than the 19% rate reported by de Kraker ME²⁸ Intriguingly, our results indicate a higher rate of resistance than that reported in an Italian study (28.1%).²⁴ In cases where *staphylococci* induce bloodstream infections, vancomycin or linezolid may be used. Vancomycin and linezolid are preferred options for treating patients with some antimicrobial gram-positive bacteria, such as MRSA, because of their effectiveness against these bacteria.³³

In this investigation, *E. faecium* was found to exhibit greater resistance to most antimicrobial antibiotic than *E. faecalis* - although tetracycline proved less resistant for the former. The rate of antibiotic resistance is high, except for vancomycin, which maintains a resistance rate to *Enterococcus faecium* of about 5%. Of note, our study found a higher prevalence of vancomycin resistance in enterococci compared to data from a study in Africa.²³ When treating with vancomycin, it is recommended that vancomycin trough concentrations be ≥ 15 mg/L while trying not to exceed 20 mg/L to avoid excessive nephrotoxicity.³⁴ Underscoring the importance of promptly sending microbiological specimens for early clarification of pathogenesis and antibiotic resistance when treating suspected bloodstream infections caused by *E. faecium* in order to avoid the use of ineffective antimicrobials.

Limitations of This Study

It should be noted that our evaluation and discussion was limited to instances from within our hospital, which may not fully represent broader patterns. Going forward, we aspire to conduct a multi-center study in order to obtain more comprehensive results.

Conclusions

To sum up, the prevalence of *Enterobacteriaceae* bacteria in bloodstream infections was found to be high in our hospital, especially among patients with liver disease, severe illness, urinary and hematologic disorders, as well as major medication resistance of *A. baumannii*. Bloodstream infection is a serious infectious condition that constitutes a risk

factor for patient mortality. These findings might help the healthcare professionals to make informed decisions and provide better care for the patients.³⁰

Data Sharing Statement

All data used for analyzing and generating the results of this study are included in this article.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Suining Central Hospital (approval number: KYLLKS20230102), which waived the requirement of written informed consent from patients. All strains are part of the routine laboratory procedures of the hospital and do not involve any human genetic resources. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Consent for Publication

All authors have read the manuscript and consent to publish.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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