

# Temporal Shifts in Etiological Agents and Trends in Antimicrobial Resistance of Bloodstream Infection in Southwest China from 2016 to 2023

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**Objective:** The purpose of this study was to assess the frequency distribution of bacterial pathogens causing bloodstream infections (BSIs) as well as the characteristics of antibiotic susceptibility and resistance to gain a deeper understanding of the drug resistance situation in the southwest China.

**Methods:** Non-duplicate pathogenic bacteria according to the American Clinical and Laboratory Standards Institute (CLSI) M100 and analyzed using WHONET 5.6 software.

**Results:** A total of 170,246 non-duplicated pathogenic bacteria were isolated from blood from 2016 to 2023. Gram-negative bacteria accounted for 59.5% and Gram-positive bacteria accounted for 40.5%. The top five detection rates were *Escherichia coli* (33.9%), coagulase-negative *staphylococci* (21.7%), *Klebsiella pneumoniae* (11.5%), *Staphylococcus aureus* (7.0%), and *Enterococcus* spp (5.4%). *Streptococcus pneumoniae*, *Salmonella* spp and  $\beta$ -Hemolytic *Streptococcus* were significantly more frequently isolated in pediatric patients than in adult patients. The rate of resistance to carbapenems was less than 1.2% in the *Escherichia coli* over the 8-year period, with a significant upward trend in the *Klebsiella pneumoniae*. The overall resistance rate of *Pseudomonas aeruginosa* to imipenem and meropenem had a slow decreasing trend. The resistance rate of *Acinetobacter baumannii* to imipenem and meropenem has been maintained at a high level, which is greater than 50%. The detection rate of MRSA was 27.70% and vancomycin- and linezolid-resistant strains were not found. The resistance rates of *Enterococcus faecium* and *Enterococcus faecalis* to vancomycin, linezolid and teicoplanin were less than 2.1%.

**Conclusion:** The pathogenic bacteria of bloodstream infection in southwest China were diversified, and the multi-drug resistant bacteria, especially Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), had increased significantly, posing a serious challenge to clinical treatment. Additionally, the situation of Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus* (VRE) also required close attention.

**Keywords:** bloodstream infections, bacterial resistance surveillance, multidrug-resistant bacteria, change of drug-resistant rate

## Introduction

Bloodstream infections (BSIs) are associated with high morbidity and mortality.<sup>1</sup> Globally, approximately 30 million people are infected each year.<sup>2</sup> In the UK, approximately 100,000 people are hospitalized with sepsis and 37,000 die each year.<sup>3</sup> Studies in the United States had shown that the incidence of bacteremia in hospitalized patients was 5.9% and the mortality rate was 15.6%.<sup>4</sup> In childhood infections in Spain, the directly related 30-day mortality rate of BSIs was 10.5%.<sup>5</sup> As the rate of resistance to bloodstream infections continues to rise, so do infection-related morbidity, mortality, and treatment costs, especially in the ICU setting.<sup>6</sup> Another meta-analysis of 72 papers showed that the weighted combined all-cause mortality rate of BSI in China was 28.7%, and the mortality rate of hospital-acquired BSI was 26.8%,

which was significantly higher than that of community-acquired BSI, which was 6.9%.<sup>7</sup> Differences in the spectrum of pathogens and patterns of bacterial resistance causing healthcare-associated infections have been reported in different regions of the world. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) to be published in 2023<sup>8</sup> and the Korean Surveillance Network (KorGLASS) from 2016 to 2017<sup>9</sup> both showed that *E. coli* and *S. aureus* were the most common pathogens causing BSI. However, the most common pathogens in Malawi and Africa causing BSI were non-typhoid *Salmonella*, *Salmonella typhi*, and *Streptococcus pneumoniae*.<sup>10</sup> However, *E. coli*, *S. aureus*, *Streptococcus spp* and *Klebsiella spp* were the most common pathogens according to Japanese data.<sup>11</sup>

Therefore, continuous and regional monitoring of the pathogenic spectrum of BSI and the trend of pathogenic bacterial drug resistance is of great significance for the effective control of the prevalence of multidrug-resistant bacteria, the development of new preventive methods, and optimizing treatment strategies. In our country, China Antimicrobial Surveillance Network (CHINET) and China Antimicrobial Resistance Surveillance System (CARSS) are responsible for the dynamic monitoring of pathogenic bacteria. CHINET focuses on the distribution of bacteria and drug resistance trends in major referral hospitals, whereas CARSS monitors bacterial drug resistance in different provinces and autonomous regions. The Antimicrobial Resistant Investigation Network of Sichuan Province (ARINSP) is a subordinate network unit of CARSS, including 109 healthcare institutions, and is responsible for monitoring the antibiotic resistance situation in the province, and the data of ARINSP represent the pattern of bacterial drug resistance in Southwest China. CARSS has reported the distribution of pathogenic bacteria and drug resistance rate of BSI in the whole country from 2014 to 2019,<sup>12</sup> and some researchers had also analyzed the BSI in central China between 1998 and 2017,<sup>13</sup> but currently the drug resistance of BSI in Southwest China has been rarely, except for Jie Zhang<sup>14</sup> and Shanshan Long,<sup>15</sup> who have reported. Therefore, we systematically analyzed the distribution of bacterial species and drug resistance in BSIs in Sichuan Province from 2016 to 2023 to further understand the situation in Southwest China.

## Materials and Methods

### Bacterial Isolates

Since isolates were collected from blood samples of outpatients and inpatients from 109 medical institutions in the Sichuan Provincial Antimicrobial Resistance Monitoring Network from 2016 to 2023. The blood culture systems used included Mérieux's BacT/ALERT VIRTUO and BacT/ALERT 3D, BD's BACTECTM 9000, Autobio's BC60 and DL-Bt system. The range of blood culture bottles used included standard aerobic bottles, resinous aerobic bottles, standard anaerobic bottles and anaerobic bottles with special components.

The main reference for the diagnosis of bloodstream infections is the Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases (2024 edition), Inclusion criteria: 1) Clinical symptoms and signs: patients presenting with fever (body temperature  $>38^{\circ}\text{C}$ ) or hypothermia (body temperature  $<36^{\circ}\text{C}$ ) with chills, shock, organ dysfunction. 2) Blood culture: positive for pathogenic bacteria. 3) Other indicators: CRP  $>10\text{mg/L}$ , PCT  $>0.5\text{ng/mL}$  and other abnormal inflammatory indicators, imaging studies. Exclusion criteria: 1) Blood culture contamination: common skin colonising bacteria are cultured, only once in multiple blood cultures and the patient has no obvious signs and symptoms of infection. 2) Clear local foci of infection: there are clear local foci of infection and the symptoms and signs of infection can be fully explained by local infection. In order to exclude duplicate strains from the selected strains, only the first strain of the same pathogen is kept in the same patient, thus ensuring the validity and accuracy of the strain data.

### Bacterial Identification and Susceptibility Testing

Bacterial identification was performed using VITEK2 automated system, BD Phoenix 100 system, or MALDI mass spectrometry system. Drug susceptibility testing was performed using the minimum inhibitory concentration (MIC) test, the Kirby-Bauer (K-B) method, and the E-test method according to Clinical Laboratory Standards Institute (CLSI) guidelines. All results were interpreted according to CLSI M100 guideline standards, except for tigecycline, which was interpreted according to FDA standards.

## Interpretation of Results and Quality Control

QC testing was performed weekly according to CLSI. Quality control strains included but were not limited to *Escherichia coli* (ATCC25922), *Klebsiella pneumoniae* (ATCC700603), *Staphylococcus aureus* (ATCC25923), *Pseudomonas aeruginosa* (ATCC27853), *Enterobacter cloacae* (ATCC700323), *Streptococcus pneumoniae* (ATCC49619) and *Haemophilus influenzae* (ATCC49247).

## Statistical Analysis

All results were analyzed using WHONET5.6 data analysis software. The general steps of WHONET5.6 for statistical analysis of drug susceptibility result data are as follows: 1) data entry: enter the strain information, antimicrobial drug name and corresponding drug susceptibility test results into the software; 2) analysis type selection: according to the statistical needs, select various types of analysis modes in the system, such as resistance analysis, sensitivity analysis, resistance spectrum analysis, etc. 3) Set analysis options: according to the data to be analysed, set the corresponding options, such as selecting the source of strains, types of strains, antimicrobial drugs of concern, etc.; 4) Generate reports; 5) Interpret the results; 6) Export the data.

## Results

### Bacterial Origin and Distribution

During 2016–2023, a total of 170,246 non-duplicated pathogenic bacteria were isolated from blood, of which 25,743 (15.1%) were from ICU sources and 11,445,503 (84.9%) were from non-ICU sources. Gram-negative bacteria detected were dominated by *E. coli* (33.9%), *K. pneumoniae* (11.5%), and *P. aeruginosa* (2.3%), while Gram-positive bacteria were mainly coagulase-negative staphylococci (CNS) predominantly (21.7%), followed by *S. aureus* (7.0%), and *Enterococci* spp (5.4%), and the variation of major clinical isolates is shown in Table 1. ICU isolates were dominated by CNS (32.4%) and non-ICU isolates were dominated by *E. coli* (36.8%), and the percentage of detected *Enterococci* spp was significantly higher in ICU (9.9%) than in non-ICU (4.6%), as shown in Table 2.

Among the 170,246 pathogenic bacteria isolated from blood, 17,038 strains were recorded with age. Of these, 11.3% (19,287 strains) were from pediatric patients <18 years of age; 11.1% (18,896 strains) were from patients ≥18 to <45 years of age; 22.4% (38,040 strains) were from patients ≥45 to <60 years of age; and 55.2% (93,815 strains) were from

**Table 1** Changes of Main Clinically Isolated Bacteria in Blood Samples from 2016 to 2023 (%)

Rank	Organism	2016–2017 (n=33629)		2018–2019 (n=42790)		2020–2021 (n=41221)		2022–2023 (n=52606)		2016–2023 (n=170246)	
		n	%	n	%	n	%	n	%	n	%
1	<i>Escherichia coli</i>	11467	34.1	14375	33.6	14386	34.9	17457	33.2	57685	33.9
2	Coagulase-negative <i>Staphylococcus</i>	7710	22.9	9328	21.8	8279	20.1	11662	22.2	36979	21.7
3	<i>Klebsiella pneumoniae</i>	3649	10.9	4720	11.0	4993	12.1	6274	11.9	19636	11.5
4	<i>S. aureus</i>	2299	6.8	2965	6.9	2926	7.1	3776	7.2	11966	7.0
5	<i>Enterococcus</i> spp	1721	5.1	2274	5.3	2226	5.4	2909	5.5	9130	5.4
6	<i>S. viridans</i>	683	2.0	1054	2.5	1163	2.8	1740	3.3	4640	2.7
7	<i>P. aeruginosa</i>	874	2.6	1014	2.4	959	2.3	1067	2.0	3914	2.3
8	<i>Acinetobacter baumannii</i>	797	2.4	1017	2.4	516	1.3	788	1.5	3118	1.8
9	<i>Enterobacter</i> spp	690	2.1	881	2.1	878	2.1	1111	2.1	3560	2.1
10	<i>S. pneumoniae</i>	551	1.6	764	1.8	623	1.5	710	1.3	2648	1.6
11	<i>Salmonella</i> spp	281	0.8	389	0.9	496	1.2	565	1.1	1731	1.0
12	Beta-hemolytic <i>Streptococcus</i>	335	1.0	419	1.0	388	0.9	366	0.7	1508	0.9
13	Others*	2572	7.6	3590	8.4	3388	8.2	4181	7.9	13731	8.1
14	Total	33629	100.0	42790	100.0	41221	100.0	52606	100.0	170246	100.0

**Note:** \*Bacteria other than the list.

**Abbreviation:** n, the number of strains.

**Table 2** Distribution of Bloodstream Infection Strains in ICU and Non-ICU Units

Organism	n	ICU		Non-ICU	
		n	%	n	%
<i>Escherichia coli</i>	57685	4555	17.7	53130	36.8
Coagulase-negative <i>Staphylococcus</i>	36979	8351	32.4	28628	19.8
<i>Klebsiella pneumoniae</i>	19636	3060	11.9	16576	11.5
<i>S.aureus</i>	11966	1130	4.4	10836	7.5
<i>Enterococcus</i> spp	9130	2537	9.9	6593	4.6
<i>S. viridans</i>	4640	663	2.6	3977	2.8
<i>P. aeruginosa</i>	3914	647	2.5	3267	2.3
<i>Acinetobacter baumannii</i>	3118	1409	5.5	1709	1.2
<i>Enterobacter</i> spp	3560	461	1.8	3099	2.1
<i>S. pneumoniae</i>	2648	278	1.1	2370	1.6
<i>Salmonella</i> spp	1731	121	0.5	1610	1.1
Beta-hemolytic <i>Streptococcus</i>	1508	116	0.5	1392	1.0
Others*	13731	2415	9.4	11316	7.8
Total	170246	25743	100.0	144503	100.0

Note: \*Bacteria other than the list.

**Table 3** Distribution of Main Bacteria Isolated from Blood Samples in Different Age Groups from 2016 to 2023 (%)

Organism	n	0~<18 (n=19287)			≥18~<45 (n=18896)			≥45~<60 (n=38040)			≥60~ (n=93815)		
		n	% <sup>a</sup>	Rank	n	% <sup>a</sup>	Rank	n	% <sup>a</sup>	Rank	n	% <sup>a</sup>	Rank
<i>Escherichia coli</i>	57565	2287	11.9	2	6012	31.8	1	12904	33.9	1	36362	38.8	1
Coagulase-negative <i>Staphylococcus</i>	36959	9012	46.7	1	3904	20.7	2	6726	17.7	2	17317	18.5	2
<i>Klebsiella pneumoniae</i>	19613	789	4.1	6	1863	9.9	4	5240	13.8	3	11721	12.5	3
<i>S.aureus</i>	11956	1266	6.6	4	1927	10.2	3	3393	8.9	4	5370	5.7	5
<i>Enterococcus</i> spp	9123	884	4.6	5	957	5.1	5	1894	5.0	5	5388	5.7	4
<i>S. viridans</i>	4638	533	2.8	8	670	3.5	6	1296	3.4	6	2139	2.3	7
<i>P. aeruginosa</i>	3906	179	0.9	11	449	2.4	7	951	2.5	7	2327	2.5	6
<i>Acinetobacter baumannii</i>	3115	155	0.8	12	417	2.2	8	716	1.9	9	1827	1.9	9
<i>Enterobacter</i> spp	3556	229	1.2	10	397	2.1	9	922	2.4	8	2008	2.1	8
<i>S. pneumoniae</i>	2646	1357	7.0	3	207	1.1	12	298	0.8	11	784	0.8	10
<i>Salmonella</i> spp	1730	566	2.9	7	270	1.4	10	307	0.8	10	587	0.6	12
Beta-hemolytic <i>Streptococcus</i>	1506	383	2.0	9	229	1.2	11	271	0.7	12	623	0.7	11
Others*	13725	1647	8.5	NA	1594	8.4	NA	3122	8.2	NA	7362	7.8	NA
Total	170038	19287	100.0	-	18896	100.0	-	38040	100.0	-	93815	100.0	-

Notes: \*Bacteria other than the list; <sup>a</sup>The ranking among all bacterial strains in different age groups.

Abbreviations: NA, not available; n, the number of strains.

patients ≥60 years of age. Among the isolates from pediatric patients <18 years old, CNS predominated. The remaining age group isolates were dominated by *E. coli*. *S. pneumoniae*, *Salmonella* spp and β-hemolytic *streptococci* were isolated more frequently in children than in adult patients. The differences in the major isolates from blood samples of patients of different age groups were significant, as shown in Table 3.

## Sensitivity and Resistance Rates of Gram-Negative Bacteria to Antimicrobials

From 2016 to 2023, *Escherichia coli* had greater than 50.0% resistance to cefazolin, cefuroxime, ceftriaxone and trimethoprim-sulfamethoxazole and greater than 50.0% resistance to ertapenem, imipenem, meropenem, and amikacin was less than 1.8%, maintaining very high activity. The resistance rate to gentamicin had a decreasing trend year by year,

**Table 4** Changes of Resistance Rates of *E. coli* to Antimicrobial Agents in 2016–2023

Antimicrobial Agent	2016 (n=5359)	2017 (n= 6133)	2018 (n=6859)	2019 (n=7560)	2020 (n=8490)	2021 (n=7877)	2022 (n=8655)	2023 (n=8871)
	R	R	R	R	R	R	R	R
Amoxicillin/clavulanate	10.1	8.7	10.5	12.4	14.3	11.3	12.4	12.4
Ampicillin–sulbactam	45.1	46.4	44.9	45.2	46.6	45.0	40.7	38.0
Piperacillin–tazobactam	2.3	2.9	3.0	2.8	3.7	2.9	2.8	3.1
Cefazolin	56.8	53.6	50.2	50.2	52.2	52.1	52.3	55.6
Cefuroxime	49.9	51.0	49.9	52.3	52.8	50.5	51.4	51.3
Ceftazidime	21.9	21.2	20.8	22.6	21.9	20.0	20.0	20.0
Ceftriaxone	50.0	50.9	49.5	49.0	50.7	49.3	50.1	51.1
Cefotaxime	49.3	49.8	50.3	48.7	51.2	50.3	50.0	50.2
Cefepime	22.2	21.3	20.6	19.2	18.9	16.3	17.1	18.9
Aztreonam	30.4	31.4	31.2	31.8	32.5	30.2	29.4	29.7
Ertapenem	1.2	0.7	1.3	1.2	1.2	0.8	0.7	1.1
Imipenem	0.7	0.7	1.1	1.1	1.3	0.9	0.9	1.2
Meropenem	1.8	1.1	1.2	1.2	1.4	1.0	1.1	1.3
Amikacin	1.4	1.4	1.2	1.4	1.6	1.2	1.2	1.0
Gentamicin	37.9	37.7	36.0	34.8	33.9	32.5	31.7	30.1
Ciprofloxacin	47.0	48.8	47.8	47.7	48.3	48.3	48.3	48.4
Levofloxacin	42.0	42.8	42.6	41.6	42.4	42.4	43.3	43.4
Trimethoprim– sulfamethoxazole	53.5	51.1	51.0	51.4	52.5	51.6	51.1	48.6
Tigecycline	0.0	0.0	0.0	0.0	0.0	0.7	0.0	0.7
Polymyxin B	0.2	0.0	0.0	0.0	0.0	0.1	0.1	0.1

**Abbreviations:** R, resistance rate; n, the number of strains.

while the resistance rate to quinolones fluctuated, with ciprofloxacin and levofloxacin resistance rates ranging from 42.0% to 48.8%, as detailed in Table 4. The resistance rates of *K. pneumoniae* to ertapenem, imipenem, and meropenem increased from 2.4%, 2.7%, and 4.1% to 9.8%, 10.0%, and 11.1%, showing a significant upward trend, and the resistance rate to amikacin, piperacillin and tazobactam maintained high sensitivity, as shown in Table 5. *E. coli* and *K. pneumoniae* showed low resistance to tigecycline ( $\leq 6.9\%$ ) and polymyxin B ( $\leq 4.2\%$ ) and were highly sensitive.

**Table 5** Changes of Resistance Rates of *K. pneumoniae* to Antimicrobial Agents in 2016–2023

Antimicrobial Agent	2016 (n=1680)	2017 (n= 1974)	2018 (n=2289)	2019 (n=2442)	2020 (n=2974)	2021 (n=2666)	2022 (n=2978)	2023 (n=3323)
	R	R	R	R	R	R	R	R
Amoxicillin/clavulanate	14.7	19.9	23.5	23.6	23.9	21.7	21.5	21.5
Ampicillin–sulbactam	24.1	30.8	30.0	32.3	32.2	29.3	28.5	28.8
Piperacillin–tazobactam	6.5	10.5	12.8	12.0	12.8	12.2	11.7	13.8
Cefazolin	32.6	35.7	33.2	18.4	33.1	24.8	15.2	26.2
Cefuroxime	29.8	35.3	33.1	35.6	32.0	29.1	28.5	29.9
Ceftazidime	13.1	18.0	18.9	18.6	19.5	17.2	17.8	18.2
Ceftriaxone	24.8	28.4	29.3	27.9	29.1	26.0	25.6	26.4
Cefotaxime	26.7	32.3	33.0	31.7	32.2	28.8	28.0	28.8
Cefepime	12.9	16.1	17.9	16.1	17.6	14.8	14.9	16.6
Aztreonam	17.2	21.2	22.7	21.3	23.2	21.2	19.8	21.5
Ertapenem	2.4	6.5	8.9	7.8	7.0	7.6	8.2	9.8
Imipenem	2.7	7.2	11.0	8.8	9.7	8.4	8.2	10.0

(Continued)

**Table 5** (Continued).

Antimicrobial Agent	2016 (n=1680)	2017 (n= 1974)	2018 (n=2289)	2019 (n=2442)	2020 (n=2974)	2021 (n=2666)	2022 (n=2978)	2023 (n=3323)
	R	R	R	R	R	R	R	R
Meropenem	4.1	9.4	12.8	11.4	11.2	9.7	9.3	11.1
Amikacin	1.2	4.1	8.2	5.7	7.7	6.3	6.3	8.0
Gentamicin	11.5	15.0	18.4	17.6	17.1	14.8	13.7	14.5
Ciprofloxacin	20.0	26.3	29.5	29.1	29.6	26.7	25.5	27.3
Levofloxacin	14.8	19.1	22.2	19.8	20.9	19.3	18.1	19.4
Trimethoprim– sulfamethoxazole	23.2	26.4	26.7	26.9	24.2	22.4	23.6	24.5
Tigecycline	0.0	0.0	0.0	0.0	1.9	6.9	4.7	1.7
Polymyxin B	4.2	1.9	1.3	0.5	1.2	1.8	1.1	1.7

**Abbreviations:** R, resistance rate; n: the number of strains.

The resistance rate of *P. aeruginosa* to commonly used antimicrobial drugs showed an overall decreasing trend, in which the resistance rate to imipenem and meropenem decreased from 13.2% and 11.6% in 2016 to 9.1% and 8.1% in 2023, respectively, and the resistance rate to aztreonam decreased from 19.7% to 13.0%; the resistance rate to ceftazidime, cefepime around 10.0%; and remained highly sensitive to polymyxin B, with no resistant strains detected, as shown in Table 6. *A. baumannii* had resistance rates higher than 50.0% to most of the tested drugs, with resistance rates of  $\geq 51.2\%$  and 53.6% to imipenem and meropenem, respectively, and remained highly susceptible to tigecycline and polymyxin B only (resistance rates of 3.1% and 8.6%) as shown in Table 7.

## Sensitivity and Resistance Rates of Gram-Positive Bacteria to Antimicrobials

There were 11966 strains of *S. aureus* isolated from the blood, and the detection rate of MRSA was 27.7%. The rates of resistance to penicillins, quinolones and aminoglycosides were higher in MRSA than in MSSA, and the rate of resistance to macrolides was the most significant; however, the rate of resistance to trimethoprim-sulfamethoxazole was slightly

**Table 6** Changes of Resistance Rates of *P. aeruginosa* to Antimicrobial Agents in 2016–2023

Antimicrobial Agent	2016 (n=400)	2017 (n=477)	2018 (n=510)	2019 (n=504)	2020 (n=590)	2021 (n=507)	2022 (n=545)	2023 (n=530)
	R	R	R	R	R	R	R	R
Piperacillin-tazobactam	8.8	6.3	9.8	9.0	8.9	7.7	6.1	9.4
Ceftazidime	10.9	10.8	12.1	11.2	11.0	10.2	9.5	10.4
Cefepime	10.6	8.7	7.6	8.2	8.0	6.6	6.9	7.2
Aztreonam	19.7	16.6	16.8	20.8	18.1	12.5	13.1	13.0
Imipenem	13.2	15.1	12.0	11.8	10.2	10.1	10.0	9.1
Meropenem	11.6	12.6	9.8	10.3	8.7	8.1	7.1	8.1
Amikacin	2.7	1.7	2.4	1.8	1.7	1.6	1.3	0.8
Gentamicin	8.5	7.9	3.8	6.4	5.6	4.4	2.7	2.2
Ciprofloxacin	13.8	12.3	10.4	10.9	9.8	9.4	7.3	7.4
Levofloxacin	14.9	11.9	11.9	11.6	11.6	9.9	10.9	12.2
Polymyxin B	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

**Abbreviations:** R, resistance rate; n, the number of strains.

**Table 7** Changes of Resistance Rates of *A. baumannii* to Antimicrobial Agents in 2016–2023

Antimicrobial Agent	2016 (n=407)	2017 (n=390)	2018 (n=439)	2019 (n=570)	2020 (n=313)	2021 (n=264)	2022 (n=374)	2023 (n=417)
	R	R	R	R	R	R	R	R
Ampicillin-sulbactam	63.5	62.7	60.6	60.0	57.6	50.9	54.4	54.5
Piperacillin-tazobactam	74.3	66.3	68.7	43.8	53.9	54.7	54.2	66.7
Ceftazidime	71.2	68.3	70.9	50.6	58.3	52.4	54.8	63.0
Cefepime	75.1	68.7	70.4	51.5	57.1	52.3	55.4	63.5
Imipenem	74.5	66.4	69.1	58.8	57.4	51.2	54.8	64.0
Meropenem	76.5	68.8	71.8	70.3	58.4	53.6	57.6	67.0
Amikacin	53.6	55.9	60.1	34.7	40.8	40.1	42.2	46.0
Gentamicin	69.1	64.4	64.2	49.8	52.1	46.6	49.2	51.1
Ciprofloxacin	74.8	67.2	69.0	53.7	58.0	51.5	52.5	62.9
Levofloxacin	53.2	55.7	59.4	45.4	47.5	43.4	48.0	58.4
Polymyxin B	0.0	0.0	3.9	0.0	8.6	0.0	0.0	0.0
Tigecycline	1.7	1.6	3.1	0.9	0.6	0.0	3.0	3.0

**Abbreviations:** R, resistance rate; n, the number of strains.

lower than that in MSSA. A small number of linezolid-resistant strains (0.4%) was isolated from MRSA, and a small number of teicoplanin-resistant strains (0.3%), in addition to a very small number of linezolid-resistant strains (0.1%), were also isolated from MSSA. No vancomycin-resistant *Staphylococcus* species were detected, as shown in Table 8.

The 9130 strains of *Enterococcus* were mainly *Enterococcus faecium* (5141 strains, 56.3%) and *Enterococcus faecalis* (2888 strains, 31.6%). The resistance rate of *E. faecium* to most of the tested drugs was significantly higher than that of *E. faecalis*, especially ampicillin (87.9% vs 4.1%), and also maintained a high level of resistance to quinolones. *E. faecalis* had high drug resistance rate against rifampin (47.7%) but maintained high activity against vancomycin, linezolid and teicoplanin. Among the drug-resistant strains of vancomycin detected, *E. faecium* (1.5%) was more than *E. faecalis* (0.2%). For Linezolid, the drug resistance rate of *E. faecium* (0.5%) was lower than *E. faecalis* (2.1%), as shown in Table 9.

**Table 8** Changes of Resistance Rate of *Staphylococcus* to Antibiotics in Blood Samples from 2016 to 2023

Antimicrobial Agent	2016–2017		2018–2019		2020–2021		2020–2023	
	MRSA (n=576)	MSSA (n=1666)	MRSA (n=738)	MSSA (n=2191)	MRSA (n=922)	MSSA (n=2353)	MRSA (n=1079)	MSSA (n=2676)
	R	R	R	R	R	R	R	R
Penicillin G	99.2	91.0	99.9	90.0	99.6	90.5	99.2	90.2
Gentamicin	30.1	16.8	18.7	0.0	11.7	11.5	11.1	9.7
Rifampin	22.0	0.9	13.5	14.3	6.2	1.0	3.0	0.6
Levofloxacin	33.5	10.0	26.0	0.7	19.4	11.2	22.7	13.8
Trimethoprim–sulfamethoxazole	13.4	17.8	9.2	11.9	10.8	15.3	13.2	13.3
Clindamycin	64.0	29.2	67.1	16.2	65.1	21.9	61.1	18.7
Erythromycin	80.2	50.0	81.7	28.5	77.1	45.1	77.4	44.2
Linezolid	0.4	0.1	0.0	0.1	0.0	0.0	0.0	0.0
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Teicoplanin	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0

**Abbreviations:** MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; R, resistance rate; n, the number of strains.



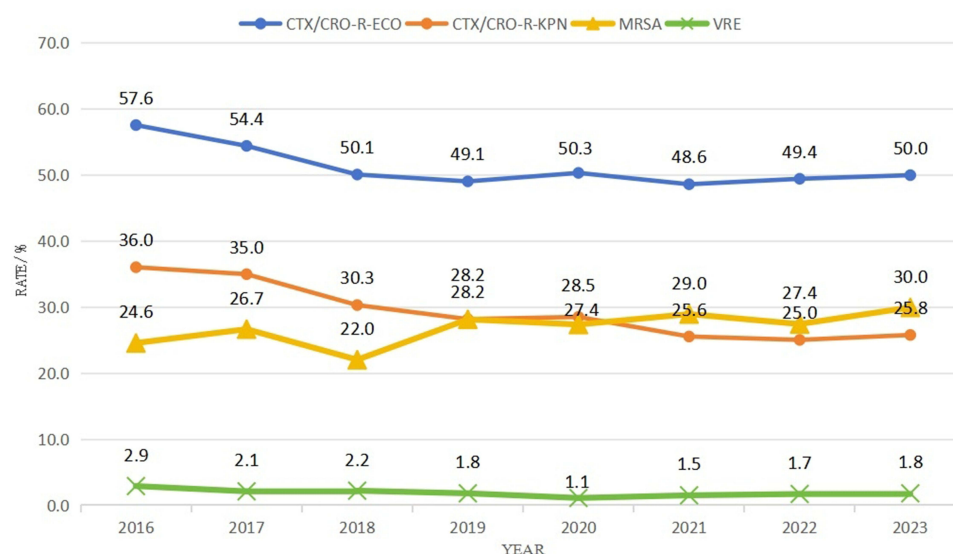
**Table 9** Resistance Rates of *Enterococcus* to Antibiotics in Blood Samples from 2016 to 2023

Antimicrobial Agent	<i>E.faecalis</i> (n=2888)	<i>E.faecium</i> (n=5141)
	R	R
Ampicillin	4.1	87.9
Gentamicin-high (120µg)	30.8	41.1
Streptomycin-high (300µg)	20.1	26.6
Rifampin	47.7	74.3
Levofloxacin	21.5	83.9
Moxifloxacin	21.2	90.3
Linezolid	2.1	0.5
Vancomycin	0.2	1.5
Teicoplanin	0	1.2

**Abbreviations:** R, resistance rate; n, the number of strains.

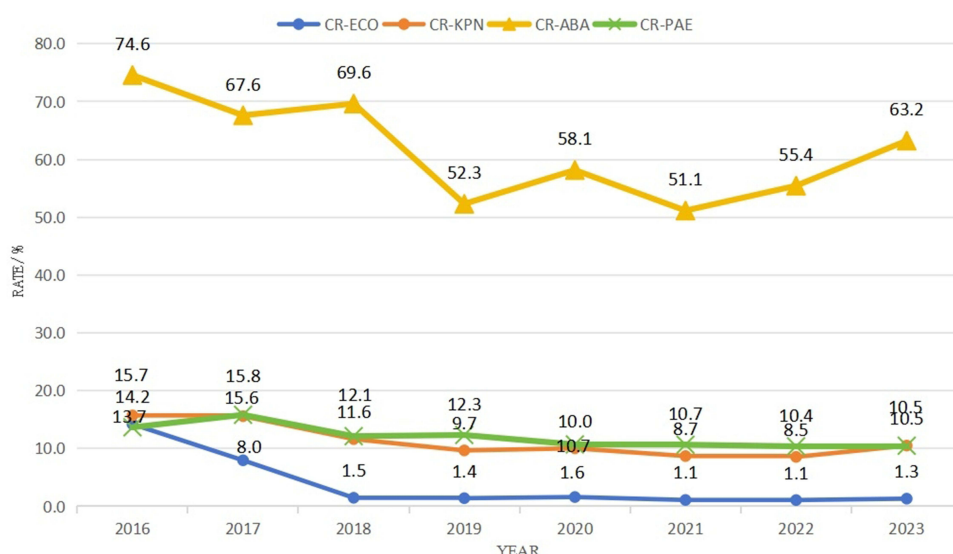
## Multidrug-Resistant Bacteria Changes

Among multidrug-resistant bacteria detected in 2016–2023, Carbapenem-resistant *Escherichia coli*(CRECO) and Carbapenem-resistant *Klebsiella pneumoniae*(CRKPN) showed a decreasing trend, Carbapenem-resistant *Acinetobacter baumannii*(CRAB) remained at a high level of detection and it showed a downward and then an upward trend. Methicillin-resistant *Staphylococcus aureus*(MRSA) showed a slight increasing trend and Vancomycin-resistant *Enterococcus* (VRE) remained at a low level (Figures 1 and 2).

**Figure 1** Distribution of multi-drug resistant strains in 2016–2023.

**Abbreviations:** CR-ECO, Carbapenem-resistant *Escherichia coli*; CR-KPN, Carbapenem-resistant *Klebsiella pneumoniae*; CR-ABA, Carbapenem-resistant *Acinetobacter baumannii*; CR-PAE, Carbapenem-resistant *Pseudomonas aeruginosa*.





**Figure 2** Trends in detection rates of major carbapenem-resistant gram-negative bacteria in 2016–2023.

**Abbreviations:** CTX/CRO-R-ECO, cefotaxime/ceftriaxone-resistant *Escherichia coli*; CTX/CRO-R-KPN, cefotaxime/ceftriaxone-resistant *Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant *Enterococcus*.

## Discussion

This surveillance showed that a total of 170,246 strains of non-repeatable pathogens of bloodstream infections were isolated from 109 healthcare institutions in Southwest China from 2016 to 2023, and the detected gram-negative organisms were dominated by *E. coli* (33.9%), *K. pneumoniae* (11.5%), and *P. aeruginosa* (2.3%), and the Gram-positive organisms were mainly coagulase-negative staphylococci (21.7%), followed by *Staphylococcus aureus* (7.0%) and *Enterococcus* spp. (5.4%). The percentage of gram-negative bacteria (59.5%) was higher than gram-positive bacteria (40.5%), which is consistent with other national reports.<sup>12,14–16</sup> The 25743 pathogenic bacteria (15.1%) isolated from ICU patients were mainly coagulase-negative staphylococci (32.4%), and the 144503 pathogenic bacteria (84.9%) isolated from non-ICU patients were predominantly *E. coli* (36.8%), and the percentage of detected *Enterococci* was significantly higher in the ICU (9.9%) than in the non-ICU (4.6%). The distribution of isolates also differed significantly between children and adults, with CNS predominating in children and *S. pneumoniae*, *Salmonella*, and  $\beta$ -hemolytic streptococci being isolated at a much higher rate than in adult patients, and *E. coli* predominating in the rest of the age groups, with the highest number of strains being isolated in the  $\geq 60$ -year age group.

In this study, it was found that the main pathogen causing BSI in this region was *E. coli*, which was consistent with the main cause of BSI in Europe.<sup>8</sup> The resistance rate of *E. coli* to carbapenems was less than 1.4%, indicating high activity, but the resistance rates of *E. coli* to cefazolin, cefuroxime, ceftriaxone, and trimethoprim-sulfamethoxazole were all greater than 50.0%. The resistance rate to quinolones was more than 41.6%. The resistance rate of *K. pneumoniae* to ceftriaxone was higher than 24.8%, the resistance rate of cefuroxime was higher than 26.7% and the resistance rate of quinolones was higher than 14.8%. From 2016 to 2023, the CTX/CRO-R-ECO detection rate remained high (47.1–57.6%), and the CTX/CRO-R-KPN detection rate ranged from 25.0% to 36.0%. The emergence of third-generation cephalosporin (3GC) and fluoroquinolone resistant strains was highly affected. It is a major change in the epidemiology of *E. coli* and *K. pneumoniae* BSI due to the production of Extended-Spectrum  $\beta$ -Lactamase (ESBLs) or AmpC.<sup>17,18</sup> In the World Health Organization's (WHO) List of Pathogens of Concern for Bacteria 2024 (BPPL-2024),<sup>19</sup> 3GCRE has been separately classified as a key priority, a change that underscores the need for targeted policies and interventions to address this threat. The high failure rate of 3GCRE treatment and the increase in healthcare costs have increased the burden on low- and middle-income countries and vulnerable populations.

The data demonstrates that the detection rate of CRAB has remained at a high level (51.1–74.6%) and exhibits a high degree of drug resistance.<sup>16</sup> In China, the clinical practice mainly relies on tigecycline, polymyxins and ceftazidime/

avibactam. However, the suboptimal distribution and concentration of tigecycline in serum,<sup>20</sup> heterogeneous resistance of polymyxins<sup>21</sup> and ineffectiveness of ceftazidime/avibactam against most *Acinetobacter baumannii* have caused significant challenges in the treatment of BSI.<sup>22</sup> The prevalence of CRPA in our region is relatively low, ranging from 10.4% to 13.7%, which was much lower than other carbapenem-resistant strains. Despite the downgrading of CRPA priorities in BPPL-2024,<sup>19</sup> there is still a need to continue to advance the development of new drugs.

In the past eight years, the resistance rate of *K. pneumoniae* to ertapenem, imipenem and meropenem increased from 2.4%, 2.7% and 4.1% in 2016 to 9.8%, 10.0% and 11.1% in 2023, showing a significant increase. The rate of CRKP detection in 2016–2019 had a significant decrease (15.7% to 9.7%) and then remained at 8.5%–10.5%, which was lower than the national level (25.5%) reported by CHINET.<sup>23</sup> Among the carbapenem-resistant gram-negative bacteria (CRGNB) that cause BSI, CRKP is the most prominent.<sup>24–26</sup> A prospective cohort study found that CRKP strains carried  $\beta$ -lactamase *K. pneumoniae* carbapenemase 2, and 73.1% of CRKP carried mucoid phenotype regulator genes A2 and iucABCD which could lead to the colonization and epidemic transmission of CRKP in surgical intensive care units.<sup>27</sup> Hunan, Henan, and Changzhou have reported a high rate of CRKP resistance to most antibiotics in ICUs, with sensitivity only to polymyxin B and tigecycline, which poses a major challenge to clinical treatment.<sup>28–30</sup> The study demonstrated that the primary resistance mechanism of CRKP in China is carbapenemase-producing enzyme, with blaKPC-2 being the predominant gene (89.4%), though the distribution of resistance genes exhibited variability across different regions. In the southwest and east, KL64 carrying blaKPC-2 was found to be particularly prevalent, while KL47 in the north and northeast, and some rare K-types, such as KL15 and KL51, carrying blaNDM resistant to ceftazidime-avibactam.<sup>31</sup> Concurrently, a novel clone ST4495 (4-1-99-1-9-5-5) carrying blaNDM-1 was identified, disseminating in the southwestern region of China.<sup>32</sup> Within the Indian region, NDM carbapenemases demonstrate a heightened prevalence, and in nations such as Japan and South Korea, beyond the enzyme-producing mechanism, the prevalence of altered outer membrane proteins, active exocytosis systems, and mucin resistance mechanisms is of heightened concern.<sup>33–35</sup> In some European countries, the co-existence of OmpK35 and OmpK36 deletion and AcrAB-TolC efflux pump expression in certain CRKP strains has been observed to enhance drug resistance.<sup>36</sup> In the context of China, there is currently a paucity of clinically available antibiotics for the treatment of CRKP, with only ceftazidime-avibactam and tigecycline being available on the market. In light of this, the KL64 and KL47 capsule types could be considered for future vaccine development.

The present data showed that Gram-positive bacteria causing BSI were dominated by CNS, followed by *Staphylococcus aureus*, which was slightly different from that in the central part of the country.<sup>13</sup> The detection rate of CNS, as a normal colonizing flora of the human skin and mucous membranes, was much higher in ICUs (32.4%) than that in non-ICUs (19.8%), which was related to the fact that critically ill patients would undergo more invasive operations, such as tracheal intubation, indwelling catheters, and medical implantable devices. Thus, when determining whether CNS is a contaminating or infectious organism, it is necessary to combine the patient's clinical symptoms and related indicators to make a comprehensive judgment. Considering that the data came from 109 hospitals in Sichuan province, there may be a lack of standardization in the collection of blood cultures, resulting in a high contamination rate. Therefore, while standardizing the collection method of blood cultures, it is recommended to puncture different parts of the body and send double bottles to multiple sets of tests to increase the positive rate and exclude contamination.

The detection rate of MRSA in this region was 27.7%, which was slightly lower than the national level, with a slight increasing trend.<sup>16</sup> The resistance rate of MRSA to penicillins, quinolones and aminoglycosides was higher than that of the MSSA strains. No non-susceptible strains to vancomycin, ticlopidine, or linezolid were detected. A recent study reported that the MRSA subclone ST764-t002 detected in seven provinces and cities in China, including our region, has the ability to form biofilms and adhere to cells, and its deletion of the SCCmec II region may contribute to widespread transmission.<sup>37</sup> Therefore, good hand hygiene and environmental cleanliness are essential, and rational drug administration based on drug susceptibility results may reduce the emergence and transmission of drug-resistant strains.

We also found that VRE strains detected decreased significantly from 2.9% in 2016 to 1.1% in 2020 but increased again in 2021–2023 (1.5% to 1.8%). This may be related to the following factors: (1) Some hospitals did not conduct VRE colonization screening for staff in key departments (such as ICU, surgery, anaesthesia) and long-term hospitalized patients; (2) The measures of gastrointestinal decolonization were not widely carried out; (3) there was insufficient space

to fully isolate patients infected with or carrying the carriage organisms in a single room. As VRE bloodstream infections (VRE BSI) can lead to high mortality rates, clinical treatment with high-dose daptomycin is currently recommended, with better prognostic outcomes compared to linezolid.<sup>38,39</sup> However, with increasing daptomycin resistance in VRE, combination therapy is required, and data suggest that combination with  $\beta$ -lactams, linezolid, aminoglycosides or tigecycline may have synergistic effects.<sup>40</sup>

## Conclusion

Currently, the pathogenic bacteria of bloodstream infections in Southwest China are dominated by *E. coli*, *K. pneumoniae*, and CNS, and it is very important to continuously and dynamically monitor the development trend of multidrug-resistant bacteria, especially CRGNB, MRSA, and VRE. Hospitals also need to strengthen the awareness of infection prevention and control, and continuously improve the preventive and control measures, in order to slow down the production of drug-resistant bacteria. The hospitals also need to strengthen the awareness of infection prevention and control and continuously improve the preventive and control measures to slow down the emergence of drug-resistant bacteria.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China (No. 2024733). The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of this study. Patients' anonymous information was provided from the microbiology hospital laboratory, which isolated the strains. The study completely followed the principles outlined in the Declaration of Helsinki.

## Disclosure

The authors report no conflicts of interest in this work.

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