Infection and Drug Resistance

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ORIGINAL RESEARCH

Distribution and Antibiotic Resistance Characteristics of Bacteria Isolated from Blood Culture in a Teaching Hospital in Vietnam During 2014–2021

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Purpose: Studies on the epidemiology of bloodstream infection (BSI) and antimicrobial resistance (AMR) are limited in Vietnam. Thus, the present study aimed to elucidate the epidemiology of BSI and AMR of BSI-causing bacteria in Vietnam.

Methods: Data regarding blood cultures from 2014 to 2021 were collected and analyzed using the chi-square test, Cochran–Armitage test, and binomial logistic regression model.

Results: Overall, 2405 (14.15%) blood cultures were positive during the study period. In total, 55.76% of BSIs occurred in patients aged ≥60 years. The male-to-female ratio of patients with BSI was 1.87:1. *Escherichia coli* (26.11%), *Staphylococcus aureus* (15.79%), *Klebsiella pneumoniae* (10.44%), *Acinetobacter baumannii* (4.70%), and *Pseudomonas aeruginosa* (3.45%) were the leading bacterial species causing BSI. The AMR rate of these bacteria isolated in the intensive care unit (ICU) was significantly higher compared with that of those in other wards. *E. coli* was the least resistant to carbapenems (2.39%–4.14%), amikacin (3.85%), and colistin (11.54%) and most resistant to penicillins (>80.0%). *S. aureus* was the least resistant to glycopeptides (0%–3.38%), quinupristin-dalfopristin (0.59%), and linezolid (1.02%) and most resistant to clindamycin (71.57%). *K. pneumoniae* was the least resistant to ertapenem (8.86%), amikacin (9.39%), and colistin (15.38%) and most resistant to aztreonam (83.33%). *A. baumannii* was the least resistant to amikacin (16.67%) and colistin (16.67%) and highly resistant to other antibiotics (≥50.0%). *P. aeruginosa* was the least resistant to colistin (16.33%) and piperacillin (28.17%) and highly resistant to other antibiotics (≥50.0%). Notably, the multidrug resistance rate of *E. coli* (76.41%) was the highest among common pathogens, followed by *A. baumannii* (71.57%), *P. aeruginosa* (64.56%), *S. aureus* (56.99%), and *K. pneumoniae* (43.72%).

Conclusion: The AMR rate of BSI-causing bacteria, particularly strains isolated from ICU, was alarmingly high. There is a need for new antibiotics, therapeutic strategies, as well as prevention and control to combat BSI and AMR.

Keywords: bloodstream infection, antimicrobial resistance, multidrug resistance, methicillin-resistant*Staphylococcus aureus*

Received: 21 December 2022
Accepted: 16 March 2023
Published: 23 March 2023

Introduction

Globally, antimicrobial-resistant bacteria (ARB) are recognized as a threat to public health. In 2019, ARB infections led to 4.95 million deaths worldwide. Notably, bloodstream infection (BSI) with ARB was the second leading cause of death, accounting for approximately 1.4 million deaths in 2019.[1] The distribution and resistance patterns of BSI-causing pathogens vary according to the time, geographical location, environment, population, and healthcare expenditure.[2,3] Although *S. aureus, E. coli*, and *K. pneumoniae* were recognized as the leading BSI-causing bacteria in the Asian population,[4,5] coagulase-negative *Staphylococcus* (CoNS) and *Salmonella* were the most common BSI-causing bacteria in European and African populations, respectively.[4–7] The proportion of resistance of BSI-causing *E. coli* and *K. pneumoniae* to third-generation cephalosporins was 10.7%–43.7% and 7.4%–45.7%, respectively. In contrast, imipenem, meropenem, amikacin, colistin, and tigecycline were among the most effective antibiotics used for treating BSI caused by *E. coli* and *K. pneumoniae*.[4,5] Further, *A. baumannii* isolated from BSI was highly resistant to most antibiotics, except for colistin and tigecycline. Similarly, these antibiotics were highly effective for the treatment of BSI caused by *P. aeruginosa*.[4,5,8] BSI-causing *S. aureus* was highly resistant to erythromycin, penicillins, and clindamycin. In contrast, *S. aureus* was least resistant to vancomycin, linezolid, quinupristin-dalfopristin, and tigecycline.[8,9] Notably, antimicrobial resistance (AMR) surveillance is important for the treatment and prevention of BSI as it provides data regarding resistance proportion, trends, and patterns, which are critical for developing treatment guidelines. Unfortunately, studies on AMR of BSI-causing pathogens in Vietnam, particularly long-term studies, are limited. Therefore, this study aimed to provide information on the epidemiology of BSI and AMR characteristics of BSI-causing bacteria in a large teaching hospital in Hanoi, Vietnam, from 2014 to 2021.

Materials and Methods

Pathogen Identification and Antimicrobial Susceptibility Test

Blood samples of patients were collected in commercial media bottles (BD, USA, and bioMérieux, France). A set of aerobic and anaerobic bottles was used for adults, whereas only aerobic bottles were used for children. Blood samples with volumes of 8–10 mL and 2–5 mL per bottle were collected from adults and children, respectively. Further, blood culture was performed using BD BACTEC FX40 (BD, USA) and BACT/ALERT 3D (bioMérieux, France). Positive blood samples were microscopically examined and subcultured on suitable media. Further, the suspected pathogens were detected using conventional biochemical tests[10,11] and an automatic identification instrument (Vitek-2 Compact system, bioMérieux, France). Moreover, antimicrobial susceptibility testing (AST) was performed according to the guidelines of the Clinical & Laboratory Standards Institute (CLSI). AST was performed using disk diffusion, gradient diffusion, broth dilution, or the Vitek-2 Compact system. Antimicrobial susceptibility test disks were purchased from Oxoid, UK, and ETEST strips were purchased from bioMérieux, France. Colistin sulfate powder (Sigma-Aldrich, France) was used for broth dilution to evaluate the colistin susceptibility of bacteria. The AST results were interpreted as susceptible, intermediate, and resistant according to the latest CLSI guidelines at the time of testing.[12,13] To control the quality of results, all laboratory activities were strictly conducted in accordance with ISO 15189.[14] Internal quality control for blood culture media, ETEST strips, and antibiotics disks was conducted once a month or before using the new batch of these materials. Moreover, internal quality control for pathogen identification and AST on the Vitek-2 Compact system was conducted once a week. *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922, NCTC 13846), and *Pseudomonas aeruginosa* (ATCC 27853) were used as reference bacterial strains for the internal quality control. Moreover, the laboratory participated in the external quality control programs for bacterial identification and AST of the Ministry of Health of Vietnam.

Data Collection

This was a retrospective study of blood culture conducted at Military Hospital 103 in Hanoi, Vietnam, from January 1, 2014, to December 31, 2021. Data were collected from the Microbiology Department, including the date and results of blood cultures as well as AST results, age, sex, and hospital ward. Only the first pathogen isolated from patients was analyzed in order to avoid bias due to duplicate isolates.

Definition of Multidrug-Resistant (MDR) Bacteria

MDR bacteria were defined as the bacteria that were nonsusceptible to ≥1 agent in ≥3 antimicrobial classes.[15]

Statistical Analysis

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. Moreover, this test was used to compare the differences in the rates of resistance to antibiotics among different bacterial species and hospital wards. Further, the Cochran–Armitage test for linear trends was performed to evaluate the significance of annual trends. The binomial logistic regression model was used to determine the potential predictors of bacterial infection, such as hospital ward, sex, and age. Statistical analysis was performed using SPSS Statistics 25.0 (IBM Corp, NY, USA) and R software version 4.2.1.

Ethical Statement

This study was approved by the Ethics Committee of Military Hospital 103, Hanoi, Vietnam (Approval number: 35/CNChT- HĐĐĐ). Moreover, the study was conducted in accordance with the principles of the Declaration of Helsinki. All patient data were anonymized before performing the analysis.

Results

Blood Culture

The total number of blood culture tests conducted from 2014 to 2021 was 17,002, of which 2405 (14.15%) were positive. The positivity rate ranged from 10.29% to 16.70% per year. The proportion of positive blood cultures was almost the same between men and women (approximately 14.0%). The rate of positive blood cultures in the age group of ≥60 years (16.09%) was significantly higher than that in the age group of 0–17 (8.66%) and 18–59 (12.48%) years. No significant difference in the rate of positive blood cultures was observed between the age groups of 0–17 and 18–59 years. Notably, among hospital wards, the intensive care unit had the highest percentage of positive blood cultures (19.27%). The rate of positive blood cultures in ICU was remarkably higher than that in other hospital wards, including the infectious disease (14.31%), internal medicine (12.21%), and surgery (12.20%) wards (Table 1).

Distribution of Bacteria

Gram-negative and gram-positive bacteria accounted for 64.12% and 28.73% of the positive blood cultures, respectively. The remaining 7.15% of the positive blood cultures were of fungus. The majority of pathogens isolated from blood cultures (accounting for 92.52% of the total pathogens) were *E. coli* (26.11%), *S. aureus* (12.56%), *Klebsiella* spp. (10.81%), *Candida* spp. (7.15%), *Streptococcus* spp. (7.07%), *Burkholderia* spp. (5.99%), *Acinetobacter* spp. (5.53%), CoNS (5.41%), *Pseudomonas* spp. (3.83%), *Enterococcus* spp. (3.33%), *Stenotrophomonas maltophilia* (2.37%), and *Enterobacter* spp. (2.37%) (Table 2). The remaining 7.48% of the pathogens included various types of bacteria with low frequency (Supplementary Table 1). Over the 8 years from 2014 to 2021, there was an upward trend in the rate of BSI caused by *E. coli, Klebsiella* spp., *Pseudomonas* spp., and *Enterococcus* spp. However, the data revealed a downward trend in the rate of BSI caused by *Streptococcus* spp., *Acinetobacter* spp., *S. maltophilia*, and *Candida* spp. (Table 2). Further, *K. pneumoniae* (251/261), *A. baumannii* (113/133), and *P. aeruginosa* (82/92) were the main species of *Klebsiella, Acinetobacter*, and *Pseudomonas* genera isolated in the present study.

Clinical Characteristics of Patients with BSI

The mean (standard deviation) age of BSI patients was 59.14 (18.86) years. Patients in the ≥60-year age group accounted for the largest proportion of BSI cases (55.76%; 1341/2405). In contrast, patients in the 0–17-year age group accounted for only 1.66% of BSI cases (40/2405). The remaining 42.58% (1024/2405) of patients with BSI were in the 18–59-year age group. The male-to-female ratio of patients with BSI was 1.87:1 (1567/838). The highest proportion of BSI cases was from the internal medicine ward (31.48%; 757/2405). The infectious disease ward and ICU had lower proportions of BSI (29.90% [719/2405] and 25.41% [611/2405], respectively). Further, surgery wards had the lowest proportion of BSI (13.22%; 318/2405) (Table 1).

Table 1 Distribution of Blood Cultures

	The Number of Blood Cultures	Positive Culture: Number (%)
Year		
2014	1419	237 (16.70)
2015	1988	286 (14.39)
2016	1798	287 (15.96)
2017	2007	250 (12.46)
2018	2672	275 (10.29)
2019	2075	311 (14.99)
2020	2612	361 (13.82)
2021	2431	398 (16.37)
Total	17,002	2405 (14.15)
Sex		
Male	11,296	1567 (13.87)
Female	5706	838 (14.69)
Total	17,002	2405 (14.15)
Age (years)		
0–17	462	40 (8.66)
18–59	8207	1024 (12.48)
≥ 60	8333	1341 (16.09)[a]
Total	17,002	2405 (14.15)
Hospital wards		
ICU	3171	611 (19.27)[b]
Infectious diseases	5026	719 (14.31)
Surgery	2607	318 (12.20)
Internal medicine	6198	757 (12.21)
Total	17,002	2405 (14.15)

Notes: [a]The positive rate of blood culture in the ≥60-year age group was significantly higher than that of other groups ($P < 0.05$). [b]The positive rate of blood culture of ICU was significantly higher than that of other hospital wards ($P < 0.05$). P values were calculated using Chi-square test.

Antibiotic Resistance Characteristics of Gram-Negative Bacteria

The resistance rate of *E. coli* isolates to carbapenems was the lowest in the Enterobacteriaceae family, and it ranged from 2.39% (ertapenem) to 4.14% (imipenem). Meanwhile, the proportion of resistance of *K. pneumoniae* and *Enterobacter* spp. to carbapenems ranged from 8.86% (ertapenem) to 29.25% (imipenem) and from 4.0% (ertapenem) to 23.26% (imipenem), respectively. However, the resistance rate of *E. coli* to fluoroquinolones and third-generation cephalosporins

Table 2 The Pathogens Causing Bloodstream Infection

Organisms	2014	2015	2016	2017	2018	2019	2020	2021	Total	Z[b]	P[c]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)		
Escherichia coli	44 (18.57)	55 (19.23)	74 (25.78)	50 (20.00)	85 (30.91)	90 (28.94)	111 (27.89)	119 (32.96)	628 (26.11)	4.92	< 0.001
Staphylococcus aureus	21 (8.86)	45 (15.73)	40 (13.94)	35 (14.00)	26 (9.45)	40 (12.86)	38 (9.55)	57 (15.79)	302 (12.56)	0.22	0.83
Klesbsiella spp.	16 (6.75)	34 (11.89)	17 (5.92)	28 (11.20)	41 (14.91)	27 (8.68)	52 (13.07)	45 (12.47)	260 (10.81)	2.54	0.01
Streptococcus spp.	21 (8.86)	29 (10.14)	21 (7.32)	27 (10.80)	18 (6.55)	16 (5.14)	17 (4.27)	21 (5.82)	170 (7.07)	−3.3	< 0.001
Burkholderia spp.	34 (14.35)	13 (4.55)	17 (5.92)	7 (2.80)	6 (2.18)	10 (3.22)	35 (8.79)	22 (6.09)	144 (5.99)	−1.62	0.1
Acinetobacter spp.	17 (7.17)	27 (9.44)	15 (5.23)	22 (8.8)	10 (3.64)	14 (4.50)	18 (4.52)	10 (2.77)	133 (5.53)	−3.73	< 0.001
Coagulase-negative *Staphylococcus*	22 (9.28)	6 (2.10)	17 (5.92)	9 (3.60)	22 (8.00)	19 (6.11)	24 (6.03)	11 (3.05)	130 (5.41)	−0.98	0.33
Pseudomonas spp.	6 (2.53)	3 (1.05)	12 (4.18)	11 (4.40)	8 (2.91)	17 (5.47)	23 (5.78)	12 (3.32)	92 (3.83)	2.29	0.02
Enterococcus spp.	0 (0.00)	5 (1.75)	4 (1.39)	3 (1.20)	10 (3.64)	17 (5.47)	26 (6.53)	15 (4.16)	80 (3.33)	3.87	< 0.001
Stenotrophomonas maltophilia	6 (2.53)	13 (4.55)	9 (3.14)	12 (4.80)	4 (1.45)	10 (3.22)	1 (0.25)	2 (0.55)	57 (2.37)	−3.75	< 0.001
Enterobacter spp.	10 (4.22)	4 (1.40)	7 (2.44)	8 (3.20)	4 (1.45)	6 (1.93)	9 (2.26)	9 (2.49)	57 (2.37)	−0.73	0.47
Other[a]	25 (10.55)	27 (9.44)	22 (7.67)	22 (8.80)	22 (8.00)	17 (5.47)	17 (4.27)	28 (7.76)	180 (7.48)	NA	NA
Candida spp.	15 (6.33)	25 (8.74)	32 (11.15)	16 (6.40)	19 (6.91)	28 (9.00)	27 (6.78)	10 (2.77)	172 (7.15)	−2.53	0.01
Total Gram negative-bacteria	158	176	172	157	180	190	265	246	1542 (64.12)	NA	NA
Total Gram positive-bacteria	64	85	83	77	76	93	106	105	691 (28.73)	NA	NA
Total	237	286	287	250	275	311	398	361	2405	NA	NA

Notes: N, number of isolates; NA, Not applicable; [a]organisms with low frequency (≤ 2%); [b]Z value > 0 indicated increase trend, and Z value < 0 indicated decrease trend; [c]P and Z values were calculated using Cochran-Armitage test.

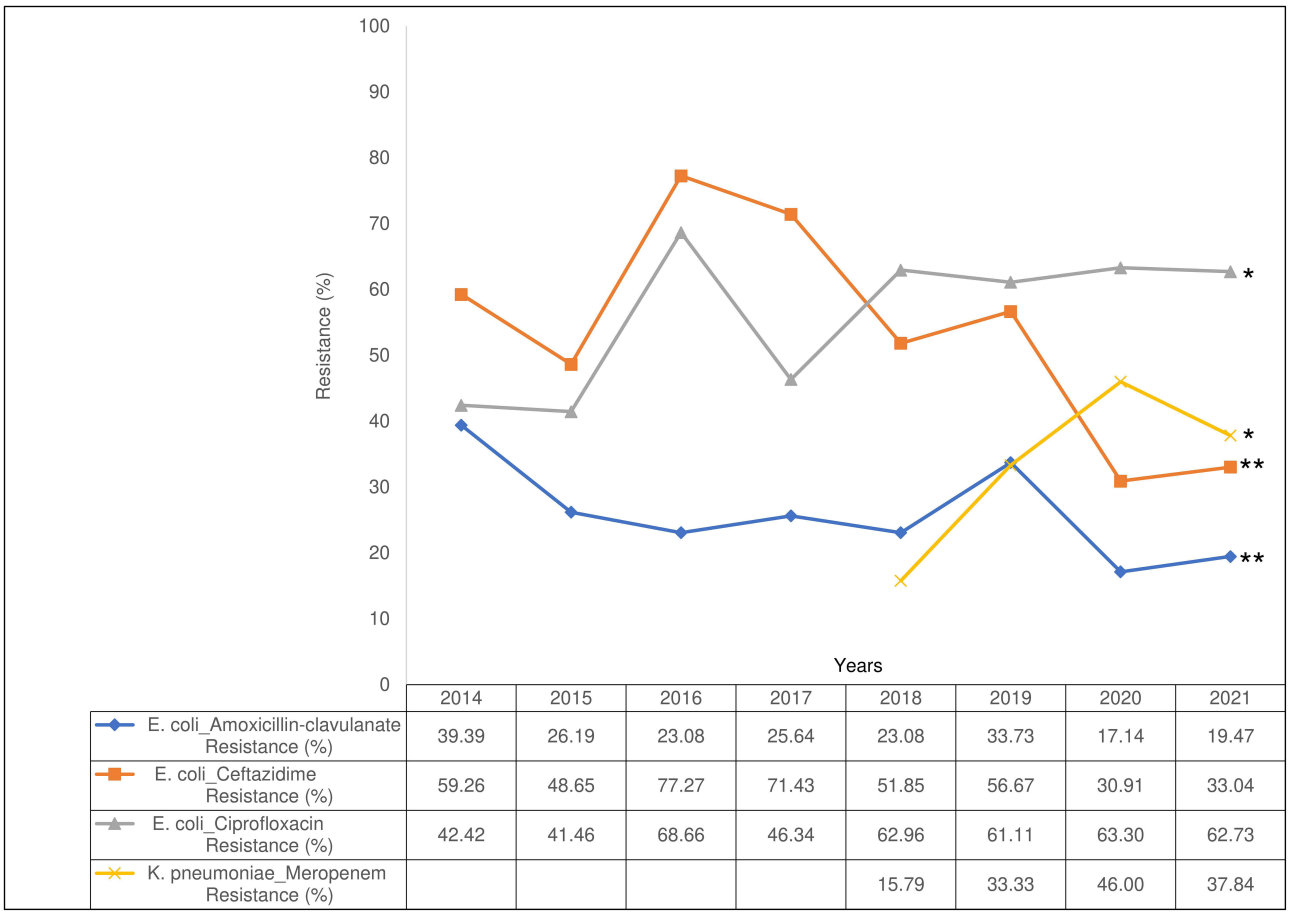
was higher than that of *K. pneumoniae* and *Enterobacter* spp. In particular, the proportion of resistance of *E. coli* to fluoroquinolones ranged from 54.27% (norfloxacin) to 61.54% (levofloxacin). However, the resistance rates of *K. pneumoniae* and *Enterobacter* spp. to fluoroquinolones ranged from 38.97% (norfloxacin) to 43.48% (levofloxacin) and from 23.08% (levofloxacin) to 33.33% (norfloxacin), respectively. Furthermore, the proportion of resistance of *E. coli* to third-generation cephalosporins ranged from 49.38% (ceftazidime) to 61.75% (cefotaxime), whereas the proportion of resistance of *K. pneumoniae* ranged from 33.33% (ceftriaxone) to 45.12% (ceftazidime) and that of *Enterobacter* spp. ranged from 39.47% (cefotaxime) to 50.0% (ceftriaxone). The resistance rate of Enterobacteriaceae to aminoglycosides varied widely. The resistance rates of *E. coli, K. pneumoniae*, and *Enterobacter* spp. isolates to aminoglycosides ranged from 3.85% (amikacin) to 37.74% (gentamicin), from 9.39% (amikacin) to 43.48% (tobramycin), and from 10.20% (amikacin) to 35.90% (gentamicin), respectively. The resistance rates of *E. coli* and *K. pneumoniae* to colistin were 11.54% and 13.58%, respectively. Although the proportion of resistance of *E. coli* was the highest against ampicillin (89.47%), piperacillin (82.61%), and trimethoprim-sulfamethoxazole (70.71%), the resistance rate of *K. pneumoniae* to aztreonam (83.33%) and piperacillin (71.41%) was the highest among the tested antibiotics (Table 3). Over the study period, there were downward trends in amoxicillin-clavulanate- and ceftazidime-resistant *E. coli*. Notably, amoxicillin-clavulanate-resistant *E. coli* isolates significantly decreased from 39.39% in 2014 to 19.47% in 2021 (annual trend P value < 0.05), and ceftazidime-resistant *E. coli* isolates declined from 59.26% in 2014 to 33.04% in 2021 (annual trend P value < 0.05). In contrast, ciprofloxacin-resistant *E. coli* isolates increased from 42.42% in 2014 to 62.73% in 2021 (annual trend P value < 0.05). Meropenem-resistant *K. pneumoniae* substantially increased from 15.79% in 2018 to 37.84% in 2021 (annual trend P value < 0.05) (Figure 1). Among the nonfermentative gram-negative bacteria, the resistance rate of *A. baumannii* to carbapenems ranged from 57.58% (imipenem) to 60.82% (meropenem), whereas the resistance rate of *P. aeruginosa* ranged from 55.41% (meropenem) to 58.67% (imipenem). The proportion of resistance of *A. baumannii* and *P. aeruginosa* to fluoroquinolones (such as ciprofloxacin and

Table 3 Antimicrobial Resistance to Selected Antibiotics of Gram-Negative Bacteria

Organism	*E. coli*			*K. pneumoniae*			*Eterobacter* spp.			*A. baumannii*			*P. aeruginosa*		
	n	N	%R	n	N	%R	n	N	%R	n	N	%R	n	N	%R
Aminoglycosides															
Amikacin	22	572	3.85	20	213	9.39	5	49	10.20	11	66	16.67	24	75	32.00
Gentamycin	197	522	37.74	53	197	26.90	14	39	35.90	55	90	61.11	40	74	54.05
Tobramycin	9	65	13.85	10	23	43.48	4	14	28.57	42	76	55.26	43	73	58.90
Monobactams															
Aztreonam	42	63	66.67	20	24	83.33	7	20	35.00	NA	NA	NA	11	22	50.00
Cephems															
Cefepime	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	33	74	44.59
Cefotaxime	318	515	61.75	82	202	40.59	15	38	39.47	20	31	64.52	NA	NA	NA
Ceftazidime	279	565	49.38	97	215	45.12	22	50	44.00	65	94	69.15	39	78	50.00
Ceftriaxone	23	43	53.49	4	12	33.33	5	10	50.00	4	8	50.00	NA	NA	NA
Carbapenems															
Ertapenem	12	503	2.39	14	158	8.86	1	25	4.00	NA	NA	NA	NA	NA	NA
Meropenem	22	566	3.89	57	217	26.27	10	47	21.28	59	97	60.82	41	74	55.41
Imipenem	23	556	4.14	62	212	29.25	10	43	23.26	57	99	57.58	44	75	58.67
Fluoroquinolones															
Levofloxacin	48	78	61.54	10	23	43.48	3	13	23.08	48	77	62.34	51	74	68.92
Ciprofloxacin	340	572	59.44	91	221	41.18	17	47	36.17	66	99	66.67	51	75	68.00
Norfloxacin	273	503	54.27	76	195	38.97	11	33	33.33						
Penicillins															
Ampicillin	459	513	89.47	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Piperacillin	38	46	82.61	15	21	71.43	2	11	18.18	51	69	73.91	20	71	28.17
β-lactam combination agents															
Amoxicillin-clavulanate	132	545	24.22	83	251	33.07	8	9	88.89	NA	NA	NA	NA	NA	NA
Piperacillin-tazobactam	3	15	20.00	71	184	38.59	12	39	30.77	48	67	71.64	4	6	66.67
Ticarcillin-clavulanate	13	39	33.33	8	15	53.33	3	9	33.33	45	65	69.23	50	74	67.57
Lipopeptides															
Colistin	3	26	11.54	2	13	15.38	0	4	0.00	8	48	16.67	8	49	16.33
Folate pathway antagonists															
Trimethoprim-sulfamethoxazole	379	536	70.71	87	206	42.23	13	40	32.50	32	86	37.21	NA	NA	NA

Notes: n, number of resistant strains; N, total of tested strains; R, Resistance; %R = n/N*100.
Abbreviation: NA, Not applicable.

levofloxacin) was >60%. The resistance rates of *A. baumannii* to piperacillin-tazobactam and ticarcillin-clavulanate were 71.64% and 69.23%, respectively, and those of *P. aeruginosa* were 66.67% and 67.57%, respectively. Further, the proportion of resistance of *A. baumannii* to aminoglycosides varied widely between 16.67% (amikacin) and 61.11%



	2014	2015	2016	2017	2018	2019	2020	2021
E. coli_Amoxicillin-clavulanate Resistance (%)	39.39	26.19	23.08	25.64	23.08	33.73	17.14	19.47
E. coli_Ceftazidime Resistance (%)	59.26	48.65	77.27	71.43	51.85	56.67	30.91	33.04
E. coli_Ciprofloxacin Resistance (%)	42.42	41.46	68.66	46.34	62.96	61.11	63.30	62.73
K. pneumoniae_Meropenem Resistance (%)					15.79	33.33	46.00	37.84

Figure 1 Resistance trend of *Escherichia coli* and *Klebsiella pneumoniae*. *Upward trend ($Z > 0$; $P < 0.05$); **Downward trend ($Z < 0$; $P < 0.05$). *P* and Z values were calculated using the Cochran–Armitage test.

(gentamicin) and that of *P. aeruginosa* varied from 32.0% (amikacin) to 58.90% (tobramycin). The resistance rates of *A. baumannii* and *P. aeruginosa* to colistin were almost the same (approximately 16.0%) (Table 3).

Antibiotic Resistance Characteristics of Gram-Positive Bacteria

The resistance rate of *Enterococcus* spp. to fluoroquinolones was the highest among gram-positive pathogens, ranging from 72.73% (levofloxacin) to 85.71% (norfloxacin). The proportion of resistance of CoNS to fluoroquinolones was considerably higher than that of *S. aureus*, except for norfloxacin. The resistance rates of CoNS to ciprofloxacin, levofloxacin, and moxifloxacin were 51.96%, 50.0%, and 37.21%, respectively, and those of *S. aureus* were 32.23%, 30.29%, and 27.78%, respectively. Meanwhile, the resistance rates of CoNS and *S. aureus* to norfloxacin were 43.75% and 46.43%, respectively. However, the resistance rate of *Streptococcus* spp. to norfloxacin was 8.87%. The proportion of resistance of *S. aureus* to macrolides (such as erythromycin, azithromycin, and clarithromycin) was approximately 70.0%, whereas that of CoNS ranged from 60.0% (clarithromycin) and 74.67% (erythromycin) and that of *Streptococcus* spp. ranged from 58.33% (azithromycin) to 80.0% (clarithromycin). The resistance rates of *S. aureus* and CoNS to doxycycline were <10.0%, whereas those of *S. aureus* and CoNS to tetracycline were >50.0%. The resistance rate of *Enterococcus* spp. isolates to tetracyclines ranged from 55.56% (doxycycline) to 84.72% (tetracycline). Further, the resistance rates of *S. aureus* and CoNS to linezolid, quinupristin-dalfopristin, and vancomycin were <9.0%; however, *Streptococcus* spp. were not resistant to linezolid and vancomycin but resistant to quinupristin-dalfopristin (>15.0%) (Table 4).

Table 4 Antimicrobial Resistance to Selected Antibiotics of Gram-Positive Bacteria

Organism	*S. aureus*			CoNS			*Streptococcus* spp.			*Enterococcus* spp.		
	n	N	%R	n	N	%R	n	N	%R	n	N	%R
Penicillins												
Ampicillin	NA	NA	NA	NA	NA	NA	18	97	18.56	38	70	54.29
Cephems												
Cefotaxime	NA	NA	NA	NA	NA	NA	18	111	16.22	NA	NA	NA
Cefoxitin	97	148	65.54	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ceftriaxone	NA	NA	NA	NA	NA	NA	20	117	17.09	NA	NA	NA
Macrolides												
Erythromycin	112	162	69.14	56	75	74.67	93	120	77.50	NA	NA	NA
Azithromycin	98	126	77.78	30	41	73.17	14	24	58.33	NA	NA	NA
Clarithromycin	30	43	69.77	9	15	60.00	8	10	80.00	NA	NA	NA
Lincosamides												
Clindamycin	146	204	71.57	50	87	57.47	85	110	77.27	NA	NA	NA
Phenicols												
Chloramphenicol	13	33	39.39	4	9	44.44	8	50	16.00	0	5	0.00
Aminoglycosides												
Gentamycin	62	204	30.39	20	91	21.98	NA	NA	NA	NA	NA	NA
Oxazolidinones												
Linezolid	2	196	1.02	1	92	1.09	0	105	0.00	1	1	100.00
Fluoroquinolones												
Ciprofloxacin	78	242	32.23	53	102	51.96	NA	NA	NA	54	73	73.97
Levofloxacin	73	241	30.29	50	100	50.00	11	124	8.87	56	77	72.73
Moxifloxacin	55	198	27.78	32	86	37.21		3	0.00	NA	NA	NA
Norfloxacin	26	56	46.43	7	16	43.75	NA	NA	NA	6	7	85.71
Streptogramin												
Quinupristin-Dalfopristin	1	169	0.59	NA	NA	NA	2	13	15.38	28	68	41.18
Ansamycins												
Rifapicin	9	177	5.08	33	80	41.25	0	4	0.00	1	1	100.00
Tetracyclines												
Tetracycine	100	171	58.48	49	94	52.13	12	14	85.71	61	72	84.72
Doxycycline	10	127	7.87	4	45	8.89	NA	NA	NA	15	27	55.56
Glycopeptides												
Vancomycin	7	207	3.38	9	101	8.91	0	106	0.00	7	75	9.33
Teicoplanin		64	0.00	1	1	100.00	NA	NA	NA		21	0.00
Folate pathway antagonists												
Trimethoprim/ sulfamethoxazole	61	222	27.48	64	98	65.31	4	5	80.00	NA	NA	NA

Notes: n, number of resistant strains; N, total of tested strains; R, resistance; %R = n/N*100.
Abbreviations: NA, Not applicable; CoNS, Coagulase-negative *Staphylococcus*.

AMR Characteristics of Methicillin-Resistant Staphylococcus Aureus (MRSA)

During the study period, the prevalence of MRSA was 65.54% (97/148). The resistance rate of MRSA to common antibiotics was higher than that of methicillin-susceptible *Staphylococcus aureus* (MSSA). Moreover, the resistance rates of MRSA and MSSA to norfloxacin, levofloxacin, ciprofloxacin, clindamycin, and erythromycin were significantly different (Figure 2).

MDR Bacteria Causing BSI

Among the five common BSI-causing bacterial pathogens, the proportion of MDR pathogens was the highest in *E. coli* (76.41%). Notably, MDR strains accounted for 71.57% of the total *A. baumannii*. Further, the MDR rates of *P. aeruginosa, S. aureus*, and *K. pneumoniae* were 64.56%, 56.99%, and 43.72%, respectively (Table 5). The MDR rate among *S. aureus* substantially increased over the 8-year period, which increased from 23.53% in 2014 to 73.21% in 2021 (annual trend *P* value < 0.05). Finally, the MDR proportion among the other bacterial species increased over the study period (Figure 3).

Analysis of AMR of Bacteria Isolated from ICU and Non-ICU Wards

Among *E. coli* isolates, the resistance rate of strains isolated from ICU to amoxicillin-clavulanate (AMC), cefotaxime (CTX), ceftazidime (CAZ), ciprofloxacin (CIP), norfloxacin (NOR), imipenem (IPM), meropenem (MEM), and fosfomycin (FOS) was significantly higher than that of strains isolated from non-ICU wards ($P < 0.05$). Moreover, the resistance rate of *E. coli* strains isolated from ICU to imipenem and meropenem was approximately three times higher than that of the strains isolated from non-ICU wards (ICU: 9.57% and 9.38%; non-ICU wards: 3.03% and 2.77%) (Figure 4A). The proportion of resistance of *S. aureus* strains isolated from ICU to fluoroquinolone agents was significantly higher than that of the strains isolated from non-ICU wards ($P < 0.05$) (Figure 4B). The proportion of resistance of *K. pneumoniae* strains isolated from ICU to all commonly tested antibiotics was significantly higher than

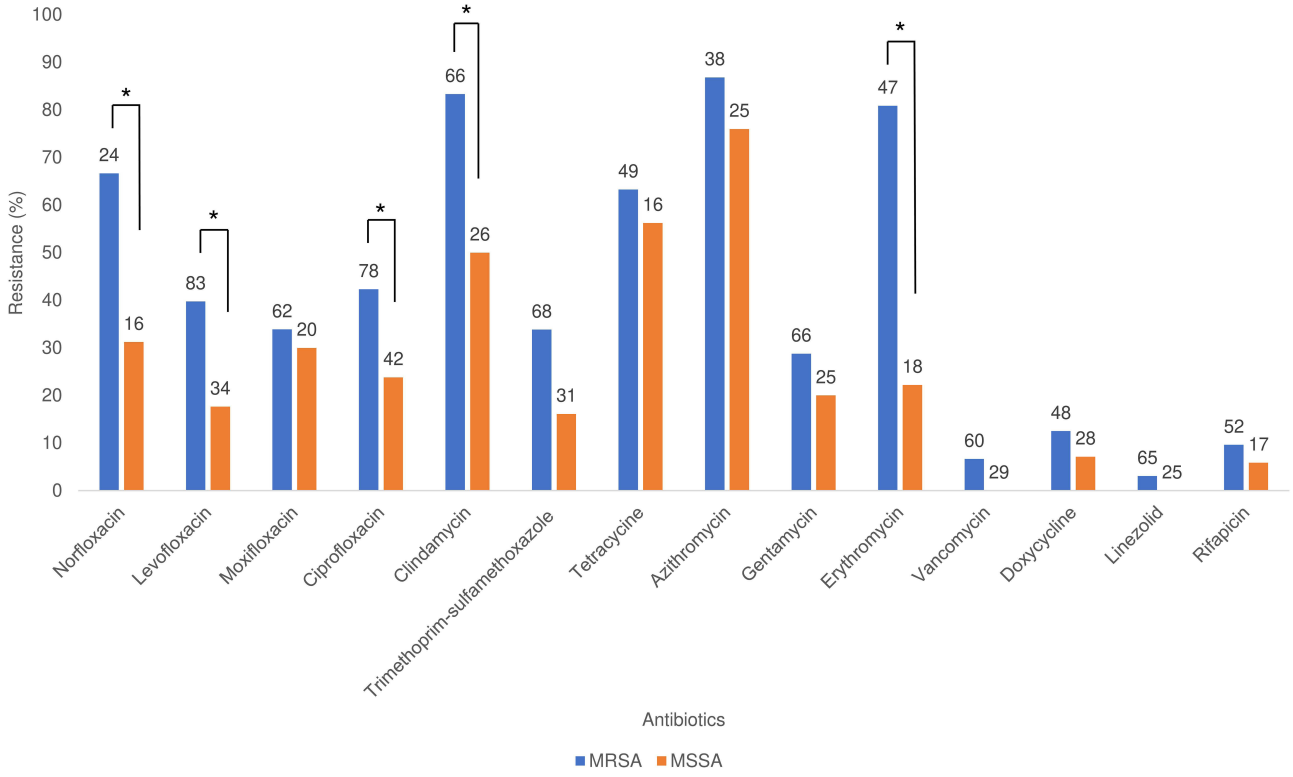


Figure 2 Antimicrobial resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA). The number on the top of each column indicates the tested bacterial strains. *$P < 0.05$ according to the chi-square test.

Table 5 Antimicrobial Resistance Pattern of Common Bacteria Causing BSI

Bacterial isolates	NS0 n (%)	NS1 n (%)	NS2 n (%)	NS3 n (%)	NS4 n (%)	NS5 n (%)	NS6 n (%)	NS7 n (%)	NS>7 n (%)	Total MDR n (%)
E. coli (602)	36 (5.98)	42 (6.98)	64 (10.63)	131 (21.76)	121 (20.10)	94 (15.61)	80 (13.29)	27 (4.49)	7 (1.16)	460 (76.41)
S. aureus (286)	39 (13.64)	40 (13.99)	44 (15.38)	55 (19.23)	48 (16.78)	34 (11.89)	17 (5.94)	8 (2.8)	1 (0.35)	163 (56.99)
K. pneumoniae (231)	72 (31.17)	42 (18.18)	16 (6.93)	10 (4.33)	5 (2.16)	14 (6.06)	25 (10.82)	2 (10.39)	23 (9.96)	101 (43.72)
A. baumannii (102)	19 (18.63)	6 (5.88)	4 (3.92)	4 (3.92)	11 (10.78)	32 (31.37)	25 (24.51)	1 (0.98)	0 (0.0)	73 (71.57)
P. aeruginosa (79)	14 (17.72)	4 (5.06)	10 (12.66)	7 (8.86)	8 (10.13)	22 (27.85)	9 (11.39)	5 (6.33)	0 (0.0)	51 (64.56)

Notes: n, number of isolates; NS0, susceptible to all antimicrobial categories tested; NS1, NS2, NS3, NS4, NS5, NS6, NS7, and NS>7, non-susceptible to one, two, three, four, five, six, seven, and more than seven antimicrobial categories, respectively.

that of the strains isolated from non-ICU wards. Furthermore, the resistance rates of *K. pneumoniae* strains isolated from ICU to ertapenem (ETP), imipenem (IMP), and meropenem (MEM) (21.88%, 59.09%, and 56.06%) were approximately four times higher than those of the strains isolated from non-ICU wards (5.56%, 15.75%, and 13.25%) (Figure 4C). The resistance rate of *A. baumannii* isolated from ICU to the most commonly detected antibiotics, except trimethoprim-sulfamethoxazole (SXT), was significantly higher than that of the strains isolated from non-ICU wards (Figure 4D). The proportion of resistance of *P. aeruginosa* strains isolated from ICU to all commonly tested antibiotics was higher than that of the strains isolated from non-ICU wards. However, a significant difference in the resistance rate was observed only for meropenem (MEM), imipenem (IMP), and ceftazidime (CAZ), as shown in Figure 4E.

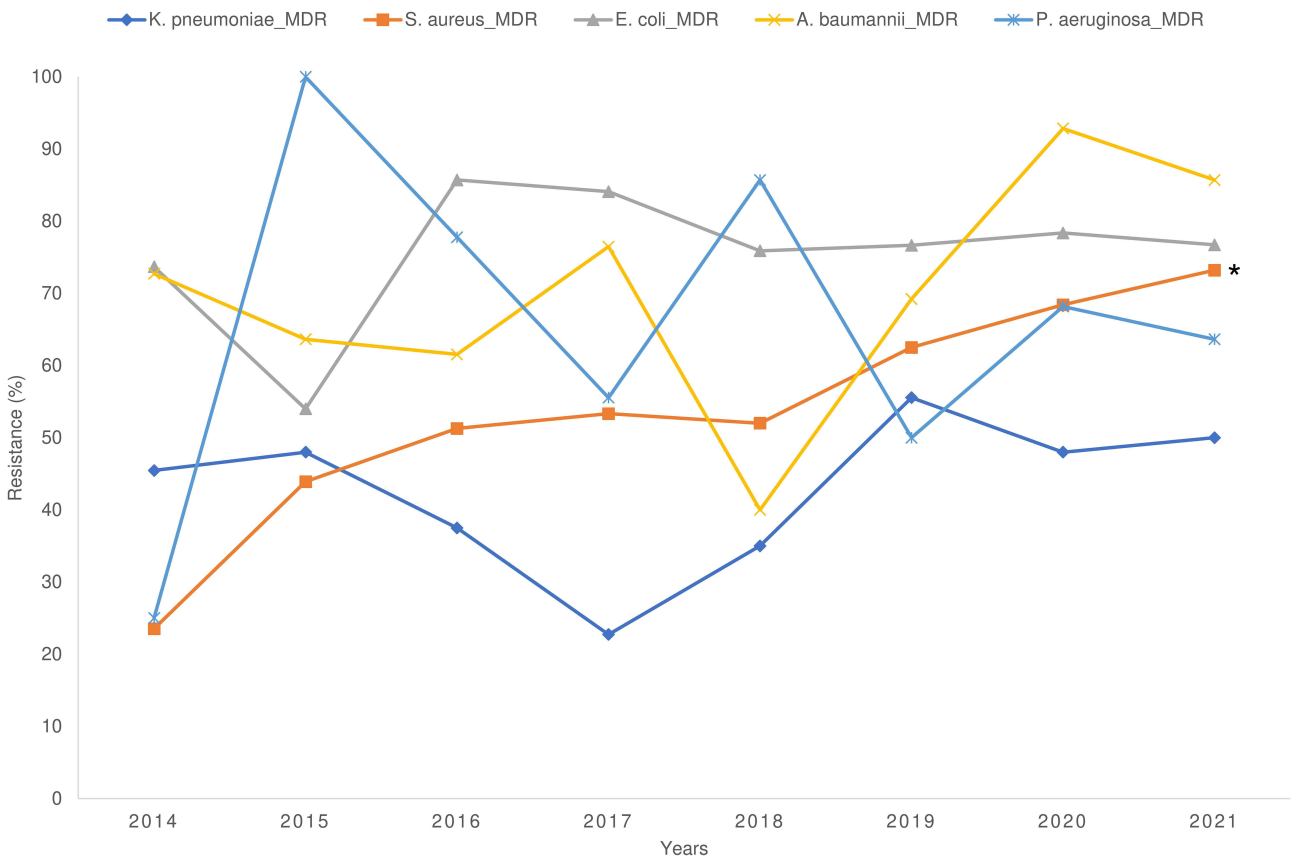


Figure 3 Trend of multidrug-resistance of bloodstream infection-causing common bacterial species. *Upward trend ($Z > 0$; $P < 0.05$). *P* and *Z* values were calculated using the Cochran–Armitage test.

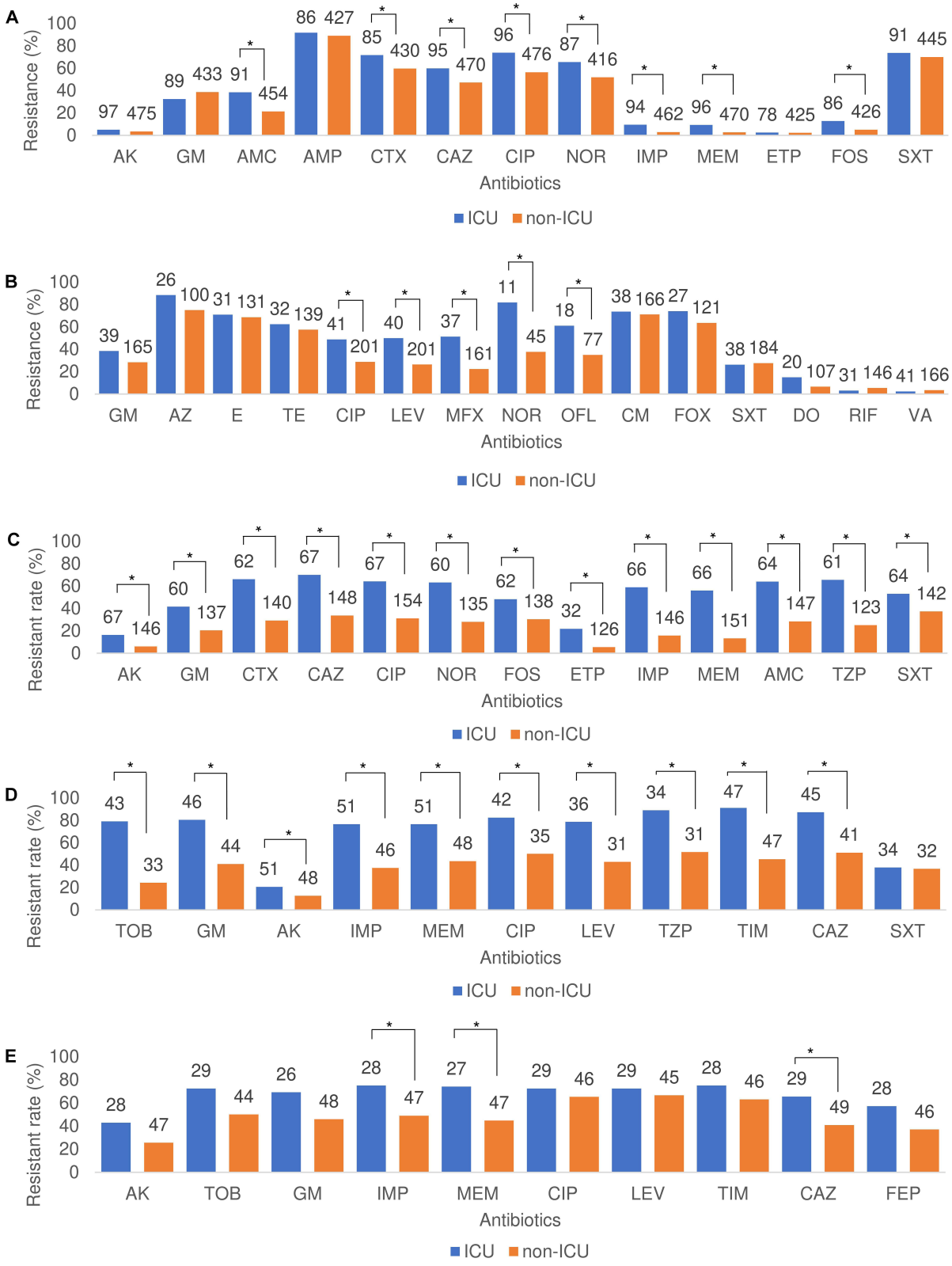


Figure 4 Resistance rate of bacteria to selected antibiotics in terms of hospital wards. (**A**) Antimicrobial resistance rate of *E. coli*. (**B**) Antimicrobial resistance rate of *S. aureus*. (**C**) Antimicrobial resistance rate of *K. pneumoniae*. (**D**) Antimicrobial resistance rate of *A. baumannii*. (**E**) Antimicrobial resistance rate of *P. aeruginosa*; the number on top of each column indicated the tested bacterial strains; *$P < 0.05$ according to the chi-square test.

Table 6 Result of Binomial Logistic Regression Analysis

Outcome	Gender[a]			Age Group (Years Old)[b]						Hospital Ward[c]		
				18–59			≥60			Non-ICU		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
E. coli	0.48	0.39–0.58	< 0.001	3.87	1.17–12.79	0.027	6.58	2.00–21.64	0.02	1.88	1.49–2.39	< 0.001
S. aureus	1.05	0.81–1.36	0.738	0.19	0.10–0.37	< 0.001	0.13	0.07–0.24	< 0.001	1.37	1.02–1.86	0.04
K. pneumoniae	1.38	1.03–1.85	0.031	181,235,180.8	0 - ∞	0.998	183,792,741.4	0 - ∞	0.998	0.86	0.64–1.15	0.307
A. baumannii	1.14	0.76–1.72	0.519	0.9	0.21–3.91	0.892	0.7	0.16–3.02	0.633	0.27	0.19–0.40	< 0.001
P. aeruginosa	1.96	1.14–3.39	0.016	1.32	0.18–9.95	0.785	1.15	0.15–8.63	0.981	0.57	0.36–0.90	0.017

Notes: [a]Reference category = female; [b]Reference category = the 0–17-year age group; [c]Reference category = ICU.
Abbreviation: ACI, Confidence Interval.

Binomial Logistic Regression Analysis

Age, sex, and hospital wards were significant predictors of bacterial pathogens (Table 6). Notably, men were more likely to be infected with *K. pneumoniae* (odds ratio [OR] = 1.38, 95% confidence interval [CI] = 1.03–1.85) and *P. aeruginosa* (OR = 1.96, 95% CI = 1.14–3.39) than women. In contrast, men were less likely to be infected with *E. coli* (OR = 0.48, 95% CI = 0.39–0.58) than women. The risks of infection with *E. coli* in the 18–59-year (OR = 3.87, 95% CI = 1.17–12.79) and ≥60-year (OR = 6.58, 95% CI = 2.00–21.64) age groups were significantly higher than those in the 0–17-year age group. In contrast, the risks of infection with *S. aureus* in the 18–59-year (OR = 0.19, 95% CI = 0.10–0.37) and ≥60-year (OR = 0.13, 95% CI = 0.07–0.24) age groups were lower than those in the 0–17-year age group. The risk of infection with *E. coli* (OR = 1.88, 95% CI = 1.49–2.39) and *S. aureus* (OR = 1.37, 95% CI = 1.02–1.86) among patients in non-ICU wards was significantly higher than that among patients in ICU. However, the risk of infection with *A. baumannii* (OR = 0.27, 95% CI = 0.19–0.40) and *P. aeruginosa* (OR = 0.57, 95% CI = 0.36–0.90) among patients in non-ICU wards was significantly lower than that of patients in ICU.

Discussion

In the present study, the total number of positive blood cultures was 2405 (14.15%). Patients aged ≥60 years accounted for >50% of the total positive cases, and the rate of positive culture in this group was significantly higher than that in the younger age groups (Table 1). These findings were consistent with those of previous studies.[16,17] Gram-negative bacteria (64.12%) were the dominant isolated pathogen group compared to gram-positive bacteria (28.73%) and fungi (7.15%). This finding was consistent with that of the Viet Nam Resistance network (VINARES),[18,19] China Antimicrobial Surveillance Network (CHINET),[20] and Korea Global AMR Surveillance System (Kor-GLASS).[5] However, this finding was different from that of several studies in Europe and Africa, which reported that gram-positive bacteria were the most common BSI-causing pathogen group.[2,8] The present study reported that *E. coli* (26.11%) was the most common BSI-causing pathogen, followed by *S. aureus* (15.79%) and *K. pneumoniae* (10.44%, 251/2405). This finding was similar to that of the VINARES report in 2016–2017 among 13 hospitals for BSI and other bacterial infections, the CHINET report in 2018 among 44 hospitals for BSI, and the Kor-GLASS report in 2017–2019 among 8 hospitals for BSI alone.[4,5,19] However, this finding was different from that of the studies in European and African hospitals, indicating that CoNS and *Salmonella* were the most common BSI-causing pathogens in Italy and the Democratic Republic of the Congo, respectively.[8,9] The variations in geographical and environmental characteristics and expenditure on healthcare may contribute to the differences in the distribution of BSI-causing bacterial pathogens between the present and other studies.[3] Infection with MDR *E. coli* significantly increased the mortality rate among infected patients.[21,22] The present study found that MDR strains accounted for >75% of the total BSI-causing *E. coli* isolates, and this proportion was higher than that in the data on MDR *E. coli* reported by VINARES (29%) (Table 5).[19] Additionally, *E. coli* was the leading cause of BSI for all 8 years. Moreover, the present study found that the proportion of *E. coli* significantly increased over the 8-year period (Table 2). These results revealed that there might be an increase in the number of MDR *E. coli* isolates at our hospital, and the treatment of BSI caused by *E. coli* might be more challenging in the future. Furthermore, the present

study found that the proportion of resistance of *K. pneumoniae* to carbapenem (22.66%, 133/587) was higher than that of other bacteria in the Enterobacteriaceae family (*Enterobacter* spp. [18.26%, 21/115] and *E. coli* [3.51%, 57/1625]) (Table 3). The VINARES report for 2016–2017 indicated that the resistance rates to carbapenems of *K. pneumoniae, Enterobacter* spp., and *E. coli* isolated in blood and cerebrospinal fluid samples were 23%, 26%, and 8%, respectively, which were slightly higher than those reported in our study.[19] In contrast, the data of Kor-GLASS on BSI from 2017 to 2019 indicated that the resistance rates of *K. pneumoniae* and *E. coli* to carbapenems were 1.0%–1.4% and 0.1%–0.2%, respectively, which were much lower than those in our study.[5] A previous study on BSI in Beijing, China, from 2010 to 2018 reported that the resistance rate of *K. pneumoniae* to carbapenems (26.58%) was moderately higher than that in our study, but the resistance rate of *E. coli* to carbapenems (2.58%) was substantially lower than that in our study.[23] Notably, there was an upward trend in meropenem-resistant *K. pneumoniae* isolates from 2018 to 2021 (15.79%–37.84%, $P < 0.05$) (Figure 1). A previous study indicated that the spread of KPC-producing Enterobacteriaceae contributed to the increase in the isolates of carbapenem-resistant bacteria in Vietnam.[24] Moreover, we observed very high resistance rates of *A. baumannii* (59.18%, 116/196) and *P. aeruginosa* to carbapenems (57.05%, 85/149) (Table 3). The resistance rate of BSI-causing *A. baumannii* to carbapenems in our study was lower than that in VINARES, Kor-GLASS, and a study on BSI conducted in Beijing, China, from 2010–2018. However, the resistance rate of *P. aeruginosa* to carbapenems in our study was significantly higher than that in these studies.[5,19,23] The data of our study indicated that the majority of the carbapenem-resistant strains of *E. coli, K. pneumoniae, A. baumannii*, and *P. aeruginosa* were MDR. Furthermore, the proportion of MDR strains of these four gram-negative bacteria and *S. aureus* was tremendously high (Table 5). Infection with carbapenem-resistant and MDR bacteria causes prolonged hospital stays as well as increases the treatment costs and mortality rate.[25,26] Carbapenems are considered the last-choice antibiotics for infections caused by MDR bacteria owing to their wide-spectrum antimicrobial activity and great potential against bacteria.[27] However, with the increase in MDR and carbapenemase-producing bacteria, the treatment of patients infected with these bacteria poses a huge challenge.[36] The proportion of colistin resistance of *E. coli* (11.54%), *A. baumannii* (16.67%), and *P. aeruginosa* (16.33%) in the present study was substantially higher than that in previous studies conducted in China, Korea, and Thailand. Moreover, the resistance rate of *K. pneumoniae* to colistin in the present study (15.38%) was higher than that in studies from China and Korea but slightly lower than that in a study from Thailand.[4,5,28] Colistin—an old bactericidal antibiotic—is one of the last-choice of therapeutics used for the treatment of infection by carbapenem-resistant bacteria.[29] Therefore, the high proportion of carbapenem-resistant bacteria in our study might lead to an increased colistin use and subsequently colistin resistance. It has been reported that genes encoding colistin resistance (*mcr-1* to *mcr-10*), especially *mcr-1*, have been reported to be distributed worldwide in animals, environment, food, and travel.[30–32] Additionally, bacterial strains harboring *mcr-1* have been isolated from clinical specimens, animals, communities, and food in Vietnam.[33,34] Notably, we recently detected *mcr-9*-carrying IncHI2 plasmids in BSI-causing Enterobacteriaceae at our hospital.[35] Thus, the spread of mobile colistin resistance genes may contribute to the high rate of resistance to colistin. The results of our study suggest that developing new antibiotics and suitable therapeutic strategies, including a combination of antibiotics, is necessary for treating MDR and carbapenem-resistant bacteria. Our data revealed that the frequency of MRSA was 65.54%, which was significantly higher than that of the data from CHINET in 2014–2017 (35.3%–44.6%) and Kor-GLASS in 2017–2019 (49.6%) but lower than that of data from VINARES in 2016–2017 (73%).[4,5,19] Furthermore, the resistance rate of MRSA to most tested antibiotics was higher than that of MSSA (Figure 2). However, MRSA remains a serious health concern. Patients infected with MRSA have a longer hospitalization and higher mortality rate than those infected with MSSA. 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.[37,38] Unfortunately, our data revealed that the resistance rates of MRSA to vancomycin and linezolid were 6.67% and 3.08%, respectively; in contrast, no MSSA strain was found to be resistant to vancomycin or linezolid (Figure 2). MRSA, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *A. baumannii*, and carbapenem-resistant *P. aeruginosa* are included in the list of bacteria that pose the greatest threat to global health based on the first report by the World Health Organization in 2017; thus, there is an urgent need for new antibiotics to treat these pathogens.[39] We observed that the proportion of resistance of *E. coli, S. aureus, K. pneumoniae, A. baumannii*, and *P. aeruginosa* isolated from ICU to the most tested antibiotics was substantially higher than that of strains isolated from non-ICU wards (Figure 4). Our finding was similar

to that of the VINARES study conducted in 13 hospitals in Vietnam between 2016 and 2017 and a previous study conducted in Greece between 2018 and 2019.[19,40] Furthermore, the present study found a very high resistance rate of *A. baumannii* and *P. aeruginosa* isolated from ICU. *A. baumannii* isolated from ICU were resistant to 8 out of 10 commonly tested antibiotics (76.47%–91.18%), excluding trimethoprim-sulfamethoxazole (SXT) (37.78%) and amikacin (AK) (20.59%). Meanwhile, *P. aeruginosa* isolated from ICU were resistant to 8 out of 10 commonly tested antibiotics (65.52%–75.0%), excluding cefepime (FEP) (57.14%) and amikacin (AK) (42.86%) (Figure 4D and E). In addition, the results of the binomial logistic regression analysis revealed that *A. baumannii* and *P. aeruginosa* were more likely to cause infections in ICU patients than in non-ICU patients (Table 6). In ICUs, patients usually have a serious condition and underlying diseases. Additionally, in the course of treating such patients, invasive devices and medical equipment, such as mechanical ventilators, are often required. These factors may contribute to the spread of bacterial pathogens, particularly MDR strains.[41,42] The results of our study indicated that the rate of positive blood cultures was significantly higher in patients in ICU than in those in other hospital wards (Table 1).

Conclusions

The present study revealed that *E. coli, S. aureus, K. pneumoniae, A. baumannii*, and *P. aeruginosa* were the leading BSI-causing bacterial species, and there was a significant upward trend for *E. coli, Klebsiella* spp., and *Pseudomonas* spp isolated from BSI. Overall, the AMR rate of BSI-causing bacteria, especially bacterial strains isolated from ICU, was alarmingly high. Although the resistance rates to amikacin and colistin were relatively high among the most common BSI-causing gram-negative bacteria, these agents are still considered the best choice for the treatment of BSI caused by gram-negative bacteria. Similarly, Enterobacteriaceae were relatively highly carbapenem-resistant. Nevertheless, carbapenems remain an effective therapeutic option for the treatment of BSI caused by Enterobacteriaceae. Glycopeptides, quinupristin-dalfopristin, and linezolid are the most effective antibiotics used to treat BSI caused by *S. aureus*. Our results indicate the need for new antibiotics, therapeutic strategies, as well as prevention and control measures to combat BSI and AMR.

Abbreviations

AK, Amikacin; GM, Gentamicin; AMC, Amoxicillin-clavulanate; AMP, Ampicillin; CTX, Cefotaxime; CAZ, Ceftazidime; CIP, Ciprofloxacin; NOR, Norfloxacin; IMP, Imipenem; MEM, Meropenem; ETP, Ertapenem; FOS, Fosfomycin; SXT, Trimethoprim-sulfamethoxazole; AZ, Azithromycin; E, Erythromycin; TE, Tetracycline; LEV, Levofloxacin; MFX, Moxifloxacin; OFL, Ofloxacin; CM, Clindamycin; FOX, Cefoxitin; DO, Doxycycline; RIF, Rifampicin; VA, Vancomycin; TZP, Piperacillin-tazobactam; TOB, Tobramycin; TIM, Ticarcillin-clavulanate; FEP, Cefepime.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Military Hospital 103, Hanoi, Vietnam (Approval No. 35/CNChT-HĐĐĐ). All patient data were anonymized before performing the analysis.

Acknowledgments

We would like to thank the staff of the Microbiology Department, Military Hospital 103, for their contributions.

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.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no competing interests in this work.

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