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Article

Sixteen-Year Trends in Antimicrobial Resistance among Enterobacteriaceae Causing Bloodstream Infections in a Tertiary Teaching Hospital in Iran: A Joinpoint Regression Analysis

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Abstract

Background: Bloodstream infections caused by Enterobacteriaceae are an important global health concern, particularly in the context of increasing antimicrobial resistance. Long-term surveillance is essential in regions where systematic longitudinal data are limited. This study investigated 16-year trends in antimicrobial resistance among Enterobacteriaceae causing BSIs in a tertiary referral setting in southern Iran. **Methods:** We retrospectively analyzed non-duplicate Enterobacteriaceae blood-culture isolates collected from March 2010 through December 2025 at the Professor Alborzi Clinical Microbiology Research Center, affiliated with Shiraz University of Medical Sciences. Species identification and antimicrobial susceptibility testing were performed using conventional microbiological methods according to CLSI criteria applicable to each study year. Resistance data were analyzed using WHONET 5.6. Temporal trends were evaluated using Joinpoint regression analysis, to identify significant changes in resistance trajectories. **Results:** Among 3,860 isolates,

Escherichia coli (38.1%), *Klebsiella* spp. (30.0%), and *Enterobacter* spp. (19.0%) were predominant. Overall resistance was highest to ampicillin (93.1%), followed by amoxicillin–clavulanic acid (80.7%), tetracycline (73.8%), cefuroxime (71.3%), and third-generation cephalosporins (64.1%). Extended-spectrum β-lactamase production was detected in 64.0% of isolates. Carbapenem resistance was 25.6% overall and reached 44.7% in 2025. Joinpoint analysis demonstrated significant changes in species distribution, including a decline in *E. coli* from 2010 to 2020 (APC −6.14%, P = 0.01), an increase in *Klebsiella* spp. from 2010 to 2016 (APC 9.68%, P = 0.01), and a subsequent increase from 2019 to 2025 (APC 10.50%, P = 0.02). Species-specific resistance trends included significant increases in resistance to multiple agents among *Klebsiella* spp., a significant increase in imipenem resistance among *Enterobacter* spp., and an increasing trend in cefuroxime resistance across Enterobacteriaceae. In contrast, resistance to trimethoprim–sulfamethoxazole, tobramycin, gentamicin, and chloramphenicol declined significantly among *E. coli*. **Conclusions:** Enterobacteriaceae causing BSIs showed persistently high resistance to commonly used antimicrobials, particularly β-lactams, accompanied by a high prevalence of ESBL production and increasing carbapenem resistance. Joinpoint regression identified heterogeneous temporal patterns across species and antimicrobial agents that may not be evident from overall resistance estimates alone. Sustained microbiological surveillance and strengthened antimicrobial stewardship are warranted to monitor evolving resistance and inform empirical treatment strategies.

Key words: Bloodstream infections; Antimicrobial resistance; Enterobacteriaceae; Joinpoint regression; Temporal trends; ESBL; Carbapenem resistance; Iran.

Introduction

Antimicrobial resistance (AMR) in bloodstream infections (BSIs) has emerged as a major global public health concern, significantly limiting treatment options and increasing morbidity and mortality [1, 2]. AMR is highly prevalent among hospitalized patients (36.5%) and is associated with a higher risk of mortality (adjusted RR = 1.58; 95% CI: 1.33–1.87) [3].

Gram-negative bacteria are major contributors to BSIs worldwide, with *E. coli* alone accounting for 44.9% of cases in 2023 [4].

The Infectious Diseases Society of America (IDSA) highlights multidrug-resistant Gram-negative bacteria as a major therapeutic challenge due to limited treatment options and widespread AMR [5]. As resistance continues to grow, many commonly used antibiotics are becoming less effective, posing a serious threat to patient outcomes [6-8].

Enterobacteriaceae, including *E. coli, Klebsiella* spp., and *Enterobacter* spp., are a major group of Gram-negative bacteria and important causes of BSIs [6]. They account for a substantial proportion of BSI cases worldwide [9], with their clinical impact further amplified by their ability to develop diverse AMR mechanisms. In the 2024 World Health Organization (WHO) Bacterial Priority Pathogens List, third-generation cephalosporin-resistant Enterobacteriaceae (3GCRE) and carbapenem-resistant Enterobacteriaceae (CRE) are classified as critical-priority pathogens, reflecting their major public health impact and limited treatment options [10]. The increasing prevalence of extended-spectrum β-lactamase (ESBL) production and other resistance mechanisms further complicates the management of BSIs and is associated with prolonged hospitalization and increased mortality [11,12].

Effective AMR surveillance is essential for guiding empirical antibiotic selection, developing local treatment guidelines, and strengthening infection control strategies [13]. Continuous and systematic surveillance at regional, national, and global levels is therefore crucial for monitoring resistance trends and informing appropriate clinical and public health responses [14]. Monitoring changes in AMR over time requires reliable trend analysis methods, such as Joinpoint regression [15]. This method can identify significant changes in resistance trends and pinpoint periods of increasing or decreasing resistance [16].

This approach can provide early warning of emerging resistance threats, clarify the long-term epidemiological patterns of resistant pathogens, and support evidence-based clinical practice. In the context of BSIs, effective surveillance is particularly important, as timely and accurate data can guide therapeutic decisions and help reduce the burden of antimicrobial-resistant infections [17].

In developing countries such as Iran, studies evaluating long-term trends in AMR among BSI pathogens, particularly within the Enterobacteriaceae family, remain limited [18]. This gap

highlights the need for updated, region-specific data to inform clinical and public health decision-making. Therefore, this study aims to investigate AMR patterns among Enterobacteriaceae isolates recovered from BSIs in a tertiary teaching hospital in Iran and to assess 16-year resistance trends using Joinpoint regression analysis.

Material and Methods:

Study design

This study included non-duplicate Enterobacteriaceae isolates from blood cultures during the 16-year period from March 2010 to December 2025 at the Professor Alborzi Clinical Microbiology Research Center (PACMRC), affiliated with Shiraz University of Medical Sciences and located at Namazee Teaching Hospital in Shiraz, Iran. Most isolates were obtained from Namazee Hospital (73%, n = 2,086), followed by other teaching hospitals in Shiraz (7%; Amir, Dastghaib, and Hafez Hospitals) and five non-teaching hospitals (3%; Markazi, Ghadir, Ordibehesht, Dena, and Alzahra Hospitals). The remaining 621 isolates (17%) originated from other teaching and non-teaching hospitals or had no documented referring hospital. Blood cultures yielding fungi or selected skin flora were excluded. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, and informed consent was waived because the study used routinely collected laboratory data.

Identification and confirmation of the isolated bacteria

Bacterial isolates were identified using standard biochemical methods, including oxidase testing, assessment of pigment production and growth at different temperatures, and culture on MacConkey agar. Species identification was further confirmed using two miniaturized biochemical identification systems, API and Microgen. For analysis, isolates were categorized into *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and other Enterobacteriaceae. The latter were analyzed as a single group because of their low annual numbers.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed using the disk diffusion method against 19 antimicrobial agents: amikacin (30 µg), aztreonam (30 µg), cefepime (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), ceftriaxone (30 µg), ciprofloxacin (5 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), colistin (10 µg), gentamicin (10 µg), imipenem (10 µg), meropenem (10 µg), piperacillin-tazobactam (100/10 µg), tetracycline (30 µg), ampicillin (10 µg), amoxicillin-clavulanic acid (20 µg), cefuroxime (30 µg), chloramphenicol (30 µg), and tobramycin (10 µg). Testing was performed on cation-adjusted Mueller–Hinton agar (Merck, Germany), and susceptibility results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The CLSI edition applicable to each study year (2010–2025) was used for interpretation. ESBL production was assessed by the disk diffusion method using cefotaxime (30 µg), cefotaxime-clavulanic acid (30/10 µg), ceftazidime (30 µg), and ceftazidime-clavulanic acid (30/10 µg) disks, in accordance with CLSI recommendations.(19) In accordance with the 2024 WHO Bacterial Priority Pathogens List, critical-priority resistance categories included carbapenem-resistant Enterobacteriaceae (CRE) and third-generation cephalosporin-resistant Enterobacteriaceae (3GCRE) [10]. CRE were defined as isolates resistant to at least one tested carbapenem (imipenem or meropenem), while 3GCRE were defined as isolates resistant to at least one of the tested third-generation cephalosporin (ceftriaxone, ceftazidime, or cefotaxime), based on the CLSI interpretive criteria applicable to each study year [19].

Statistical analysis

For the analysis, intermediate and resistant isolates were combined and classified as non-susceptible when calculating AMR rates. Data from 2010 to 2025 were analyzed annually using WHONET version 5.6. [20]. To avoid duplicate isolates, only the first isolate recovered from each patient was included. Results were reported as absolute numbers and percentages. The primary objective was to assess temporal trends in antimicrobial resistance among Enterobacteriaceae causing bloodstream infections over the 16-year study period.

For trend analysis, annual AMR data were retrieved from the corresponding yearly databases. Joinpoint Regression Program version 4.9 (National Cancer Institute, Calverton, MD, USA) was used to identify significant changes in temporal resistance trends [21]. A linear model was applied, with a minimum interval of 12 months between joinpoints.

For descriptive interpretation, resistance rates were categorized as low (<20%), moderate (20–50%), or high (>50%) [22].

Results:

Description of Clinical Isolates

A total of 3,860 Enterobacteriaceae isolates were isolated from blood cultures between March 2010 and December 2025. The annual distribution of Enterobacteriaceae isolates is presented in Table 1. The most frequently isolated organisms were *Escherichia coli* (1,471; 38.1%), followed by *Klebsiella* spp. (1,158; 30.0%) and *Enterobacter* spp. (734; 19.0%). The remaining 497 (12.9%) isolates comprised *Serratia* spp. (232; 6.0%), *Salmonella* spp. (101; 2.6%), *Citrobacter* spp. (104; 2.7%), *Proteus* spp. (30; 0.8%), *Morganella* spp. (19; 0.5%), and *Pantoea* spp. (11; 0.3%). Regarding patient sex, 2,082 (53.9%) isolates were from male patients, 1,569 (40.6%) from female patients, and 209 (5.5%) from patients with unknown sex. The annual trend in Frequency of Enterobacteriaceae Pathogens by Years are presented in Figure 1.

Table 1. Annual distribution of Enterobacteriaceae organisms causing blood-stream infections

Year	*E. coli* (n, %)	*Klebsiella* spp. (n, %)	*Enterobacter* spp. (n, %)	Other *Enterobacteriaceae* (n, %)	Total Enterobacteriacea (n)
2010	86 (45)	39 (20.4)	14 (7.3)	52 (27.3)	191
2011	17 (63)	6 (22.2)	1 (3.7)	3 (11.1)	27
2012	92 (55.1)	35 (21)	14 (8.4)	26 (15.6)	167
2013	109 (50.5)	69 (31.9)	14 (6.5)	24 (11.1)	216
2014	114 (44.5)	69 (27)	38 (14.8)	35 (13.7)	256
2015	91 (42)	58 (26.7)	30 (13.8)	38 (17.5)	217
2016	78 (39.2)	79 (39.7)	25 (12.6)	17 (8.5)	199
2017	94 (44.3)	62 (29.2)	26 (12.3)	30 (14.2)	212
2018	100 (44.8)	63 (28.3)	33 (14.8)	27 (12.1)	223
2019	100 (27.9)	85 (23.7)	108 (30)	66 (18.4)	359
2020	104 (26.7)	104 (26.7)	145 (37.1)	37 (9.5)	390
2021	122 (33.8)	99 (27.4)	113 (31.3)	27 (7.5)	361
2022	96 (33.1)	80 (27.6)	86 (29.6)	28 (9.7)	290

Year	*E. coli* (n, %)	*Klebsiella* spp. (n, %)	*Enterobacter* spp. (n, %)	Other *Enterobacteriaceae* (n, %)	Total Enterobacteriacea (n)
2023	83 (33.1)	110 (43.8)	24 (9.6)	34 (13.5)	251
2024	122 (35.8)	131 (38.4)	48 (14.1)	40 (11.7)	341
2025	63 (39.4)	69 (43.1)	15 (9.4)	13 (8.1)	160
Total	1471 (38.1)	1158 (30.0)	734 (19.0)	497 (12.9)	3860

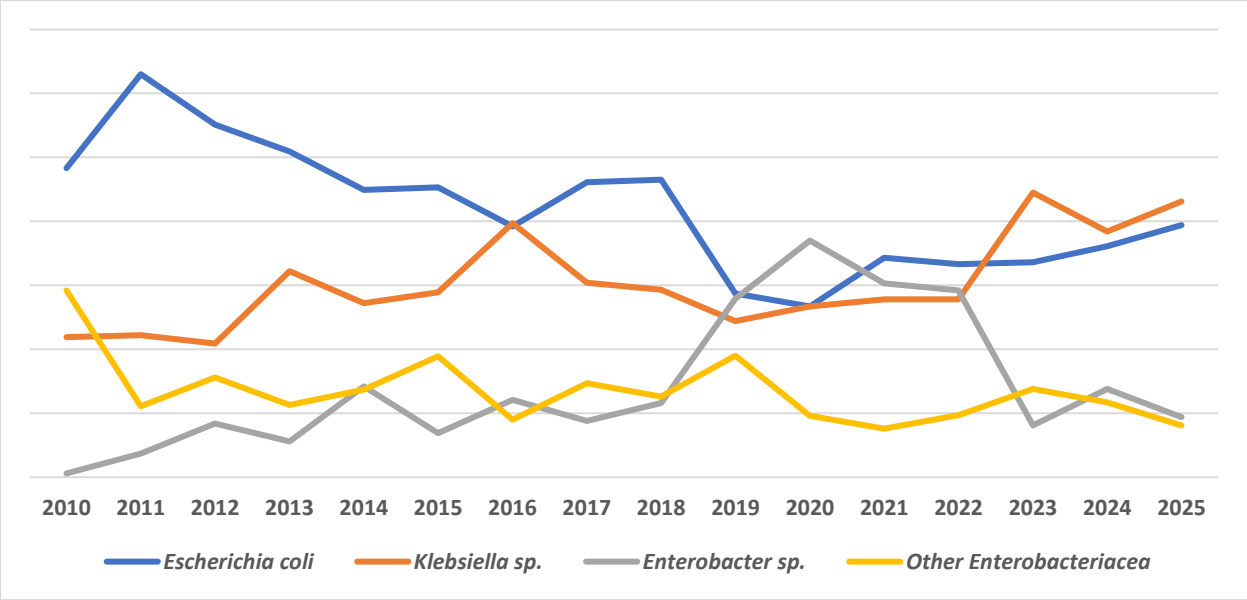


Figure 1: Annual trend in Frequency of Enterobacteriaceae Pathogens by Years; [a]

[a] Values are presented as (%).

Trend analysis of Enterobacteriaceae distribution

Trend analysis revealed the four distinct temporal patterns across the Enterobacteriaceae species over the study period. In the first pattern, *Escherichia coli* showed a significant decreasing trend during the earlier years of the study (2010-2020), followed by a non-significant increasing trend during the later period (2020–2025). In the second pattern, *Klebsiella* spp. demonstrated a significant increasing trend during the initial phase (2010-2016), followed by a non-significant

decreasing trend (2016-2019), and subsequently showed another significant increasing trend toward the end of the study period (2019-2025). In the third pattern, *Enterobacter* spp. showed a marked and significant increase during the early years (2010-2012); however, no significant trends were observed during the subsequent periods (2012–2021 and 2021–2025). In the fourth pattern, other Enterobacteriaceae exhibited a non-significant decreasing trend throughout the study period. Trends in the distribution of Enterobacteriaceae species are presented in Table S1 in the supplementary Data.

Antimicrobial resistance rates of pathogenic isolates

Antimicrobial resistance rates of *Escherichia coli* isolates

A total of 1,471 *Escherichia coli* isolates isolated from blood cultures between 2010 and 2025 were included in the analysis. Overall, *E. coli* isolates exhibited high resistance rates to several commonly used antibiotics. Resistance to ampicillin and tetracycline remained consistently high throughout the study period, with overall resistance rates of 91.3% and 74.0% respectively. High resistance was also observed for amoxicillin–clavulanic acid (77.1%) and trimethoprim–sulfamethoxazole (72.1%). Resistance to third-generation cephalosporins was high, with overall resistance rates of 64.5% for cefotaxime and 63.4% for ceftriaxone. Ciprofloxacin resistance was also high, with an overall rate of 61.0%. Consistently high resistance to third-generation cephalosporins (3GCR) was observed (69.6%). ESBL production was detected in 69.4% of isolates. Aminoglycosides demonstrated comparatively low to moderate resistance, with overall rates of 28.3% for gentamycin and 9.6% for amikacin. In contrast, resistance to carbapenems remained low for most years. The overall resistance rates were 8.3% for meropenem and 5.7% for imipenem. Overall carbapenem resistance was low (10.6%). The lowest resistance rates were observed for colistin, which remained below 4% throughout the study period. The annual resistance rates to commonly used antibiotics among *Escherichia coli* isolates are presented in Table 2.

Table 2. Annual Anti-Microbial Resistance for *Escherichia coli* isolates of BSI

Antibiotic name	Year (Number)																
	Total (1471)	2010 (86)	2011 (17)	2012 (92)	2013 (109)	2014 (114)	2015 (91)	2016 (78)	2017 (94)	2018 (100)	2019 (100)	2020 (104)	2021 (122)	2022 (96)	2023 (83)	2024 (122)	2025 (63)

AMP	91.3	90.7	94.1	92.8	93.6	95.6	90.0	89.2	92.0	91.7	91.9	91.1	89.4	95.7	87.9	88.5	88.7
AMC	77.1	80.0	88.2	85.9	84.9	93.8	80.9	80.8	84.1	84.7	69.7	77.1	74.4	85.4	64.2	55.0	46.8
TCY	74.0	86.3	82.4	73.6	83.0	71.2	81.6	82.9	83.1	68.7	72.2	67.7	68.6	81.3	63.8	60.3	74.6
SXT	72.1	NT	NT	77.1	72.0	83.6	81.1	84.4	78.9	68.0	63.2	68.7	67.8	70.2	69.5	63.3	66.7
CXM	71.4	70.2	76.5	64.1	66.0	77.4	74.1	77.6	78.9	67.3	69.4	75.5	66.4	80.2	67.1	71.8	79.0
CTX	64.5	51.9	NT	62.0	61.3	65.5	70.1	77.0	67.4	64.3	64.9	60.2	58.2	80.2	61.0	63.3	69.8
CRO	63.4	59.5	66.7	60.9	64.4	64.0	67.8	73.1	64.8	61.0	64.6	60.0	56.2	74.0	59.8	62.0	61.9
CIP	61.0	51.2	52.9	51.6	54.8	63.4	71.9	68.0	67.4	60.2	54.5	61.0	59.9	72.7	59.7	59.0	66.7
FEP	58.1	51.2	41.2	38.4	45.3	55.0	65.9	67.6	59.5	62.1	71.7	57.1	54.6	71.6	60.3	58.8	58.1
CAZ	56.7	58.3	58.8	54.4	48.5	61.3	66.3	70.7	64.1	59.4	58.8	51.0	54.9	62.7	52.5	47.1	41.0
ATM	56.4	59.3	43.8	55.4	50.5	61.1	66.7	72.0	64.5	56.6	55.6	48.5	47.5	58.1	60.2	51.3	46.8
TOB	38.8	53.8	43.8	52.3	61.0	35.1	46.1	34.2	35.2	33.3	31.6	28.7	32.5	43.7	31.7	32.2	34.9
CHL	35.1	34.1	58.8	46.7	38.5	34.8	43.7	42.7	54.9	30.2	22.2	35.0	37.7	30.8	18.8	23.0	33.3
GM	28.3	33.7	29.4	32.6	47.5	23.7	26.7	29.5	28.3	32.3	26.0	22.5	23.8	35.4	18.5	22.1	22.2
TZP	15.9	16.7	0	12.0	8.5	12.4	28.4	15.6	29.7	19.2	21.0	5.9	10.9	12.5	6.2	20.5	27.9
AN	9.6	4.8	0	12.0	5.7	12.3	14.8	15.8	20.7	21.2	8.2	2.0	8.2	5.3	9.7	3.3	4.8
MEM	8.3	1.2	11.8	18.7	0.9	4.4	5.6	5.1	12.9	2.0	9.1	17.0	11.5	6.3	2.4	4.9	9.5
IMP	5.7	1.2	0	1.1	0	2.6	2.2	5.2	9.8	0	6.1	6.0	5.0	5.3	1.2	4.9	27
CS	1.4	NT	NT	4.2	1.0	0	1.1	0	0	1.0	1.0	1.0	2.5	2.1	2.4	2.6	3.2
ESBL	69.4	NT	NT	NT	NT	64.3	71.6	73.0	74.4	71.4	68.4	60.2	59.8	79.6	65.8	64.4	71.2
CR	10.6	2.3	11.8	19.6	1.8	5.3	6.6	5.1	15.9	2.0	14.0	19.2	11.5	9.4	2.4	6.0	6.3
3GCR	69.6	77.9	100	68.5	69.7	66.7	72.5	78.2	73.4	66	67	65.4	59.8	80.2	65.1	65.6	69.8

Abbreviations: NT, not tested; AMP, ampicillin; AMC, amoxicillin/clavulanic acid; TCY, tetracycline; SXT, trimethoprim/sulfamethoxazole; CXM, cefuroxime; CTX, cefotaxime; CRO, ceftriaxone; CIP, ciprofloxacin; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; TOB, tobramycin; CHL, chloramphenicol; GM, gentamicin; TZP, piperacillin/tazobactam; AN, amikacin; MEM, meropenem; IMP, imipenem; CS, colistin; ESBL, extended spectrum Beta-Lactamases, CR, carbapenem resistance; 3GCR, third generation cephalosporin resistance. In these tables, stable patterns are indicated in yellow, decreasing trends in green, and increasing trends in orange color.

Antimicrobial resistance trends of *Klebsiella* spp. isolates from blood cultures

A total of 1,158 *Klebsiella* spp. isolates were recovered from blood cultures between March 2010 and December 2025. Overall, *Klebsiella* isolates exhibited high resistance rates to several antimicrobial agents, particularly β-lactams. Ampicillin resistance was nearly universal throughout the study period (99.7%). Resistance to amoxicillin–clavulanic acid was also high

(81.5%), with considerable year-to-year variation. Overall, *Klebsiella* isolates exhibited high resistance rates to several antimicrobial agents, particularly β-lactams. High overall resistance rates were observed for tetracycline (73.0%), cefuroxime (72.2%), cefotaxime (65.4%), and ceftriaxone (64.4%). Third-generation cephalosporin resistance (3GCR) was widespread, with an overall resistance rate of 68.9%. Although 3GCR fluctuated substantially across individual years, it increased to 82.6% in 2025. ESBL production was detected in 69.5% of isolates overall and showed considerable temporal variation, reaching 83.3% in 2025. Fluoroquinolone resistance was also considerable, with an overall ciprofloxacin resistance rate of 53.9%, increasing from 25.6% in 2010 to 80.9% in 2025. Resistance to aminoglycosides was moderate, with overall resistance rates of 43.8% for gentamycin and 44.2% for amikacin. Carbapenem resistance showed a marked increase over the study period. Overall resistance rates were 44.4% for meropenem and 39.9% for imipenem, increasing from 2.6% for both agents in 2010 to 78.3% and 75.4%, respectively, in 2025. Overall carbapenem resistance (CR) was 46.9%, increasing from 5.1% in 2010 to 75.4% in 2025. Colistin had the lowest overall resistance rate among the tested antimicrobials (10.6%). Resistance remained below 12% through 2023 but increased sharply to 27.8% in 2024 and 28.1% in 2025. The annual resistance rates of commonly used antibiotics among *Klebsiella* spp. isolates are presented in Table 3.

Table 3. Annual Anti-Microbial Resistance for *Klebsiella* sp. isolates of BSI

Antibiotic name	Year (Number)																
	Total (1158)	2010 (39)	2011 (6)	2012 (35)	2013 (69)	2014 (69)	2015 (58)	2016 (79)	2017 (62)	2018 (63)	2019 (85)	2020 (104)	2021 (99)	2022 (80)	2023 (110)	2024 (131)	2025 (69)
AMP	99.7	100	100	96.9	98.6	98.5	100	100	100	100	100	100	100	100	100	100	100.0
AMC	81.5	84.2	83.3	70.6	89.9	91.2	80.7	84.8	78.0	82.3	77.1	84.0	80.6	88.6	78.2	74.6	81.2
TCY	73.0	81.1	100	64.7	60.9	71.0	70.2	74.7	66.7	59.0	68.3	72.3	76.3	81.0	77.9	71.8	89.9
CXM	72.2	68.4	66.7	50.0	63.8	62.7	63.0	77.3	70.3	65.6	67.5	NT	71.1	80.5	78.7	78.0	85.5
CTX	65.4	60.0	NT	50.0	47.8	59.4	54.4	74.7	66.1	61.3	56.6	66.7	56.3	73.4	75.0	73.1	82.6
SXT	64.9	NT	NT	82.4	48.4	80.9	50.9	80.8	72.1	51.6	41.0	60.8	53.8	68.8	78.5	70.0	69.1
FEP	64.8	47.2	66.7	40.0	44.8	50.7	52.6	71.6	59.3	58.1	75.0	68.6	58.8	73.4	73.1	73.1	82.6
CRO	64.4	51.4	80.0	50.0	49.3	56.5	54.5	72.7	62.3	61.9	56.6	67.0	52.6	75.0	74.5	71.5	82.6
CAZ	64	46.2	66.7	50.0	45.6	59.4	57.9	79.7	61.7	58.7	57.8	67.6	56.1	69.6	73.1	73.3	72.5
ATM	62.9	46.9	66.7	50.0	45.6	55.2	56.1	76.9	58.3	61.3	51.8	66.0	50.0	69.2	75.2	71.5	82.6

TOB	58.2	54.3	83.3	45.5	48.4	50.8	54.4	65.8	60.0	52.5	41.0	55.3	45.9	65.8	72.2	66.4	76.5
CIP	53.9	25.6	50.0	32.4	34.8	46.3	42.9	62.0	58.3	41.3	37.3	60.5	48.0	62.5	66.4	66.2	80.9
TZP	50	12.8	16.7	23.5	23.5	33.3	33.3	54.4	59.0	50.0	52.5	51.5	37.9	57.0	60.4	71.3	79.1
MEM	44.4	2.6	0	35.3	19.1	29.4	12.5	44.3	52.5	32.8	39.0	46.5	35.4	55.0	58.7	66.4	78.3
CHL	46.7	31.6	66.7	35.3	32.8	43.8	32.1	54.4	58.3	36.1	25.3	43.0	44.8	52.6	51.4	55.7	79.7
GM	43.8	39.5	66.7	33.3	36.9	34.8	40.4	53.9	50.0	39.7	37.3	50.5	42.3	55.7	42.7	46.6	39.1
AN	44.2	33.3	50.0	14.7	38.2	36.2	43.9	41.8	46.7	48.4	34.6	33.3	33.7	41.3	61.5	63.1	58.0
IPM	39.9	2.6	0	8.8	14.5	20.3	14.3	42.1	46.8	27.0	40.2	37.9	29.5	55.0	56.0	62.0	75.4
CS	10.6	NT	0	8.3	1.5	11.8	0	1.3	6.5	8.3	9.6	7.7	3.1	11.4	11.3	27.8	28.1
ESBL	69.5	NT	NT	60.9	NT	56.8	61.8	75.8	72.7	73.9	54.7	68.6	55.6	73.3	74.8	77.8	83.3
CR	46.9	5.1	0.0	37.1	20.3	39.1	19.0	46.8	54.8	34.9	44.7	48.1	38.4	57.5	59.1	67.2	75.4
3GCR	68.9	74.3	100	51.4	50.7	71.0	60.3	79.7	66.1	61.9	60.0	71.1	59.6	75.0	75.4	75.6	82.6

Abbreviations: NT, not tested; AMP, ampicillin; AMC, amoxicillin/clavulanic acid; TCY, tetracycline; CXM, cefuroxime; CTX, cefotaxime; SXT, trimethoprim/sulfamethoxazole; FEP, cefepime; CRO, ceftriaxone; CAZ, ceftazidime; ATM, aztreonam; TOB, tobramycin; CIP, ciprofloxacin; TZP, piperacillin/tazobactam; MEM, meropenem; CHL, chloramphenicol; GM, gentamicin; AN, amikacin; IMP, imipenem; CS, colistin; ESBL, extended spectrum Beta-Lactamases, CR, carbapenem resistance; 3GCR, third generation cephalosporin resistance. In these tables, stable patterns are indicated in yellow, decreasing trends in green, and increasing trends in orange color.

Antimicrobial resistance trends of *Enterobacter* spp. isolates from blood cultures

A total of 734 *Enterobacter* spp. isolates were recovered from blood cultures between March 2010 and December 2025. Overall, *Enterobacter* spp. isolates demonstrated high resistance to β-lactam antibiotics, particularly ampicillin and amoxicillin–clavulanic acid, with overall resistance rates of 99.6% and 96.9%, respectively. Resistance to tetracycline was also high (76.0%), with substantial year-to-year fluctuations and lower resistance in the final years. Resistance to cephalosporins was generally high, with overall resistance rates of 70.7% for cefuroxime, 51.0% for ceftriaxone, 50.2% for cefotaxime, and 47.4% for ceftazidime. Third-generation cephalosporin resistance (3GCR) was common, with an overall resistance rate of 50.1%, showing substantial year-to-year fluctuations and declining to 8.3% in 2024. ESBL production was detected in 54.8% of isolates overall, with marked fluctuations over time and a peak prevalence of 81.5% in 2015. Aztreonam resistance showed a similar pattern, with an

overall resistance rate of 47.4%. Fluoroquinolone and aminoglycoside resistance ranged from low to moderate. The overall resistance rate to ciprofloxacin was 33.9%, while resistance rates to gentamycin and amikacin were 40.1% and 16.2%, respectively. Carbapenem resistance was generally low to moderate, with overall resistance rates of 19.4% for meropenem and 17.0% for imipenem. Overall carbapenem resistance was 25.4%, with substantial year-to-year fluctuations. Colistin resistance remained low overall (2.9%) but showed a gradual increase in the final years of the study, reaching 13.3% in 2025. The annual resistance rates of commonly used antibiotics among *Enterobacter* spp. isolates are presented in Table 4.

Table 4. Annual Anti-Microbial Resistance for *Enterobacter* spp. isolates of BSI

Antibiotic name	Year (Number)																
	Total (734)	2010 (14)	2011 (1)	2012 (14)	2013 (14)	2014 (38)	2015 (30)	2016 (25)	2017 (26)	2018 (33)	2019 (108)	2020 (145)	2021 (113)	2022 (86)	2023 (24)	2024 (48)	2025 (15)
AMP	99.6	100	NT	100	100	100	100	100	95.7	100	100	98.6	100	100	100	100	100
AMC	96.9	100	NT	92.9	100	97.3	100	92.0	95.5	93.3	100	95.0	97.3	98.8	95.5	95.7	92.9
TCY	76.0	66.7	NT	85.7	85.7	60.5	96.6	82.6	76.0	58.1	92.2	63.8	90.9	89.3	66.7	45.8	20.0
CXM	70.7	42.9	NT	85.7	69.2	54.5	77.8	52.0	76.5	57.6	79.6	69.4	84.8	90.4	70.0	23.4	42.9
FEP	51.4	23.1	NT	30.8	33.3	25.7	83.3	34.8	33.3	27.3	73.7	54.7	67.0	67.9	14.3	12.8	13.3
CRO	51.0	38.5	NT	57.1	50	42.1	79.3	25.0	32.0	28.1	64.6	47.1	69.4	73.8	23.8	8.3	13.3
CTX	50.2	NT	NT	50.0	41.7	52.6	76.7	30.4	34.6	31.3	61.8	41.7	69.1	75.0	21.7	6.3	13.3
CAZ	47.4	30.8	NT	42.9	42.9	45.9	80.0	32.0	30.8	31.3	56.7	38.4	69.9	68.2	17.4	6.3	14.3
ATM	47.4	33.3	NT	35.7	50.0	38.9	79.3	52.0	26.9	32.3	58.6	37.3	65.1	65.9	39.1	8.5	13.3
CHL	45.8	35.7	NT	64.3	18.2	67.6	73.3	68.0	50.0	43.8	76.2	31.2	49.1	31.8	22.7	16.7	26.7
TOB	44.5	NT	NT	57.1	64.3	45.9	80.0	24.0	16.0	12.9	54.3	37.4	58.2	62.4	36.4	17.0	0.0
SXT	43.0	NT	NT	NT	23.1	42.1	73.3	50.0	52.0	37.5	57.3	32.6	54.1	42.2	36.4	12.5	6.7
GM	40.1	28.6	NT	35.7	35.7	37.1	70.0	20.8	16.7	9.7	54.9	35.9	55.9	58.1	17.4	8.5	0.0
CIP	33.9	14.3	NT	7.1	15.4	14.3	46.7	4.2	16	25.8	55.9	37.8	57.7	31.0	13.6	4.2	0.0
TZP	25.0	15.4	NT	15.4	23.1	13.5	40.0	25.0	24.0	25.0	34.3	23.0	33.0	26.7	18.2	6.4	0.0
MEM	19.4	7.1	NT	42.9	7.7	18.4	10.0	8.0	16.0	15.6	19.2	23.4	33.6	14.0	20.8	6.3	0.0
IPM	17.0	0.0	NT	7.1	0.0	18.4	6.9	4.0	7.7	18.8	23.8	16.4	29.5	14.0	25.0	4.2	0.0
AN	16.2	23.1	NT	30.8	23.1	28.9	53.3	25.0	8.3	15.6	19.4	7.7	16.1	15.1	8.3	6.3	0.0
CS	2.9	NT	NT	NT	8.3	8.3	0.0	4.3	4.0	3.0	1.0	0.0	0.9	4.7	4.3	7.1	13.3
ESBL	54.8	NT	NT	NT	NT	40.6	81.5	45.0	66.7	50.0	61.6	43.9	71.8	71.8	26.7	13.5	15.4
C R	25.4	7.1	NT	42.8	14.3	36.8	13.3	8.0	26.9	24.2	30.5	26.9	36.3	17.4	33.3	6.2	0.0
3GCR	50.1	92.8	NT	78.6	50.0	60.5	83.3	40.0	50.0	36.4	66.7	54.5	71.7	76.7	33.3	8.3	20.0

Abbreviations: NT, not tested; AMP, ampicillin; AMC, amoxicillin/clavulanic acid; TCY, tetracycline; CXM, cefuroxime; FEP, cefepime; CRO, ceftriaxone; CTX, cefotaxime; CAZ, ceftazidime; ATM, aztreonam; CHL, chloramphenicol; TOB, tobramycin; SXT, trimethoprim/sulfamethoxazole; GM, gentamicin; CIP, ciprofloxacin; TZP, piperacillin/tazobactam; MEM, meropenem; IMP, imipenem; AN, amikacin; CS, colistin; ESBL, extended spectrum Beta-Lactamases, CR, carbapenem resistance; 3GCR, third generation cephalosporin resistance. In these tables, stable patterns are indicated in yellow, decreasing trends in green, and increasing trends in orange color.

Antimicrobial resistance trends of other Enterobacteriaceae isolates from blood cultures

A total of 497 isolates belonging to other Enterobacteriaceae species were recovered from blood cultures between March 2010 and December 2025. Overall, resistance rates varied substantially across antimicrobial classes, ranging from low to high. Ampicillin resistance was observed in 74.0% of isolates and was generally high throughout the study period. High resistance rates were also observed for tetracycline (73.8%) and amoxicillin–clavulanic acid (69.3%). Cephalosporin resistance was common among these isolates. The overall resistance rates were 69.6% for cefuroxime, 39.3% for cefotaxime, 37.2% for ceftriaxone, 33.5% for ceftazidime, and 34.7% for cefepime. ESBL production was identified in 45.3% of isolates, with substantial temporal variation and the highest prevalence observed in 2023 (68.0%).

Resistance to aztreonam was observed in 31.8% of isolates, with substantial annual variability. Resistance to chloramphenicol and trimethoprim–sulfamethoxazole was moderate, with overall rates of 39.1% and 39.8%, respectively. Aminoglycoside resistance was comparatively lower, with overall resistance rates of 21.4% for gentamycin, 20.5% for amikacin, and 37.7% for tobramycin.

Fluoroquinolone resistance was relatively low, with ciprofloxacin resistance observed in 19.6% of isolates. Resistance to piperacillin–tazobactam was also low (17.0%). Carbapenem resistance was relatively low overall, with resistance rates of 11.5% for imipenem and 9.1% for meropenem. However, substantial year-to-year variation was observed, particularly for meropenem. Colistin resistance was observed in 47.9% of isolates and showed substantial temporal variation, reaching 76.3% in 2024 and 75.0% in 2025. The annual resistance rates of commonly used antibiotics among other Enterobacteriaceae isolates are presented in Table 5.

Table 5. Annual Anti-Microbial Resistance for Other Enterobacteriaceae isolates of BSI

Antibiotic name	Year (Number)																
	Total (497)	2010 (52)	2011 (3)	2012 (26)	2013 (24)	2014 (35)	2015 (38)	2016 (17)	2017 (30)	2018 (27)	2019 (66)	2020 (37)	2021 (27)	2022 (28)	2023 (34)	2024 (40)	2025 (13)
Amp	74.0	79.6	NT	72.7	70.8	51.4	76.3	64.7	64.3	66.7	77.0	75.0	81.5	75.0	90.9	77.5	66.7
TCY	73.8	77.6	NT	76.9	78.3	42.4	76.3	73.3	83.3	55.6	65.6	75.7	70.4	92.9	87.9	80.6	83.3
CXM	69.6	69.6	NT	65.4	55.0	47.8	73.5	46.7	66.7	63.0	74.6	77.8	81.5	74.1	87.1	72.7	66.7
AMC	69.3	63.8	NT	76.0	66.7	44.1	71.1	56.3	65.5	74.1	73.0	80.6	70.4	67.9	88.2	70.0	54.5
CS	47.9	NT	NT	NT	40.9	20.0	68.4	47.1	64.3	46.2	33.9	32.4	34.6	46.4	71.0	76.3	75.0
SXT	39.8	NT	NT	68.8	12.5	25.7	10.5	43.8	41.4	25.9	61.4	61.1	38.5	46.4	44.1	32.5	41.7
CTX	39.3	46.3	NT	61.5	31.8	22.9	37.8	35.3	28.6	42.3	47.5	41.7	30.8	21.4	60.6	35.0	25.0
CHL	39.1	46.0	NT	50.0	44.4	22.9	41.7	47.1	63.0	25.9	36.1	37.8	40.7	28.6	33.3	41.0	41.7
TOB	37.7	40.8	NT	61.5	54.5	21.9	47.4	40.0	50.0	26.9	18.8	27.0	18.5	35.7	75.8	36.1	25.0
CRO	37.2	43.5	NT	53.8	23.8	17.1	36.8	35.3	25.9	40.7	49.2	43.2	25.9	21.4	60.6	32.5	16.7
FEP	34.7	26.5	NT	50.0	30.4	11.8	26.3	31.3	32.1	32.0	50.0	44.4	29.6	21.4	62.5	35.0	16.7
CAZ	33.5	29.4	NT	50.0	20.8	20.0	31.6	41.2	30.0	37.5	42.2	43.2	19.2	21.4	60.6	25.6	16.7
ATM	31.8	26.8	NT	57.7	17.4	20.0	34.2	40.0	35.7	34.6	38.1	32.4	14.8	21.4	64.3	23.1	8.3
GM	21.4	26.0	NT	46.2	16.7	11.4	8.1	12.5	20.0	14.8	12.9	22.2	14.8	25.0	56.7	23.7	16.7
AN	20.5	26.0	NT	38.5	20.8	11.4	24.3	23.5	37.9	18.5	3.4	5.6	7.4	3.6	57.6	25.6	16.7
CIP	19.6	25.0	NT	23.1	20.8	20.0	0.0	12.5	20.0	7.7	19.0	33.3	30.8	28.6	17.6	20.0	8.3
TZP	17.0	4.2	NT	17.4	0.0	17.1	26.3	18.8	25.9	19.2	12.9	25.0	7.7	3.6	41.2	20.5	16.7
IMP	11.5	0.0	NT	26.9	0.0	8.6	5.4	11.8	14.3	7.7	19.4	16.7	11.1	10.7	8.8	15.0	8.3
MEM	9.1	0.0	NT	42.3	0.0	8.6	0.0	11.8	10.3	0.0	6.5	19.4	11.1	0.0	6.1	10.5	25
ESBL	45.3	NT	NT	NT	NT	13.8	36.1	NT	NT	NT	NT	46.2	25.0	30.0	68.0	39.3	37.5

Abbreviations: NT, not tested; AMP, ampicillin; TCY, tetracycline; CXM, cefuroxime; AMC, amoxicillin/clavulanic acid; CS, colistin; SXT, trimethoprim/sulfamethoxazole; CTX, cefotaxime; CHL, chloramphenicol; TOB, tobramycin; CRO, ceftriaxone; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; GM, gentamicin; AN, amikacin; CIP, ciprofloxacin; TZP, piperacillin/tazobactam; IMP, imipenem; MEM, meropenem; ESBL, extended spectrum Beta-Lactamases. In these tables, stable patterns are indicated in yellow, decreasing trends in green, and increasing trends in orange color.

Annual Anti-Microbial Resistance for all Enterobacteriaceae isolates of BSI

A total of 3,860 non-duplicate *Enterobacteriaceae* isolates were recovered from blood cultures between March 2010 and December 2025. Overall, resistance rates varied considerably across antimicrobial agents, with particularly high resistance observed to several β-lactam antibiotics.

Ampicillin resistance was very high, with an overall resistance rate of 93.1% and consistently high rates throughout the study period, ranging from 89.8% in 2010 to 96.1% in 2022. Resistance to amoxicillin–clavulanic acid was also high overall (80.7%), although a gradual decline was observed in the later years, reaching 66.9% in 2025. Tetracycline resistance was also high (73.8%), with substantial year-to-year variation. Cephalosporin resistance was common. The overall resistance rates were 71.3% for cefuroxime, 58.7% for cefotaxime, 57.9% for ceftriaxone, 55.7% for cefepime, and 54.0% for ceftazidime. Third-generation cephalosporin resistance (3GCR) was widespread, with an overall resistance rate of 64.1% and substantial annual variation, ranging from 58.2% in 2013 to 71.9% in 2022. Extended-spectrum β-lactamase (ESBL) production was detected in 64.0% of isolates, with annual rates ranging from 50.3% in 2014 to 72.9% in 2018.

Resistance to aztreonam was also high (53.4%), while ciprofloxacin resistance was moderate overall (48.7%). Resistance to tobramycin and chloramphenicol was 45.3% and 40.8%, respectively, whereas gentamicin resistance was lower (33.9%). Amikacin resistance was 22.3% overall. Resistance to piperacillin–tazobactam was 27.8% overall, with an increase from 12.1% in 2010 to 46.5% in 2025. Carbapenem resistance was lower overall but increased substantially in the later years. Overall resistance rates were 21.4% for meropenem and 19.0% for imipenem, increasing from 1.1% for both agents in 2010 to 39.4% and 44.0%, respectively, in 2025. Overall carbapenem resistance was 25.6%, increasing from 2.2% in 2010 to 44.7% in 2025. Colistin resistance remained comparatively low overall (10.4%), although resistance increased in the final years, reaching 22.0% in 2024 and 20.6% in 2025. The annual resistance rates of commonly tested antibiotics among all *Enterobacteriaceae* isolates are presented in Table 6.

Table 6. Annual Anti-Microbial Resistance for all *Enterobacteriaceae* Isolates of BSI

Antibiotic name	Year (Number)																
	Total (3860)	2010 (191)	2011 (27)	2012 (167)	2013 (216)	2014 (256)	2015 (217)	2016 (199)	2017 (212)	2018 (223)	2019 (359)	2020 (390)	2021 (361)	2022 (290)	2023 (251)	2024 (341)	2025 (160)
AMP	93.1	89.8	96.3	90.7	93.2	91.0	91.0	92.8	90.6	91.5	93.4	94.7	94.9	96.1	94.6	93.3	93.1
AMC	80.7	76.2	85.2	81.4	86.0	87.0	80.4	81.8	80.3	81.8	80.1	86.1	82.8	88.5	76.1	69.6	66.9
TCY	73.8	82.0	85.2	73.7	75.1	64.8	78.1	78.8	77.8	63.7	74.9	68.7	77.3	84.6	74.8	64.8	76.9
CXM	71.3	70.0	74.1	62.5	64.2	67.0	70.9	71.7	71.0	65.6	72.9	73.1	73.6	83.0	75.5	66.5	77.8

SXT	59.9	NT	NT	77.0	53.2	68.4	57.5	75.5	68.8	53.5	55.7	52.5	56.6	59.0	67.6	54.7	60.4
CTX	58.7	52.5	NT	58.0	51.7	56.0	58.2	66.8	58.8	56.5	59.3	53.1	58.4	68.0	64.5	55.6	66.3
CRO	57.9	53.7	66.7	56.5	53.3	52.3	57.4	63.8	55.6	55.0	59.9	55.3	56.4	68.5	64.2	54.5	62.5
FEP	55.7	43.2	40.7	39.5	41.5	43.8	54.5	62.0	53.2	54.1	69.0	58.1	56.8	65.7	63.2	55.0	61.6
CAZ	54.0	47.2	51.9	51.2	43.2	52.8	56.8	66.8	55.4	54.0	55.2	50.1	56.7	61.6	60.3	48.7	50.3
ATM	53.4	47.7	42.3	52.4	44.3	50.6	56.8	68.9	55.2	52.1	52.3	47.5	50.1	60.1	66.4	49.9	56.0
CIP	48.7	37.4	44.4	39.8	40.7	45.8	48.5	52.8	53.7	43.9	44.0	49.7	53.4	53.5	53.9	49.4	62.3
TOB	45.3	49.7	50.0	52.1	55.7	39.3	50.3	45.8	43.1	35.3	37.6	38.7	42.3	54.2	56.4	43.4	49.1
CHL	40.8	36.8	51.9	46.4	35.6	40.4	41.8	51.5	56.2	33.0	39.6	36.6	42.4	36.4	36.3	36.5	53.8
GM	33.9	33.0	33.3	34.8	38.9	27.0	28.6	36.6	32.0	29.6	34.2	34.7	37.3	46.3	34.6	29.7	27.5
TZP	27.8	12.1	4.0	15.2	12.6	19.1	30.3	32.7	37.4	28.8	30.7	26.1	24.9	27.5	36.3	37.9	46.5
AN	22.3	17.7	11.1	18.0	18.2	21.3	26.4	28.1	29.1	28.2	17.0	12.8	16.3	17.1	39.3	29.0	28.1
MEM	21.4	1.1	7.4	27.5	6.5	14.1	7.0	21.6	24.3	12.1	19.3	27.6	24.8	21.3	29.8	29.3	39.4
IMP	19.0	1.1	0.0	7.2	5.0	10.9	6.6	20.0	22.3	10.6	22.3	19.4	19.6	22.3	28.9	27.6	44
CS	10.4	NT	NT	NT	6.7	7.1	14.1	5.1	12.0	9.3	9.1	6.0	4.5	10.4	15.6	22.0	20.6
ESBL	64.0	NT	NT	NT	NT	50.3	61.5	70.4	71.9	72.9	60.9	55.1	59.8	71.5	68.8	60.8	69.3
C R	25.6	2.2	7.4	28.4	7.7	26.3	11.4	22.6	30.1	14.6	29.0	30.3	26.8	25.7	31.6	30.3	44.7
3GCR	64.1	72.6	100	63.9	58.2	63.2	62.4	71.4	65.0	58.4	64.6	61.2	61.4	71.9	66.4	57.7	67.1

Abbreviations: NT, not tested; AMP, ampicillin; TCY, tetracycline; CXM, cefuroxime; AMC, amoxicillin/clavulanic acid; CS, colistin; SXT, trimethoprim/sulfamethoxazole; CTX, cefotaxime; CHL, chloramphenicol; TOB, tobramycin; CRO, ceftriaxone; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; GM, gentamicin; AN, amikacin; CIP, ciprofloxacin; TZP, piperacillin/tazobactam; IMP, imipenem; MEM, meropenem; ESBL, extended spectrum Beta-Lactamases, CR, carbapenem resistance; 3GCR, third generation cephalosporin resistance. In these tables, stable patterns are indicated in yellow, decreasing trends in green, and increasing trends in orange color.

Temporal Trends in Antimicrobial Resistance Based on Joinpoint Analysis

Temporal Trends in Antimicrobial Resistance among *Escherichia coli*

Joinpoint regression analysis showed that most antimicrobial resistance trends among *E. coli* isolates remained stable throughout the study period. Significant declining trends were observed in resistance to trimethoprim–sulfamethoxazole, tobramycin, chloramphenicol, and gentamicin throughout the study period .Ciprofloxacin resistance increased significantly during 2010–2015 and subsequently remained stable during 2015–2025. Resistance to aztreonam and ceftazidime

remained stable during 2010–2016 but declined significantly thereafter. Amoxicillin–clavulanate resistance remained stable during 2010–2022, followed by a significant decline during 2022–2025. Cefepime resistance showed a complex pattern, with a significant decline during 2010–2012, followed by a significant increase during 2012–2015 and stabilization thereafter. No significant temporal changes were observed for the remaining antimicrobial agents. Detailed trend estimates, including APCs, 95% confidence intervals, and corresponding P values, are presented in Table S2 in the supplementary Data.

Temporal Trends in Antimicrobial Resistance among *Klebsiella* spp.

Joinpoint regression analysis demonstrated significant increasing trends in resistance to cefepime, cefotaxime, ceftazidime, aztreonam, ciprofloxacin, and colistin among *Klebsiella* spp. isolates throughout 2010–2025. Ampicillin resistance showed a significant decrease during 2010–2012, followed by a significant increase during 2012–2015 and stabilization thereafter. Piperacillin–tazobactam resistance increased significantly during 2010–2017, remained stable during 2017–2021, and increased again during 2021–2025. In contrast, resistance to meropenem, imipenem, amikacin, gentamicin, tobramycin, trimethoprim–sulfamethoxazole, amoxicillin–clavulanate, chloramphenicol, ceftriaxone, tetracycline, cefuroxime, and carbapenems remained stable throughout the study period. Similarly, no significant temporal changes were observed in ESBL and 3GCR rates. Detailed Joinpoint regression estimates are presented in Table S3 in the supplementary Data.

Temporal Trends in Antimicrobial Resistance among *Enterobacter* spp.

Joinpoint regression analysis revealed predominantly stable resistance trends for ampicillin, amoxicillin–clavulanate, colistin, and meropenem during the earlier study period. Imipenem resistance increased significantly during 2010–2023, followed by a significant decline during 2023–2025. Several antimicrobial agents demonstrated significant declines in resistance during the later years of the study. These included cefuroxime during 2022–2025, chloramphenicol during 2016–2025, tetracycline during 2023–2025, ceftazidime, aztreonam, cefotaxime, and ceftriaxone during 2022–2025, and amikacin, ciprofloxacin, gentamicin, piperacillin–tazobactam, and tobramycin during 2023–2025. Cefepime resistance increased significantly

during 2010–2021 but subsequently declined significantly during 2021–2025. TMP–SMX resistance increased significantly during 2013–2015, remained stable during 2015–2023, and declined significantly during 2023–2025. Similarly, ESBL and 3GCR rates remained stable during the earlier study period but showed significant declines from 2022 to 2025. Detailed Joinpoint regression estimates are presented in Table S4 in the supplementary Data.

Temporal Trends in Antimicrobial Resistance among Other Enterobacteriaceae

Joinpoint regression analysis demonstrated predominantly stable antimicrobial resistance trends among other Enterobacteriaceae throughout the study period. No significant temporal changes were observed for most tested antimicrobials, including β-lactams, aminoglycosides, fluoroquinolones, carbapenems, colistin, and ESBL rates. The only significant temporal changes were observed for ciprofloxacin resistance, which decreased during 2010–2018, increased during 2018–2021, and subsequently decreased during 2021–2025. Detailed Joinpoint regression estimates are presented in Table S5 in the supplementary Data.

Temporal Trends in Antimicrobial Resistance among All Enterobacteriaceae

Joinpoint regression analysis demonstrated several significant temporal changes in antimicrobial resistance among all Enterobacteriaceae isolates. Resistance to cefuroxime and ciprofloxacin increased significantly throughout the study period. Meropenem resistance increased significantly during 2010–2012 and subsequently remained stable through 2025. Amikacin resistance showed a fluctuating pattern, with a significant increase during 2010–2017, a significant decline during 2017–2020, and a subsequent significant increase during 2020–2025. ESBL rates increased significantly during 2014–2016 and remained stable thereafter, while carbapenem resistance increased significantly during 2010–2012 and subsequently remained stable. Amoxicillin–clavulanate resistance remained stable during 2010–2022, followed by a significant decline during 2022–2025. Cefepime resistance increased significantly during 2010–2019 and remained stable thereafter. Colistin resistance remained stable during 2013–2021 but increased significantly during 2021–2025. No significant temporal changes were observed for the remaining antimicrobial agents. Detailed Joinpoint regression estimates are presented in Supplementary Table S6.

Discussion:

BSIs caused by Enterobacteriaceae remain a major clinical challenge worldwide, accounting for a substantial proportion of BSIs in many surveillance studies [9, 23]. In this long-term surveillance study conducted from March 2010 through December 2025, we evaluated the epidemiology and antimicrobial resistance patterns of major Enterobacteriaceae pathogens isolated from blood cultures. Our findings demonstrate the predominance of *E. coli* and *Klebsiella* spp., a high burden of ESBL production, and substantial antimicrobial resistance, particularly among *Klebsiella* spp. The observed temporal changes provide important insights into the evolving resistance landscape and its implications for empirical antimicrobial therapy and stewardship.

E. coli and *Klebsiella* spp. were the most frequently isolated pathogens in our cohort, accounting for 38.1% and 30.0% of all *Enterobacteriaceae* bloodstream isolates, respectively, during 2010–2025. Similarly, a recent 12-year surveillance study from three university hospitals in Shiraz reported *E. coli* and *Klebsiella* spp. as the most frequent Gram-negative bloodstream pathogens, accounting for 42.65% and 17.02% of isolates, respectively, and documented substantial antimicrobial resistance among Enterobacteriaceae [24]. These findings are consistent with global surveillance data identifying *E. coli* as a leading cause of Gram-negative BSIs in both community and healthcare-associated settings [9]. However, previous longitudinal studies have reported heterogeneous temporal patterns for *E. coli* BSIs, with some regions showing increasing incidence and changing resistance profiles over time [25-27]. In contrast, our longitudinal analysis demonstrated a gradual decline in the relative proportion of *E. coli* isolates during the earlier years of surveillance.

Given that *E. coli* represented the largest proportion of bloodstream isolates in our cohort, its resistance profile has important implications for empirical treatment. ESBL production was detected in 69.4% of *E. coli* isolates, while resistance to third-generation cephalosporins and ciprofloxacin was 69.6% and 61.0%, respectively. Resistance to ampicillin (91.3%) and amoxicillin–clavulanate (77.1%) was also high, potentially limiting the utility of these agents for empirical treatment of suspected *E. coli* BSIs. In accordance with IDSA recommendations, carbapenems are preferred for ESBL-producing Enterobacterales infections outside the urinary tract, whereas piperacillin–tazobactam is not recommended as the preferred treatment for ESBL-

producing Enterobacterales BSIs, even when in vitro susceptibility is demonstrated(5). Although carbapenem resistance remained relatively limited during much of the study period, the high resistance rates observed in 2025, particularly for meropenem (39.4%) and imipenem (44.0%), are concerning because they may further narrow available empirical treatment options. These findings are consistent with broader concerns regarding the projected global increase in resistance among *E. coli*. Ndoye et al. reported a 10-year retrospective analysis of *E. coli* resistance at a major hospital in Dakar, demonstrating substantial temporal increases in resistance to several β-lactams and fluoroquinolones and emphasizing the need for sustained surveillance [28]. Alvarez-Uria et al. projected that resistance to third-generation cephalosporins in *E. coli* could increase from 64.5% in 2015 to 77% by 2030, while carbapenem resistance could increase from 5.8% to 11.8% over the same period [29].

Although *Klebsiella* spp. accounted for a smaller proportion of BSIs isolates than *E. coli*, their increasing representation during the later years of the study and their resistance profile are of particular clinical relevance. ESBL production was detected in 69.5% of *Klebsiella* isolates, while resistance to meropenem and imipenem reached 78.3% and 75.4%, respectively, in 2025. These findings indicate a substantial burden of multidrug resistance and carbapenem resistance among *Klebsiella* spp. in the later years of surveillance. Han et al. recently reported a nine-year surveillance study of carbapenem-resistant Enterobacterales in a tertiary hospital in Central China, documenting temporal variation in CRE prevalence and resistance patterns [30]. International surveillance studies have similarly identified the emergence and dissemination of multidrug-resistant and carbapenem-resistant *Klebsiella pneumoniae* as important challenges in healthcare settings worldwide [9, 31-34]. Naik et al. also reported that approximately 40% of Enterobacteriaceae isolates were carbapenem-resistant, highlighting the substantial burden of carbapenem resistance in tertiary-care settings [35]. In addition, van Gorp et al. analyzed *Enterobacter cloacae* complex and *Klebsiella aerogenes* over 2012–2023 using national surveillance data, providing further evidence of the importance of long-term monitoring of resistance among clinically important Enterobacterales [36]. In our study, aminoglycosides generally showed comparatively lower and more stable resistance rates, suggesting that some activity against *Klebsiella* spp. may have been retained. However, the significant increase in colistin resistance during 2021–2025 warrants close surveillance [37]. Given that carbapenems are

generally preferred for ESBL-producing Enterobacterales BSIs from non-urinary sources [5]. the high level of carbapenem resistance observed among our *Klebsiella* isolates represents an important therapeutic challenge. Similar concerns have been reported by Borcan et al., who described a high prevalence of multidrug-resistant and ESBL-producing *Klebsiella pneumoniae* bloodstream isolates, together with increasing colistin resistance and carbapenemase-producing strains over time [32].

Beyond *E. coli* and *Klebsiella* spp., our analysis of 734 *Enterobacter* spp. and 497 other Enterobacteriaceae isolates demonstrated considerable resistance across additional members of the family. *Enterobacter* spp. showed high resistance to β-lactams and third-generation cephalosporins, with 50.1% resistance to third-generation cephalosporins and an ESBL rate of 54.8%. A recent review by Cirkovic et al. highlighted *Enterobacter* spp. as an important reservoir of carbapenemase genes in Europe [38]. According to the 2025 IDSA guidance, cefepime is a preferred treatment option for invasive infections caused by Enterobacterales at moderate-to-high risk of clinically significant AmpC production when the isolate is susceptible [39]. In our study, however, cefepime resistance among *Enterobacter* spp. showed an increase during 2010–2021 followed by a significant decline during 2021–2025. This temporal pattern should be interpreted cautiously because changes in resistance over time may reflect multiple factors, including antimicrobial exposure, infection-control practices, and changes in the composition of circulating strains. The group classified as other Enterobacteriaceae also demonstrated substantial resistance variability, with ESBL production reaching 68.0% in 2023 [9]. This finding indicates that high-level resistance was not restricted to the two predominant species in our cohort. Across all 3,860 isolates, resistance to ampicillin and amoxicillin–clavulanate remained high, further emphasizing the limited reliability of these agents for empirical treatment in this setting. Importantly, overall carbapenem resistance reached 44.7% in 2025. This finding underscores the growing therapeutic challenge posed by carbapenem-resistant Enterobacterales and supports the need for continued surveillance, antimicrobial stewardship, and strengthened infection-prevention measures.

Joinpoint regression provided a useful framework for characterizing temporal changes and identifying periods in which resistance patterns changed significantly. The findings demonstrated substantial species-specific differences in the evolution of antimicrobial resistance. Among *E. coli*, resistance to most antimicrobials remained stable or showed declining trends, although significant

increases were observed for selected agents such as ciprofloxacin. In contrast, *Klebsiella* spp. showed significant increases in resistance to several β-lactams and ciprofloxacin, as well as an increase in colistin resistance during the final years of the study. *Enterobacter* spp. demonstrated a different temporal pattern, with several resistance rates declining during the later years of surveillance. These differences emphasize that AMR is not uniform across Enterobacteriaceae and that species-specific surveillance can provide information that may be obscured by analyses of the entire bacterial group. The observed temporal patterns may reflect a combination of antimicrobial selection pressure, changes in infection-control practices, antimicrobial stewardship interventions, and shifts in the distribution of circulating clones; however, these factors could not be directly evaluated in the present study because clinical, antimicrobial-consumption, and molecular epidemiological data were unavailable. Nevertheless, the long observation period and application of Joinpoint regression allowed identification of significant temporal changes that may be useful for guiding future surveillance and stewardship strategies. Findings from multicenter surveillance studies in Iran have reported broadly comparable resistance patterns, providing some support for the external relevance of our observations [40].

Limitations and Strengths

Several limitations should be considered when interpreting our findings. First, although microbiological analyses were performed at a single reference laboratory (PACMRC), the dataset included blood culture isolates referred from multiple university-affiliated and non-university hospitals, encompassing both public and private healthcare facilities. Therefore, the study was not restricted to a single hospital population. However, the participating hospitals were not selected using a nationally representative sampling framework, and regional differences in antimicrobial use, patient populations, and infection-control practices may have influenced the observed resistance patterns. Second, bacterial identification relied primarily on conventional phenotypic and biochemical methods rather than advanced molecular techniques. In addition, detailed clinical information, including patient outcomes, underlying comorbidities, and antimicrobial exposure, was not available because of the retrospective laboratory-based study design. Finally, molecular characterization of resistance mechanisms was not routinely performed; therefore, the specific genetic mechanisms underlying the observed resistance patterns could not be determined. Nevertheless, all microbiological analyses were performed in

the same reference laboratory using standardized procedures and the CLSI guidelines applicable during each study year, which enhanced methodological consistency across the study period.

Despite these limitations, the study has several important strengths. The long observation period, from March 2010 through December 2025, provides an extended assessment of antimicrobial resistance among Enterobacteriaceae causing bloodstream infections in Iran. The inclusion of isolates from multiple hospitals, encompassing both public and private healthcare settings, broadened the source population and captured resistance patterns across diverse healthcare settings. The use of Joinpoint regression allowed significant changes in resistance trajectories to be identified rather than assuming a single linear trend across the entire study period. In addition, species-specific analyses demonstrated substantial differences in resistance patterns among E. coli, Klebsiella spp., Enterobacter spp., and other Enterobacteriaceae. Collectively, these findings provide valuable local and regional evidence that may support antimicrobial stewardship, empirical treatment strategies, infection-control planning, and future molecular surveillance.

Conclusion

This 16-year surveillance study demonstrated a substantial and evolving burden of antimicrobial resistance among Enterobacteriaceae causing BSIs in southern Iran. *E. coli* and *Klebsiella* spp. were the predominant pathogens, with high rates of ESBL production and resistance to several commonly used antimicrobial agents. The temporal analysis revealed important species-specific differences in resistance trajectories, including increasing resistance to several key agents among *Klebsiella* spp., whereas resistance patterns among *E. coli* were generally more stable. The high levels of carbapenem resistance observed in *Klebsiella* spp. and across the overall cohort in 2025 are of particular clinical concern. These findings highlight the importance of sustained antimicrobial resistance surveillance, species-specific monitoring, and strengthened antimicrobial stewardship and infection-prevention strategies. Further multicenter studies incorporating antimicrobial consumption data and molecular characterization of resistance mechanisms are warranted to better understand the drivers of these trends and guide locally appropriate treatment and control strategies.

Supplementary Materials: Table S1. Temporal trends in Enterobacteriaceae pathogen distribution: A Joinpoint analysis

Table S2. Temporal trends in antimicrobial resistance among *E. coli* isolates based on Joinpoint regression analysis.

Table S3. Temporal trends in antimicrobial resistance among *Klebsiella* spp. isolates based on Joinpoint regression analysis.

Table S4. Temporal trends in antimicrobial resistance among *Enterobacter* spp. isolates based on Joinpoint regression analysis .

Table S5. Temporal trends in antimicrobial resistance among other Enterobacteriaceae based on Joinpoint regression analysis.

Table S6. Temporal trends in antimicrobial resistance among all Enterobacteriacea isolates based on Joinpoint regression analysis.

Abbreviations

The following abbreviations are used in this manuscript:

BSIs Bloodstream infections

AMR Antimicrobial resistance

IDSA Infectious Diseases Society of America

CLSI Clinical and Laboratory Standards Institute

NT not tested

AMP ampicillin

AMC amoxicillin/clavulanic acid

TCY tetracycline

SXT trimethoprim/sulfamethoxazole

CXM cefuroxime

CTX cefotaxime

CRO ceftriaxone

CIP ciprofloxacin

FEP cefepime

CAZ ceftazidime

ATM aztreonam

TOB tobramycin

CHL chloramphenicol

GM gentamicin

TZP piperacillin/tazobactam

AN amikacin

MEM meropenem

IMP imipenem

CS colistin

ESBL extended spectrum Beta-Lactamases

CR carbapenem resistance

3GCR third generation cephalosporin resistance

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1404.228). This Ethics Committee has waived the requirement for informed consent in this study, as the study utilized laboratory management data.

Consent for publication

Not applicable.

Clinical trial number

Clinical trial number: not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable institutional and ethical restrictions.

Competing interests

The authors declare no competing interests.

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Authors' contributions

G.P. and A.S. conceived and designed the study. Z.J. performed the data management and statistical analyses using WHONET and contributed to the initial and final drafting of the manuscript. S.N. performed the Joinpoint regression analysis. B.P. contributed to the study design and interpretation of the findings. All authors critically reviewed the manuscript, contributed to its revision, and approved the final version.

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