

Effectiveness of Carbapenem-Sparing Antibiotics Versus Carbapenems for Treating Non-Bacteremic Extended-Spectrum Beta-Lactamase-Producing Enterobacterales Infections

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Introduction: Extended-spectrum β -lactamase-producing Enterobacterales (ESBL-E) pose a significant public health threat. While carbapenems are known to be superior in treating bacteremic infections, the evidence is unclear for non-bacteremic infections.

Objective: To assess the effectiveness of carbapenem-sparing therapies compared to carbapenems for non-bacteremic ESBL-E infections.

Methodology: This is a retrospective observational cohort study involving patients aged 18 years or older with confirmed diagnoses of ESBL-E non-bacteremic infections who received either carbapenems or carbapenem-sparing targeted therapy during the study period. The primary outcomes were clinical cure and 30-day all-cause mortality. Secondary outcomes included microbiological eradication, recurrence of ESBL-E infection within 6 months, and the 30-day incidence of new multidrug-resistant infections.

Results: The study included 216 patients: 117 in the carbapenem group and 99 in the carbapenem-sparing group. Both groups showed no significant differences in 30-day all-cause mortality and clinical resolution. However, notable statistical differences were observed in three secondary outcomes: the carbapenem group had a higher recurrence rate of ESBL infections (RR 1.65, 95% CI: 1.05–2.59, $P = 0.025$) and more secondary multidrug-resistant infections (RR 1.92, 95% CI: 1.11–3.31, $P = 0.015$), including carbapenem-resistant Enterobacterales infections (RR 2.26, 95% CI: 1.10–4.63, $P = 0.020$).

Conclusion: The study demonstrates that carbapenem-sparing therapies for ESBL-E nonbacteremic infections are non-inferior to carbapenems, with comparable 30-day all-cause mortality, clinical cure, and bacteriological resolution rates. Additionally, carbapenem-sparing options showed lower recurrence rates of ESBL-E infections and reduced development of secondary multidrug-resistant infections, including CRE infections.

Keywords: carbapenem, carbapenem-sparing antibiotics, enterobacterales, ESBL-E, non-bacteremic infection

Introduction

In 2019, the Centers for Disease Control and Prevention (CDC) identified extended-spectrum β -lactamase-producing Enterobacterales (ESBL-E) as a critical public health threat, attributing them to 197,400 hospitalizations, 9,100 deaths, and an estimated economic burden of \$1.2 billion in 2017.¹ The prevalence of infections caused by ESBL-E has increased globally. Castanheira et al reported that ESBL genes were detected in 8.2%, 12.8%, 15.4%, and 30.3% of isolates in Europe, the USA, Asia-Pacific, and Latin America, respectively.² In Saudi Arabia, the prevalence of ESBL-E infections is notably high, reaching up to 30.5%, and significantly impacting hospitalization rates and healthcare costs.³ Al-Sweih reported that increasing rates of ESBL-E correlate with challenging treatment outcomes and escalating healthcare expenditures, highlighting the urgent need for effective infection control measures and alternative treatment strategies in the region.⁴ ESBL-E strains resist most β -lactam antibiotics, including penicillins, cephalosporins, and aztreonam, but remain susceptible to carbapenems, the current standard of care.^{1,5,6} However, the extensive use of carbapenems raises concerns about developing antibiotic resistance, presenting a significant public health challenge.^{7,8} A randomized controlled trial found that piperacillin-tazobactam (TZP) was less effective than carbapenems for treating bacteremia caused by ESBL-producing organisms.⁹ According to the 2024 guidelines from the Infectious Diseases Society of America (IDSA), carbapenem use should be restricted to non-urinary tract ESBL-E infections to preserve their efficacy.⁵ Various carbapenem-sparing therapy options for non-bacteremic ESBL-E infections were suggested, including penicillins + beta-lactamase inhibitors (TZP or amoxicillin-clavulanic acid), cephamycins, cephalosporins $\pm$ beta-lactamase inhibitors (cefepime, ceftazidime/avibactam, or ceftolozane-tazobactam), fluoroquinolones (ciprofloxacin or levofloxacin), aminoglycosides (gentamicin, amikacin, or plazomycin), trimethoprim and sulfamethoxazole (TMP/SMX).^{4-6,10}

Studies evaluating carbapenem-sparing β -lactams, such as TZP, cefepime, and cephamycin, have produced mixed results. Gutiérrez-Gutiérrez and Rodríguez-Baño conducted a systematic review and meta-analysis, indicating that while some carbapenem-sparing regimens can be effective, their efficacy varies, especially in severe infections.¹⁰ Tamma et al found that while TZP and cefepime can be effective, they often have higher failure rates than carbapenems.⁹ Carbapenem-sparing treatments yielded mixed results, with success rates influenced by infection severity.⁸ On the other hand, Seo et al found that TZP and ertapenem had comparable high efficacy rates of 94%.⁷

In comparison, cefepime had a significantly lower success rate of 33.3%, leading to the cessation of the cefepime arm of the study due to high treatment failure. A recent retrospective study comparing outcomes for patients with TZP-non-susceptible /ceftriaxone-susceptible infections showed no significant difference in clinical outcomes between those treated with carbapenems and those treated with carbapenem-sparing agents, suggesting that carbapenem-sparing options could be viable alternatives.¹¹ Despite these findings, there is a notable lack of research in Saudi Arabia. To the best of our knowledge, no published studies from Saudi Arabia have compared carbapenem-sparing antibiotics versus carbapenems for treating ESBL-E infections. Our study aims to address this gap by evaluating the effectiveness of carbapenem versus carbapenem-sparing therapies for non-bacteremic ESBL-E infections at a tertiary care hospital in the Eastern Province of Saudi Arabia, seeking to provide valuable insights into optimizing treatment strategies and combating antibiotic resistance in our region.

Materials and Methods

Study Design, Setting, and Population

This retrospective observational study was conducted at King Fahd Hospital of the University of Khobar, Eastern Province of Saudi Arabia. King Fahd University Hospital is a tertiary care center with a capacity of around 550 beds. Patients were deemed eligible if they were 18 years or older and had a confirmed diagnosis of ESBL-E non-bacteremic infections. Eligibility further required that patients had received targeted antibiotic therapy for at least 72 hours following the release of ESBL-E positive culture results, regardless of whether they had received prior empirical therapy. Patients were excluded if they had ESBL-E bacteremia, polymicrobial infections, or were not hospitalized during the treatment period. In our study, we evaluated the treatment of ESBL-E infections collectively without conducting subgroup analyses. Notably, the carbapenem-sparing group includes any antibiotic used that is microbiologically active against ESBL-E, as determined by the susceptibility results, without preference for specific antibiotics.

Investigated Outcomes

The study's primary outcomes were the clinical cure within seven days of starting definitive therapy and the 30-day all-cause mortality rate. Clinical cure was defined as the complete resolution of infection-related signs and symptoms initially present before treatment, which was assessed within seven days after the culture results were released. The secondary outcomes included microbiological resolution, defined as eradicating the ESBL-producing organism, as confirmed by follow-up cultures within 30 days. Recurrence of ESBL infection was assessed within six months of the initial treatment. The incidence of secondary multidrug-resistant infections, defined as infections caused by multidrug-resistant organisms, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, Carbapenem-resistant Enterobacterales (CRE), and other less frequently isolated multidrug-resistant (MDR) bacteria occurring within 30 days, was also evaluated.

Data Collection

The data of patients with non-bacteremic ESBL-E infections over a six-year period (between January 2017 and December 2022) were obtained from electronic medical records. Patients were screened for eligibility, and those who met the criteria were included. The first incidence of confirmed ESBL-E infection in non-bacteremic sources during the study period was evaluated.

A data collection form was developed based on a review of the relevant literature. It was initially developed by a clinical pharmacist, after which an infectious disease consultant reviewed it, and infectious disease fellows collected data. This multi-step review process aimed to enhance data accuracy and consistency through expert validation and cross-verification. The form consisted of four major domains: patient-related, admission-related, history-related, and therapeutic management-related. The initial domain was designed to obtain patient-related data, including patient demographics, comorbidities (ie, diabetes mellitus, heart failure, chronic kidney disease, renal transplant, cancer, structural lung disease, immunosuppression, and others), Charlson comorbidity index,¹² and renal function (ie, baseline renal function “eGFR and serum creatinine”). Immunosuppressive therapy was defined as receiving any well-known immunosuppressive agent or prednisolone at a dose of ≥ 20 mg or equivalent for at least 14 days within the last 30 days.^{9,13,14} Creatinine clearance was estimated using the Cockcroft-Gault equation.¹⁵

The second domain included admission-related information, such as the level of care (ie, critical versus non-critical), number of days of hospital stay, and recent hospital admission within 12 months. The length of hospital stay was defined as the number of days from admission to discharge. The third domain contained history-related information, such as previous ESBL-E infection within 12 months and previous exposure to systemic antibiotic therapy within six months. The fourth domain captured antimicrobial management-related details, including empirical and definitive antibiotic treatment, infectious syndrome characteristics (community- vs hospital-acquired, site of infection), and microbiological data (culture source, antimicrobial susceptibility).

Empirical antibiotic therapy was defined as administering antibiotics within 24 hours of taking the microbiological samples. Definitive antibiotic therapy was defined as administering antibiotics after the release of ESBL-E antimicrobial sensitivity, which was either carbapenem therapy (meropenem or imipenem-cilastatin) or carbapenem-sparing therapy, consisting of penicillins (TZP or amoxicillin-clavulanic acid), cephalosporins (cefepime or ceftazidime/avibactam), fluoroquinolones (ciprofloxacin or levofloxacin), aminoglycosides (gentamicin), TMP/SMX, or nitrofurantoin. Moreover, the outcome-related information domain included clinical cure, bacteriological resolution, 30-day all-cause mortality, and recurrence of ESBL-E infection within six months of the primary infection.

Microbiological Data

The data related to sample collection, microbiological identification, and antibiotic sensitivity testing were collected. Bacterial strains were isolated by inoculating both selective and nonselective media, followed by incubation at 37°C with 5% CO₂. Colonies were identified via MALDI-TOF MS using VITEK[®] MS (bioMérieux, Durham, NC), followed by Gram staining and subculture of positively flagging bottles. Antibiotic susceptibility testing of pure colonies was performed on the VITEK[®] 2 automated system (bioMérieux, Durham, NC). Strains not susceptible to any third-generation cephalosporin underwent confirmatory ESBL testing. ESBL production was confirmed by disk diffusion according to the Clinical and Laboratory Standards Institute (CLSI) standards, using cefotaxime 30 µg and ceftazidime 30 µg disks with and without clavulanic acid 10 µg.¹⁶

Statistical Analysis

Categorical variables were displayed as frequencies and percentages, while the minimum, maximum, mean, standard deviation, median, and interquartile range were used to present the numerical variables. To compare demographics, clinical characteristics, risk factors, and antibiotic therapy profile between the carbapenem therapy group and the carbapenem-sparing therapy group, chi-square test or Fisher's exact test for categorical variables, and independent sample Mann–Whitney *U*-test or *t*-test for continuous variables were used. Furthermore, relative risks (RR) and confidence intervals (CI) were calculated to compare the therapy outcomes and analyze mortality risk factors. Moreover, univariate and multivariable logistic regression analyses were performed to adjust the study findings based on patient background variables. A boxplot was created to display the duration of definitive antibiotic therapy for patients treated with carbapenems compared to those receiving carbapenem-sparing therapy. The data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp., Armonk, New York), and the level of significance was set at $P \leq 0.05$.

Results

A total of 521 patients with confirmed ESBL-E infections were initially identified. After applying the eligibility criteria, 216 patients were included in the study: 117 in the carbapenem group and 99 in the carbapenem-sparing group. A detailed patient screening and allocation process is illustrated in Figure 1. The mean age $\pm$ standard deviation (SD) was 61.6 ± 19.08 years. Of these, 122 (56.4%) were females and 94 (43.5%) were males. The acquisition of infections was community-acquired in 77 patients (35.6%) and hospital-acquired in 139 (64.4%), with no statistically significant difference between the carbapenem and carbapenem-sparing groups ($P = 0.29$). The non-bacteremic treated infections

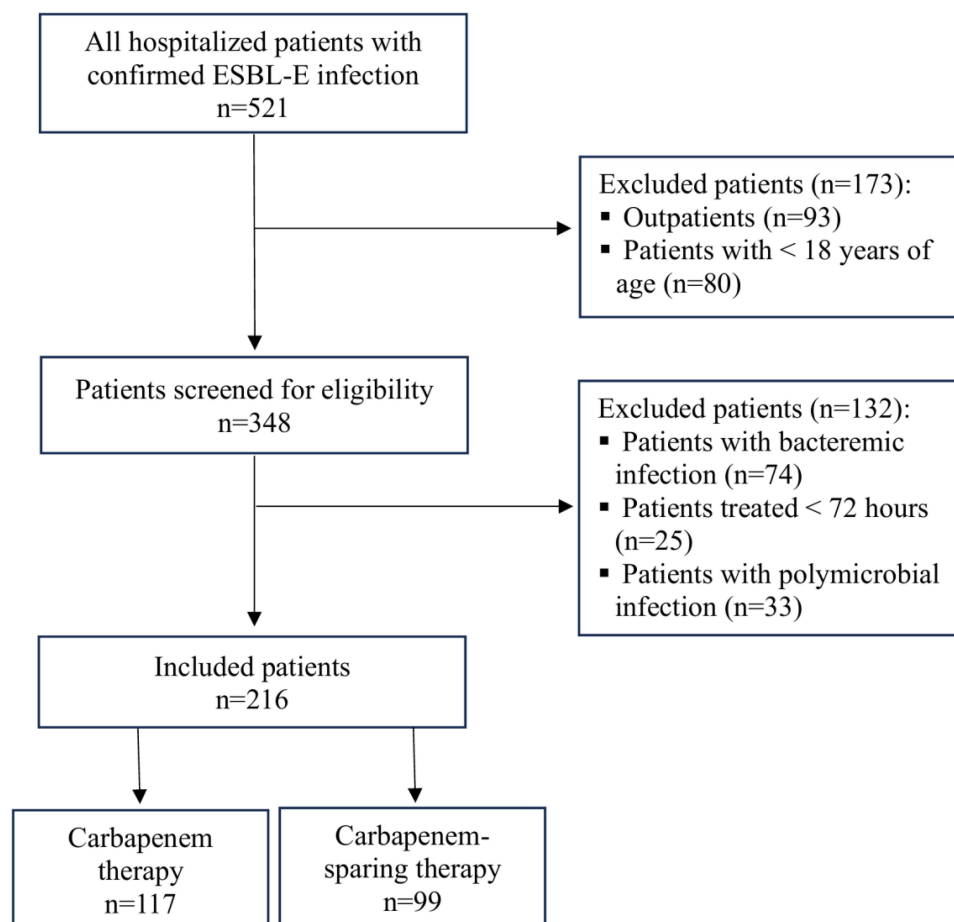


Figure 1 Carbapenems versus carbapenem-sparing therapy study flow chart.

include urinary tract infections (UTIs), skin and soft tissue infections (SSTIs), intra-abdominal infections, respiratory infections, and bone/joint infections. Statistically significant differences were observed regarding therapy options; patients with UTIs or bone/joint infections received more carbapenem-sparing agents, whereas patients with SSTIs, intra-abdominal infections, or respiratory infections received more carbapenems (Table 1).

Table 1 Demographics and Clinical Characteristics of the Patients with ESBL-E Non-Bacteremia Infections (n=216)

Characteristics	Total (n = 216) No (%)	Carbapenem Group (n=117) No (%)	Carbapenem- Sparing Group (n = 99) No (%)	P-value
Age (Mean ± SD)	61.63 ± 20.75	62.65 ± 21.21	60.42 ± 20.22	0.433
Age > 65 years	106 (49.1)	58 (49.6)	48 (48.5)	0.873
Gender (male)	94 (43.5)	57 (48.7)	37 (37.4)	0.094
Place of Infection Acquisition				
Community-acquired	77 (35.6)	38 (32.5)	39 (39.4)	0.290
Hospital-acquired	139 (64.4)	79 (67.5)	60 (60.6)	
Infection Site				
Urinary	125 (57.9)	52 (44.4)	73 (73.7)	<0.001*
Respiratory	14 (6.5)	11 (9.4)	3 (3.0)	0.048*
Skin and soft tissue	59 (27.3)	42 (35.9)	17 (17.2)	0.002*
Intraabdominal	15 (6.9)	13 (11.1)	3 (3.0)	0.035*
Bone/joint	3 (1.4)	0 (0.0)	3 (3.0)	0.095
Others	3 (1.4)	3 (2.6)	0 (0.0)	0.252
Comorbidities				
Myocardial infarction	39 (18.1)	24 (20.5)	15 (15.2)	0.307
Congestive heart failure	29 (13.4)	18 (15.4)	11 (11.1)	0.359
Peripheral vascular disease	17 (7.9)	9 (7.7)	8 (8.1)	0.916
Cerebrovascular disease	59 (27.3)	31 (26.5)	28 (28.3)	0.769
Dementia / chronic cognitive deficit	24 (11.1)	12 (10.3)	12 (12.1)	0.664
Chronic pulmonary disease	18 (8.3)	12 (10.3)	6 (6.1)	0.266
Connective tissue disease	8 (3.7)	2 (1.7)	6 (6.1)	0.147
Peptic ulcer disease	3 (1.4)	1 (0.9)	2 (2.0)	0.594
Liver disease/mild	7 (3.2)	3 (2.6)	4 (4.0)	0.705
Liver disease/mod. or severe	2 (0.9)	0 (0.0)	2 (2.0)	0.209
Noncomplicated DM	71 (32.9)	37 (31.6)	34 (34.3)	0.672
Complicated DM	40 (18.5)	26 (22.2)	14 (14.1)	0.128
Hemiplegia or paraplegia	42 (19.4)	24 (20.5)	18 (18.2)	0.666

(Continued)

Table 1 (Continued).

Characteristics	Total (n = 216) No (%)	Carbapenem Group (n=117) No (%)	Carbapenem- Sparing Group (n = 99) No (%)	P-value
Moderate/Severe renal disease	72 (33.3)	42 (35.9)	30 (30.3)	0.385
Solid Malignancy localized	10 (4.6)	8 (6.8)	2 (2.0)	0.113
Solid Malignancy with mets.	3 (1.4)	2 (1.7)	1 (1.0)	0.998
Leukemia	1 (0.5)	1 (0.9)	0 (0.0)	0.998
HIV/AIDS	1 (0.5)	0 (0.0)	1 (1.0)	0.458
Comorbidities ≥ 3	106 (49.1)	63 (53.8)	43 (43.4)	0.127
Charlson score (Mean $\pm$ SD)	4.82 $\pm$ 3.27	5.05 $\pm$ 3.45	4.56 $\pm$ 3.03	0.268
Serum Creatinine (Median $\pm$ IQR)	0.90 $\pm$ 0.90	0.96 $\pm$ 1.05	0.80 $\pm$ 0.56	0.047*
Creatinine Clearance (Mean $\pm$ SD)	78.32 $\pm$ 44.04	74.54 $\pm$ 44.95	82.78 $\pm$ 42.73	0.171

Note: *Significant P value.

Abbreviations: DM, Diabetes mellitus; HIV/AIDS, Acquired human immunodeficiency virus/immunodeficiency syndrome; IQR, interquartile range; SD, standard deviation.

No significant differences were observed regarding the patient comorbidities between the carbapenem and carbapenem-sparing groups. The most common comorbidities were chronic kidney disease in 72 patients (33.3%), noncomplicated diabetes mellitus (DM) in 71 patients (32.9%), cardiovascular diseases/transient ischemic attack in 59 patients (27.3%), and paralysis (hemiplegia or paraplegia) in 42 patients (19.4%). Among the risk factors evaluated for ESBL-E infection, statistically significantly more patients in the carbapenem group compared to the carbapenem-sparing group had a central venous catheter (18.8% vs 7.1%, $P = 0.012$) and urinary catheter (53.8% vs 38.4%, $P = 0.023$), respectively. Additionally, significantly more patients in the carbapenem group were recently hospitalized, admitted to the intensive care unit (ICU), had central venous or urinary catheters, or were on mechanical ventilation (Table 2).

Table 2 Risk Factors and Antibiotic Therapy Profile of ESBL-E Non-Bacteremic Infections (n=216)

	Total (n = 216) No (%)	Carbapenem Group (n=117) No (%)	Carbapenem- Sparing Group (n = 99) No (%)	P-value
ESBL-E infection risk factors				
Previous AB therapy ^a	149 (69.0)	83 (70.9)	66 (66.7)	0.499
ESBL-E Colonization	28 (13.0)	17 (14.5)	11 (11.1)	0.456
Previous ESBL infection ^b	29 (13.4)	15 (12.8)	14 (14.1)	0.777
Immunosuppressive therapy	19 (8.8)	9 (7.7)	10 (10.1)	0.533
Central venous catheter	29 (13.4)	22 (18.8)	7 (7.1)	0.012*
Urinary catheter	101 (46.8)	63 (53.8)	38 (38.4)	0.023*
Recent hospital admission ^b	127 (58.8)	76 (65.0)	51 (51.5)	0.046*
ICU admission	44 (20.4)	31 (26.5)	13 (13.1)	0.015*
Mechanical ventilation	29 (13.4)	22 (18.8)	7 (7.1)	0.012*

(Continued)

Table 2 (Continued).

	Total (n = 216) No (%)	Carbapenem Group (n=117) No (%)	Carbapenem- Sparing Group (n = 99) No (%)	P-value
Empirical AB therapy				
Penicillin/beta-lactamase inhibitor	10 (4.6)	3 (2.6)	10 (10.1)	0.192
Cephalosporins	29 (13.4)	18 (15.4)	11 (11.1)	0.359
Carbapenems	7 (3.2)	3 (2.6)	4 (4.0)	0.705
Fluoroquinolones	17 (7.9)	7 (6.0)	10 (10.1)	0.263
TMP/SMX	2 (0.9)	2 (1.7)	0 (0.0)	0.501
Aminoglycosides	1 (0.5)	1 (0.9)	0 (0.0)	0.999
Colistin	3 (1.4)	3 (2.6)	0 (0.0)	0.252
Tigecycline	3 (1.4)	3 (2.6)	0 (0.0)	0.252
Oral step-down AB therapy				
Amoxicillin/clavulanic acid	24 (11.1)	11 (9.4)	13 (13.1)	0.385
Ciprofloxacin	18 (8.3)	11 (9.4)	7 (7.1)	0.537
TMP/SMX	2 (0.9)	1 (0.9)	1 (1.0)	0.999
Cefuroxime	1 (0.5)	1 (0.9)	0 (0.0)	0.999
Definitive Therapy Duration (Mean ± SD)	11.12 ± 7.37	13.77 ± 8.59	7.98 ± 3.65	<0.001*
Oral Stepdown AB duration (n=45) (Mean ± SD)	9.91 ± 5.41	10.29 ± 4.09	9.48 ± 6.69	0.620

Notes: ^aDuring the past 6 months. ^bDuring the past 12 months. *Significant P value.

Abbreviations: AB, Antibiotics; ICU, intensive care unit; SD, standard deviation.

The main isolated ESBL-Es were *Escherichia coli* (69.5%), followed by *Klebsiella pneumoniae* (29.1%), as shown in Figure 2. The highest resistance rates for the used carbapenem-sparing options were 80.9% for levofloxacin, 73.2% for ciprofloxacin, and 64.8% for TMP/SMX (Table 3). In addition, no statistically significant differences were found in antimicrobial susceptibility results between community-acquired and hospital-acquired ESBL-E infections.

There were no statistically significant differences between patients who received empiric antibiotics, except for penicillins, which were prescribed more for patients in the carbapenem group. The carbapenem-sparing agents used for definitive therapy are presented in Figure 2. The mean definitive therapy duration was significantly longer in the carbapenem group compared to the carbapenem-sparing group: (11.12 ±SD 7.3 days vs 7.9 ±SD 3.6, P<0.001) (Table 2).

Regarding the primary outcomes, there were no significant differences between the two groups in 30-day all-cause mortality or clinical resolution. In contrast, statistical differences were observed in three secondary outcomes; the carbapenem-sparing group experienced a lower rate of ESBL-E infection recurrence within six months, had lower incidences of secondary multidrug-resistant (MDR) infections, and had lower incidences of secondary carbapenem-resistant Enterobacterales (CRE) infections (Table 4). The multivariable logistic regression reveals that carbapenem therapy was an independent risk factor for developing carbapenem-resistant Enterobacterales CRE infections, and ESBL-E colonization was an independent predictor of infection recurrence within 6 months (Table 5).

Based on the findings in Table 6, our study identified key factors associated with mortality in patients with non-bacteremic infections caused by ESBL-E. Among the 216 patients analyzed, 14 (6.5%) did not survive within 30 days of the diagnosis of infection. Notably, the presence of a central venous catheter, ICU admission, and mechanical ventilation

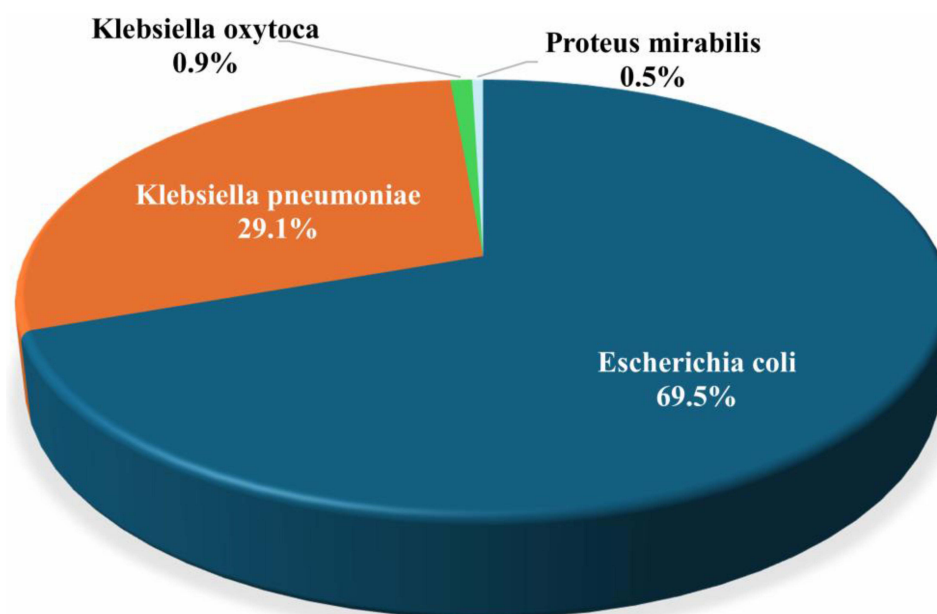


Figure 2 Types of extended-spectrum beta-lactamase-producing Enterobacterales detected in the study population.

were associated with higher mortality rates. However, multivariable logistic regression analysis was inconclusive. Additionally, other factors, such as age, gender, and comorbidities, did not reveal significant differences in mortality risk. Importantly, the type of antibiotic therapy (carbapenem versus carbapenem-sparing) did not significantly impact mortality rates.

Figures 3 and 4 illustrate the duration of definitive antibiotic therapy for patients treated with carbapenems compared to those receiving carbapenem-sparing therapies. The box plots reveal that the median duration of therapy was longer in the carbapenem group than in the carbapenem-sparing group. Specifically, the interquartile range for the carbapenem group (indicated by the boxes) was from 10 to 14 days, whereas the carbapenem-sparing group had a slightly narrower

Table 3 Susceptibility Profile of Detected Extended-Spectrum Beta-Lactamase-Producing Enterobacterales for the Used Carbapenem-Sparing Options

	Number of Tested Isolates	Resistant n (%)	Hospital-Acquired (%)	Community-Acquired (%)	P-value
Amoxicillin/clavulanic acid	116	41 (35.3%)	32.4%	39.6%	0.422
Piperacillin-tazobactam	52	17 (32.7%)	34.5%	30.4%	0.823
Cefepime	36	20 (55.6%)	56.0%	54.5%	0.721
Ceftazidime avibactam	32	2 (6.3%)	9.5%	0.0%	0.526
Ciprofloxacin	157	115 (73.2%)	75.2%	69.6%	0.447
Levofloxacin	89	72 (80.9%)	78.3%	86.2%	0.375
Gentamicin	134	34 (25.4%)	26.3%	24.1%	0.776
Amikacin	72	10 (13.9%)	12.8%	15.2%	0.776
TMP-SMX	210	136 (64.8%)	58.4%	68.4%	0.115
Nitrofurantoin	83	14 (16.9%)	17.8%	15.8%	0.809

Table 4 Therapy Outcomes Comparisons (Carbapenems Group vs Carbapenem-Sparing Group)

	Total (n = 216) No (%)	Carbapenem Group (n=117) No (%)	Carbapenem- Sparing Group (n = 99) No (%)	RR (95% CI)	P-value
30-day all-cause mortality	14 (6.5)	9 (7.7)	5 (5.1)	1.52 (0.53–4.39)	0.432
Clinical Resolution	139 (64.4)	72 (61.5)	67 (67.7)	0.91 (0.75–1.11)	0.348
Bacteriological Resolution	165 (76.4)	88 (75.2)	77 (77.8)	0.97 (0.83–1.12)	0.658
Recurrence of an ESBL infection within 6 months	62 (28.7)	41 (35.0)	21 (21.2)	1.65 (1.05–2.59)	0.025*
Secondary MDR within 30 days	49 (29.1)	34 (29.1)	15 (15.2)	1.92 (1.11–3.31)	0.015*
Secondary CRE within 30 days	33 (15.3)	24 (20.5)	9 (9.1)	2.26 (1.10–4.63)	0.020*

Note: *Significant P value.

Abbreviations: CRE, Carbapenem-resistant Enterobacterales; CI, confidence interval; MDR, Multidrug-Resistant; RR, relative risk.

Table 5 Multivariable Logistic Regression Analysis* of Identified Predictors Linked to the Study Outcomes in Hospitalized Patients with Non-Bacteremic ESBL-E Infections

Identified risk factors	Univariable Logistic Regression		Multivariable Logistic Regression	
	Crude Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
30-day mortality				
ICU admission	12.35 (3.66–41.70)	<0.001	5.32 (0.64–44.17)	0.122
Central venous catheter	11.49 (3.64–36.33)	<0.001	3.09 (0.40–23.77)	0.278
Mechanical ventilation	11.49 (3.64–36.33)	<0.001	1.07 (0.17–9.90)	0.951
Concomitant infection	1.98 (0.85–8.30)	0.998	1.60 (0.42–6.12)	0.496
Immunosuppressive therapy	11.49 (3.64–36.33)	<0.001	2.48 (0.21–29.72)	0.473
Recurrence of an ESBL infection within 6 months				
ESBL Colonization	5.89 (2.53–13.69)	<0.001	7.18 (2.15–24.05)	0.001
Urinary catheter	1.73 (1.95–3.13)	0.071	1.65 (0.80–3.37)	0.173
Recent hospital admission ^b	1.54 (0.84–2.85)	0.166	1.83 (0.84–4.02)	0.132
ICU admission	1.38 (0.68–2.79)	0.377	1.81 (0.53–6.24)	0.346
Carbapenem therapy	2.00 (1.09–3.70)	0.260	1.80 (0.87–3.51)	0.087
Secondary MDR within 30 days				
Previous AB therapy ^a	1.51 (0.73–3.13)	0.263	1.72 (0.70–4.22)	0.234
ESBL-E Colonization	1.16 (0.46–2.91)	0.754	2.87 (0.70–11.79)	0.143
Urinary catheter	2.39 (1.24–4.60)	0.009	1.56 (0.69–3.49)	0.283
Recent hospital admission ^b	1.27 (0.66–2.46)	0.470	1.27 (0.56–2.86)	0.573
ICU admission	4.11 (2.01–8.40)	<0.001	1.75 (0.50–6.09)	0.379
Mechanical ventilation	4.82 (2.13–10.92)	<0.001	2.83 (0.57–13.99)	0.202
Carbapenem therapy	2.94 (1.16–4.52)	0.017	1.71 (0.82–3.55)	0.150

(Continued)

Table 5 (Continued).

Identified risk factors	Univariable Logistic Regression		Multivariable Logistic Regression	
	Crude Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Secondary CRE within 30 days				
Previous AB therapy ^a	1.51 (0.73–3.13)	0.263	1.91 (0.71–5.09)	0.198
ESBL Colonization	1.16 (0.46–2.91)	0.754	1.82 (0.38–8.63)	0.454
Urinary catheter	2.39 (1.24–4.60)	0.009	1.73 (0.71–4.21)	0.230
Mechanical ventilation	4.82 (2.13–10.92)	<0.001	1.13 (0.18–6.95)	0.896
Carbapenem therapy	2.29 (1.16–4.52)	0.017	2.39 (1.01–5.65)	0.047

Notes: ^aDuring the past 6 months. ^bDuring the past 12 months. *The multivariable logistic regression model for 30-day mortality includes age, gender, Charlson comorbidity index score, ICU admission, central venous catheter, mechanical ventilation, recent hospitalization, previous antibiotic therapy, concomitant infection, previous ESBL infection, immunosuppressive therapy, and receiving carbapenem therapy. Additionally, a multivariable logistic regression model was run to identify predictors of secondary outcomes. The model includes previous AB therapy, ESBL-E colonization, previous ESBL-E infection, immunosuppressive therapy, central venous catheter, urinary catheter, recent hospital admission, ICU admission, mechanical ventilation, and carbapenem therapy.

Table 6 Mortality Risk Factors of Patients with Non-Bacteremic Infections Caused by ESBL-E

	Total (n = 216) No (%)	Survive (n = 202) No (%)	Non-Survive (n = 14) No (%)	RR (95% CI)	P-value
Age (mean ± SD)	-	61.40 ± 20.96	65.00 ± 17.89	-	0.531
Age > 65 years	106 (49.1)	99 (49.0)	7 (50.0)	0.98 (0.57–1.69)	0.943
Gender (male)	94 (43.5)	87 (43.1)	7 (50.0)	0.86 (0.49–1.49)	0.613
Immunosuppressive therapy	19 (8.8)	18 (8.9)	1 (7.1)	1.43 (0.20–10.00)	0.999
Central venous catheter	29 (13.4)	21 (10.4)	8 (57.1)	0.18 (0.09–0.33)	<0.001*
ICU admission	44 (20.4)	34 (16.8)	10 (71.1)	0.24 (0.15–0.37)	<0.001*
Mechanical ventilation	29 (13.4)	21 (10.4)	8 (57.1)	0.18 (0.09–0.33)	<0.001*
Congestive heart failure	29 (13.4)	27 (13.4)	2 (14.3)	0.94 (0.25–3.54)	0.999
Dementia / Chronic cognitive deficit	24 (11.1)	21 (10.4)	3 (21.4)	0.49 (0.16–1.43)	0.193
Chronic pulmonary disease	18 (8.3)	17 (8.4)	1 (7.1)	1.18 (0.17–8.22)	0.999
Liver disease	9 (4.2)	7 (3.5)	2 (14.3)	0.24 (0.06–1.06)	0.108
Diabetes mellitus	111 (51.4)	106 (52.5)	5 (35.7)	1.47 (0.72–3.00)	0.225
Moderate/ Severe renal disease	72 (33.3)	65 (32.2)	7 (50.0)	0.64 (0.37–1.13)	0.239
Comorbidities ≥ 3	106 (49.1)	100 (49.5)	6 (42.9)	1.16 (0.62–2.15)	0.630
Charlson score (mean ± SD)	-	4.82 ± 3.29	4.93 ± 2.92	-	0.902
Carbapenem therapy	117 (54.2)	108 (53.5)	9 (64.3)	0.83 (0.55–1.25)	0.366
Carbapenem-sparing therapy	99 (45.8)	94 (46.5)	5 (35.7)	1.30 (0.64–2.67)	0.432

Note: *Significant P value.

Abbreviations: CI, confidence interval; ICU, intensive care unit; RR, relative risk; SD, standard deviation.

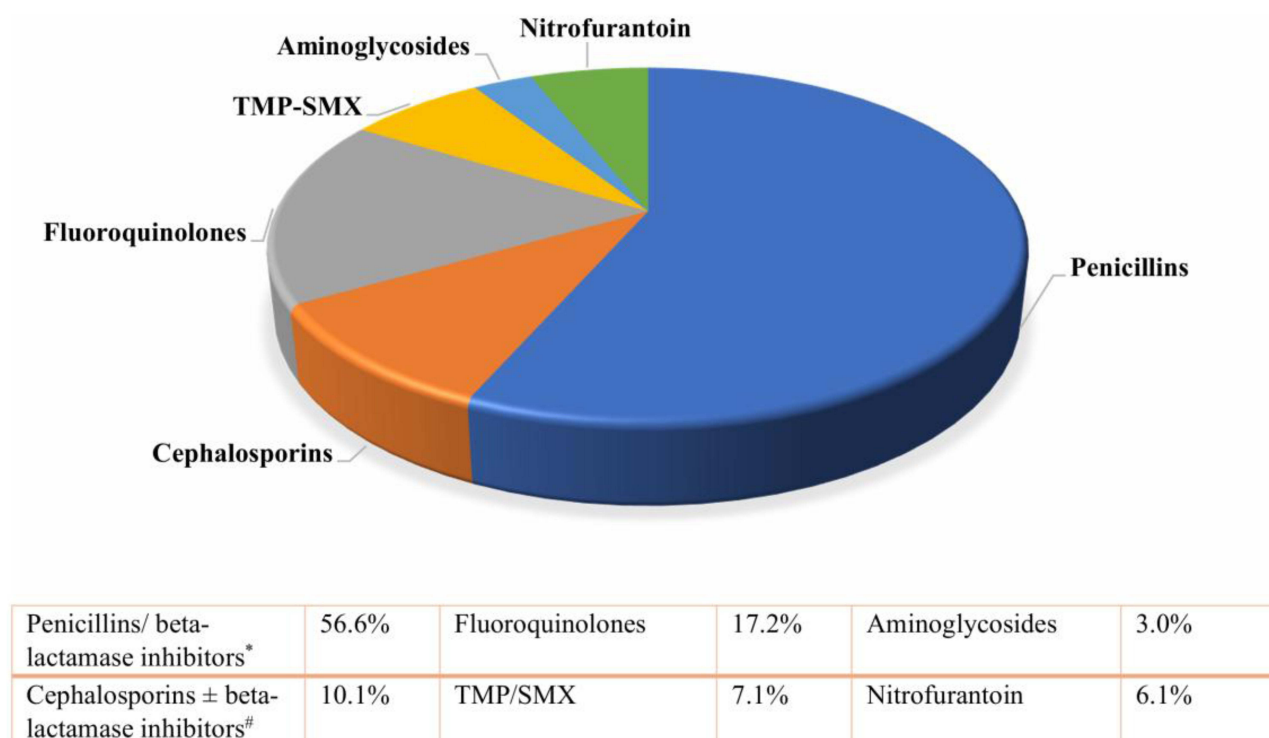


Figure 3 Antibiotics used for carbapenem-sparing therapy in patients with ESBL-E non-bacteremic infections. *Piperacillin-tazobactam or amoxicillin-clavulanic acid. [#]cefepime or ceftazidime/avibactam.

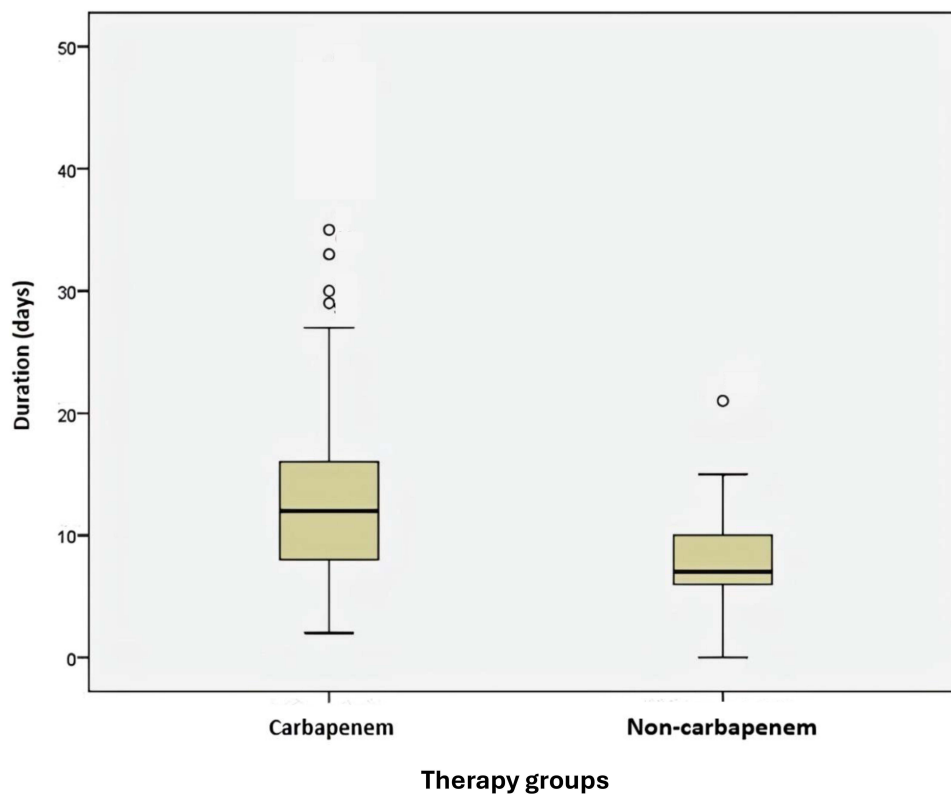


Figure 4 Definitive antibiotic therapy duration (carbapenem group vs carbapenem-sparing group). Boxes indicate the 25th to 75th percentile of both groups.

range, typically from 7 to 12 days ($P < 0.001$). The 25th to 75th percentile ranges suggest that while both groups had variability in therapy duration, patients in the carbapenem group generally received treatment for a longer period.

Discussion

ESBL-E infections have emerged as a significant global public health threat in the era of multidrug resistance. The majority of published studies from Saudi Arabia and the Arabian Peninsula have pointed to a high prevalence of ESBL-E and an increasing emergence of CRE, mainly due to the misuse of antibiotics, including carbapenems. However, these studies have primarily focused on microbiological or molecular aspects, particularly resistance mechanisms.^{17,18}

Two primary outcomes were investigated: 30-day all-cause mortality and clinical cure. Regarding 30-day mortality, our data showed a statistically insignificant difference between carbapenems and carbapenem-sparing groups, which was consistent with previous studies comparing carbapenems and carbapenem-sparing options for treating urinary tract infections (UTIs),^{19,20} severe infections in ICU patients,²¹ and bloodstream infections (BSIs).^{22,23} In addition, some studies have shown that aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole are alternative options to carbapenems for treating BSIs caused by susceptible ESBL-E.^{24–26} Furthermore, our findings were consistent with the conclusions of a meta-analysis of 35 studies that revealed no difference in overall mortality when carbapenems were compared to non-beta-lactam/beta-lactamase inhibitor combinations (non-BL/BLIs), cephalosporins, or BL/BLIs in empirical therapy, or when carbapenems were compared to quinolones in definitive therapy.²⁷ However, other researchers raise concerns regarding the inferiority of carbapenem-sparing susceptible beta-lactams, such as TZP or cefepime, for treating ESBL-E BSIs with increased mortality.^{9,13,28}

The other co-primary outcome investigated was clinical cure, which was statistically insignificant between the two groups (clinical cure in the carbapenem group 61.5% vs 67.7% in the carbapenem-sparing group, $P = 0.35$). The comparable clinical cure rates between carbapenems and other antimicrobial therapy options have also been reported in previous studies, including patients with complicated or uncomplicated UTIs,^{20,29–32} hospitalized patients,¹¹ or even patients with BSIs.^{14,27,33} However, some studies showed significant clinical failure in BSI patients treated with cefepime.^{7,13} In summary, our findings regarding mortality rates and clinical cure support the conclusions of earlier studies regarding the efficacy of carbapenem-sparing therapy for nonbacteremic ESBL-E infections.

Four secondary outcomes were investigated: bacteriologic resolution, recurrence of an ESBL-E infection within six months, secondary MDR within 30 days, and secondary CRE within 30 days. Our data showed that bacteriological resolution was comparable between the two groups (75.2% vs 77.8% in carbapenem and carbapenem-sparing groups, respectively, $P = 0.658$). This finding was consistent with reported bacteriologic resolution in previous studies.^{7,29,34,35} Furthermore, other studies reported higher bacteriologic resolution in the carbapenem-sparing group.^{20,30} This non-inferiority or even better bacteriologic resolution supports the use of carbapenem-sparing agents as an attractive alternative to carbapenems.

In terms of ESBL-E infection recurrence within six months, our findings showed significantly lower recurrence in the carbapenem-sparing group (35.0% vs 21.2%, $P = 0.025$), which aligns with previous studies comparing the relapse rates between carbapenem and carbapenem-sparing therapies in patients with ESBL-E UTIs.^{30,34} The ESBL-E colonization was an independent risk factor for repeated infections (Table 5). However, other studies did not find statistical significance of ESBL-E infection recurrence in patients with complicated UTIs, including acute pyelonephritis, ICU patients, and BSIs.^{14,20,21} A likely explanation for the discrepancy in findings regarding ESBL-E recurrence is the observed differences in population size and the length of the recurrence period investigated. In addition, one study claimed that aminoglycosides were inferior to carbapenems or TZP in terms of the recurrence of ESBL-E bacteriuria.²⁴ In our study, however, only 3.0% of the patients received aminoglycosides as definitive antimicrobial therapy.

Doubtlessly, the global irrational use of penicillins and cephalosporins played a vital role in the emergence of MDR organisms, including ESBL-Es, which in turn led to the subsequent widespread use of carbapenems. However, the vicious circle of antimicrobial resistance continues as the selective pressure of carbapenems leads to the emergence of more difficult-to-treat superbugs, namely CRE.³⁶ Our study findings showed that the incidences of secondary MDR and CRE infections were notably lower in the carbapenem-sparing group (29.1% vs 15.2% for secondary MDR within 30 days, $P = 0.015$, and 20.5% vs 9.1% for secondary CRE within 30 days, $P = 0.020$). Multivariable logistic regression also reveals that carbapenem therapy was an independent risk factor for developing CRE infections; however, it was

inconclusive regarding the development of secondary MDR infection. These findings were consistent with earlier published data indicating a lower incidence of MDR and fungal infections in patients treated with carbapenem-sparing agents compared to those with carbapenems.²² Other published data did not show an increased risk of emerging MDR or CRE in patients treated with carbapenem-sparing regimens compared to carbapenems.²⁶

Our study findings suggest that while clinical outcomes are similar, carbapenem-sparing therapies may offer further benefits by reducing the risk of infection recurrence and de-escalating the dynamic process of developing more potent MDR organisms. In addition, the observed significant trend of carbapenem use in patients with central venous catheters, urinary catheters, hospitalization during the past year, and mechanical ventilation (Table 2) indicates that carbapenems are frequently used to treat ESBL-E severe infections with a more complicated clinical course. Moreover, the data show that the median duration of therapy was longer in the carbapenem group, with the 25th to 75th percentile range spanning from 10 to 14 days, compared to 7 to 12 days in the carbapenem-sparing group, which was consistent with previously reported shorter carbapenem-sparing therapy durations.^{14,20,30} The longer duration of carbapenem therapy may reflect its use in more severe cases or the need for a more intensive approach to managing complex infections. These differences underscore the potential impact of antibiotic choice on treatment duration and highlight the need for further research to optimize therapy duration based on antibiotic efficacy and patient outcomes.

Regarding mortality risk factors, the statistical analysis identified three factors linked to higher mortality risk: having a central venous catheter, being admitted to the ICU, and requiring mechanical ventilation (Table 6), although these were inconclusive in multivariable logistic regression analysis (Table 5). Nevertheless, these factors predict complicated clinical courses rather than infection-related mortality and underscore the importance of closely monitoring patients with invasive devices and those requiring intensive care, as they are at a higher risk of mortality, regardless of the antibiotic regimen employed. Other ESBL-E infection mortality predictors identified in the literature were neutropenia, hospital-acquired infections, pneumonia, and severe sepsis /septic shock.³⁷ In addition, the analysis showed that the type of antibiotic therapy, whether carbapenem or carbapenem-sparing, did not significantly impact mortality outcome, suggesting that other clinical factors play a more substantial role in determining patient survival.

Finally, an evidence-based approach is crucial for treating patients with ESBL-E infections. The majority of published articles reveal the noninferiority of carbapenem-sparing options for treating ESBL-E infections, especially nonbacteremic ones. The updated IDSA guideline for treating infections caused by Gram-negative MDR bacteria recommends carbapenem-sparing options for treating noncomplicated, nonbacteremic ESBL-E infections.³ However, in real-life practice, the use of carbapenems to treat such infections remains high, even after the frequent publication of updated antimicrobial therapy guidelines.³⁶

Our study had important limitations. First, it was a retrospective study, and there could be missing or incomplete data despite robust data collection. Second, most demographic and clinical characteristics were similar between the two groups; however, UTIs were more prevalent in the carbapenem-sparing group, whereas respiratory, skin and soft tissue, and intra-abdominal infections were more prevalent in the carbapenem group. Third, this study had a relatively small sample size, which prevented the generalization of study findings. Fourth, the genotypic analyses were unavailable, which prevented determining the relevant beta-lactamases and ESBL genes, such as TEM-1, SHV-1, and OXA-10 beta-lactamases, or the currently globally predominant CTX-M ESBLs. However, this was the first study in Saudi Arabia to compare available therapy options for ESBL-E infections, offering updated insights to bridge the knowledge gap and reveal the efficacy of carbapenem-sparing therapies for treating non-bacteremic ESBL-E infections.

Conclusion

ESBL-E infections are a significant healthcare concern globally, and using carbapenems to treat such infections escalates the antimicrobial resistance problem with the emergence of more potent MDR microorganisms. Our comparative study demonstrates that carbapenem-sparing therapies are as effective as carbapenems, with comparable 30-day all-cause mortality, clinical cure rates, and bacteriological resolution. In addition, carbapenem-sparing options showed lower recurrence of ESBL-E infections and reduced development of secondary MDR or CRE infections within 30 days. These findings support using carbapenem-sparing agents as the first choice for treating noncomplicated, nonbacteremic ESBL-E

infections. The potential impact of these findings on the healthcare system is significant. Further comparative studies are necessary to explore other antimicrobial therapy options.

Abbreviations

BL/BLI, β -lactam/ β -lactamase inhibitor; CRE, Carbapenem-resistant Enterobacterales; ESBL-E, Extended-spectrum β -lactamase-producing Enterobacterales; IDSA, Infectious Disease Society of America; IRB, Institutional Review Board; MDR, Multidrug-resistant; RR, Relative Risk; SD, Standard Deviation; SSTI, Skin and Soft Tissue Infection; TZP, Piperacillin-Tazobactam; UTI, Urinary Tract Infection.

Data Sharing Statement

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author(s).

Ethics Approval

Ethical approval was obtained from the Institutional Review Boards (IRB) of Imam Abdulrahman bin Faisal University [IRB number: IRB-UGS-2022-05-177]. All study steps adhered to the ethical standards outlined in the Declaration of Helsinki and its amendments. As the study is a retrospective cohort study, informed consent was not required. Moreover, the patient data were confidentially treated and all identifying information was anonymized.

Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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