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ORIGINAL RESEARCH

Characteristics and Outcomes of Patients Treated with Carbapenem Versus Non-carbapenem Therapy for AmpC-Producing Enterobacterales Bacteremia: A Retrospective Study

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ABSTRACT

***Introduction*:** Inducible AmpC β-lactamases in Gram-negative Enterobacterales pose therapeutic challenges. Although carbapenems are the preferred treatment, other antibiotics can serve as a viable alternative. Studies comparing treatment options report varied outcomes. This study evaluates 30-day mortality, treatment failure, and length of hospitalization in patients with AmpC-producing Enterobacterales bacteremia.

***Methods*:** This retrospective cohort study included adult patients with bacteremia caused by AmpC-producing Enterobacterales. Exclusion criteria included: therapy duration < 72 h, coinfection, resistant isolates, and death within 72 h of diagnosis. Patients were divided into definitive carbapenem and noncarbapenem therapy. The primary outcome was 30-day mortality, while secondary outcomes evaluated treatment failure and length of hospitalization. Statistical analysis used descriptive statistics, group comparisons, and logistic regression.

***Results*:** Of 214 screened patients, 80 met the inclusion criteria. *Enterobacter cloacae* (60%) was the predominant pathogen, primarily originating from line-related infections (55%). Carbapenems were the primary empirical (45%) and definitive (75%) therapies; 30-day mortality was higher in the non-carbapenem group (20% versus 3.3%, $p = 0.08$). Treatment failure was significantly higher in the non-carbapenem group (20% versus 1.6%, $p < 0.01$). The mean hospital stay was longer in the carbapenem group (26 ± 38.40 days) than the non-carbapenem group (11.15 ± 7.15 days, $p = 0.87$). Older age was significantly associated with higher mortality (odds ratio (OR) 1.07, 95% confidence intervals (CI): 0.98–12.20, $p = 0.015$).

***Conclusions*:** Carbapenem use was significantly associated with improved survival, highlighting its importance in treatment strategies. Age significantly affects survival, stressing the need for personalized treatments. Further research and strategies are needed to address clinical failures and enhance antimicrobial stewardship.

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Keywords: AmpC β-lactamase; Carbapenems; Enterobacterales; Bacteremia

Key Summary Points

Why carry out this study?

AmpC β-lactamase-producing Enterobacterales pose a treatment challenge owing to inducible resistance, leading to potential clinical failure.

Understanding the effectiveness of carbapenem versus non-carbapenem therapy can help guide better treatment decisions and improve patient outcomes.

What was learned from this study?

Carbapenems were the most commonly used definitive therapy and were associated with significantly lower mortality.

Non-carbapenem therapy had a higher treatment failure rate compared with carbapenems.

Older patients had a significantly higher risk of mortality.

INTRODUCTION

Inducible AmpC β-lactamases are enzymes produced by a group of Gram-negative Enterobacterales, conferring resistance to β-lactam antibiotics, particularly third-generation cephalosporins. AmpC β-lactamase production can be detected through phenotypic and molecular methods. Phenotypic approaches include cefoxitin resistance screening, the AmpC disk test, and enzyme inhibition assays, while molecular techniques such as polymerase chain reaction (PCR) provide definitive identification of AmpC genes [1]. However, AmpC production poses a significant clinical challenge because antibiotic exposure typically induces its expression, potentially leading to treatment failure despite in vitro susceptibility results [2]. In clinical practice, organisms are often managed on the basis of their likelihood of AmpC production rather than routine confirmatory testing. The most common organisms associated with moderate-to-high risk, clinically significant AmpC production include *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*. AmpC enzyme production is also observed, though less frequently, in *Morganella morganii*, *Providencia* spp., and *Serratia marcescens*. This inducible resistance mechanism increases the risk of clinical failure, even when in vitro susceptibility testing suggests effectiveness [2–4].

Carbapenems have traditionally been considered the preferred treatment for infections caused by AmpC-producing organisms. However, the Infectious Diseases Society of America (IDSA) recommends cefepime as a first-line option when the minimum inhibitory concentration (MIC) is ≤ 2 mcg/mL, reserving carbapenems for higher MICs (≥ 4 mcg/mL) [2]. Given concerns about carbapenem overuse and resistance, alternative therapies may be viable in specific scenarios. Non-carbapenem therapies such as cefepime, piperacillin–tazobactam, third-generation cephalosporins (e.g., ceftriaxone), fluoroquinolones (e.g., ciprofloxacin), polymyxins (e.g., colistin), trimethoprim–sulfamethoxazole, and tigecycline have been explored as potential alternatives [5, 6]. An observational study found that the use of ceftriaxone for treating monomicrobial infections caused by *Enterobacter*, *Citrobacter*, or *Serratia* spp. demonstrated comparable treatment failure rates to cefepime, piperacillin–tazobactam, and meropenem [7]. Furthermore, a meta-analysis of observational studies found no difference in mortality between piperacillin–tazobactam or carbapenems for the treatment of bloodstream infections [8].

The MERINO-2 trial compared meropenem and piperacillin-tazobactam for the treatment of bloodstream infections caused by AmpC-producing organisms, finding no significant differences in the primary composite outcomes of 30-day mortality, clinical failure, microbiological failure, or microbiological relapse, though the findings were inconsistent across individual outcomes [9]. A meta-analysis included 11 observational studies; however, no randomized controlled trials have been specifically

designed to directly compare the efficacy of β-lactam/β-lactamase inhibitors such as piperacillin–tazobactam with carbapenems. Only one study identified the empirical use of piperacillin–tazobactam as independently associated with improved survival, and cefepime demonstrated equivalent efficacy to carbapenems for *Enterobacter* bloodstream infections, even after adjusting for comorbidities and propensity to receive carbapenems. Similarly, other studies reported favorable outcomes with cefepime as a potential alternative to carbapenems for bloodstream infections caused by *E. cloacae* or other AmpC producers [10].

The aim of this study is to evaluate 30-day mortality, treatment failure, and length of hospitalization in patients with AmpC-producing Enterobacterales bacteremia, comparing carbapenems with other antibiotics and analyzing patient characteristics and factors influencing survival.

METHODS

Study Design and Settings

This was a single-center, retrospective cohort study conducted at King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia.

The study included adult patients 18 years or older with a positive blood culture for an AmpC-producing Enterobacterales, including *E. cloacae*, *K. aerogenes*, *C. freundii*, *M. morganii*, *Providencia* spp., and *S. marcescens*, between January 2018 and December 2021.

Patients were excluded if they received therapy for less than 72 h, had incomplete medical records, experienced bloodstream coinfection with other organisms, died within 72 h of diagnosis, or had an isolate resistant to ceftriaxone, cefepime, or piperacillin–tazobactam.

The included patients were divided into two groups for analysis on the basis of the choice of definitive therapy: the carbapenem group, which received any carbapenem agent (meropenem, imipenem, or ertapenem), and the non-carbapenem group, which received alternative activity against AmpC-producing organisms. These included β-lactams such as cefepime, piperacillin–tazobactam, ceftazidime, and ceftriaxone, as well as non β-lactams agents such as aminoglycosides (e.g., amikacin and gentamicin), fluoroquinolones (e.g., ciprofloxacin and levofloxacin), colistin, trimethoprim–sulfamethoxazole, and tigecycline.

The primary outcome was 30-day mortality from the date of index blood culture, while the secondary outcome was treatment failure and hospital length of stay.

Ethical Approval

This study received institutional review board (IRB) approval from King Abdullah International Medical Research Center (KAIMRC) (approval number: NRC22R/053/01). The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. Informed consent was waived by the IRB.

Definitions

Active antibiotics are those reported as susceptible by in vitro susceptibility testing [11]. Active empirical therapy refers to an antibiotic administered for at least 48 h before susceptibility results become available [12]. Active definitive therapy refers to an antibiotic administered for at least 48 h after susceptibility results were known [11]. Combination therapy is the use of two or more active antibiotics; 30-day mortality is defined as death occurring within 30 days of the index culture. Treatment failure is defined as the requirement for escalation in antibiotic therapy, as determined by the treating physician. [13].

Statistical Analysis

Descriptive statistics are presented as mean (standard deviation (SD)) or median with interquartile range (IQR; 25th to 75th percentile) for continuous variables and as frequencies (percentages) for categorical variables. Comparisons of baseline characteristics between groups were

performed using an independent samples *t*-test for normally distributed continuous variables or the Mann–Whitney *U* test for nonnormally distributed continuous variables. The chi-squared test (or Fisher's exact test, where appropriate) was used for categorical variables.

A logistic regression model was constructed to evaluate the association between relevant clinical predictors and survival (binary outcome). Predictors included age, length of hospital stay, empirical or definitive carbapenem use, and source control. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported to quantify both the strength and direction of associations with survival. Statistical significance was defined as a *p*-value less than 0.05.

All analyses were conducted using Python (Statsmodels library, version 0.13.5), Microsoft Excel (version 16.29), and GraphPad Prism 10.

RESULTS

In this retrospective cohort study, we evaluated 214 patients, of whom 80 met the inclusion criteria, and 134 patients were excluded. The primary reasons for exclusion were polymicrobial bloodstream infections ($n=118$ patients) and missing data ($n=13$ patients). Details of excluded patients are summarized in Fig. 1.

The baseline characteristics of the included patients are presented in Table 1. The median age was 60 years, with a slightly higher proportion of men ($n=43$ patients, 53.75%) than women. The most common comorbidity was diabetes, affecting 53 patients (66.25%), followed by chronic kidney disease in 41 (51.25%) and cardiovascular diseases in 33 (41.25%). *E. cloacae* was the most frequent causative pathogen of bacteremia, identified in 48 patients (60%), followed by *S. marcescens* ($n=21$, 26.25%) and *K. aerogenes* ($n=7$, 8.75%). The primary sources of bacteremia were line-related in 44 patients (55%), followed by urinary tract infections in 10 (12.5%), and intra-abdominal infections in 8 (10%). Source control was done in 53 patients (66.25%).

Regarding treatment, carbapenems were the most frequently used empirical therapy ($n=36$, 45%), followed by piperacillin–tazobactam ($n=19$, 23.75%). Empirical combination therapy was used in seven patients (8.75%). Definitive therapy was primarily carbapenems in 60 patients (75%), followed by aminoglycosides in 14 (17.5%) and ciprofloxacin in 10 (12.5%). Combination therapy was used in 12 patients (15%) during definitive therapy (Table 2).

Empirical combination therapy was given to four patients (6.67%) in the carbapenem group and three patients (15%) in the non-carbapenem group ($p=0.5$). For definitive therapy, seven patients (11.67%) in the carbapenem group and five patients (25%) in the non-carbapenem group received combination therapy ($p=0.42$). Meropenem plus gentamicin was the most frequently prescribed (3.75%), followed by meropenem plus amikacin (1.25%), meropenem plus ciprofloxacin (1.25%), and meropenem plus colistin (1.25%). Nonmeropenem-based combinations included ciprofloxacin plus gentamicin (3.75%), ciprofloxacin plus tigecycline (1.25%), and piperacillin–tazobactam plus gentamicin (1.25%). The duration of therapy was shorter in the carbapenem group (10.28 day) compared with the non-carbapenem group (28.44 days), with a *p*-value of 0.38 (Tables 2, 3).

When evaluating patients on the basis of definitive therapy used, 75% (60 patients) received carbapenems, while 25% (20 patients) received non-carbapenem agents. The median age was comparable between the carbapenem (60.43 years) and the non-carbapenem (60.05 years) groups ($p=0.12$). Patients in the carbapenem group were predominantly men (50% versus 35%; $p=0.002$). The majority of patients in both groups were admitted initially to the general wards, 100% in the carbapenem group versus 95% in the non-carbapenem group. However, 25% of patients in the carbapenem group required intensive care unit (ICU) admission during the hospital stay compared with 15% of the non-carbapenem group ($p=0.7$). Comorbid conditions were prevalent among both groups. Chronic kidney disease was reported in 51.6% of patients in the carbapenem group and 50% in the non-carbapenem group

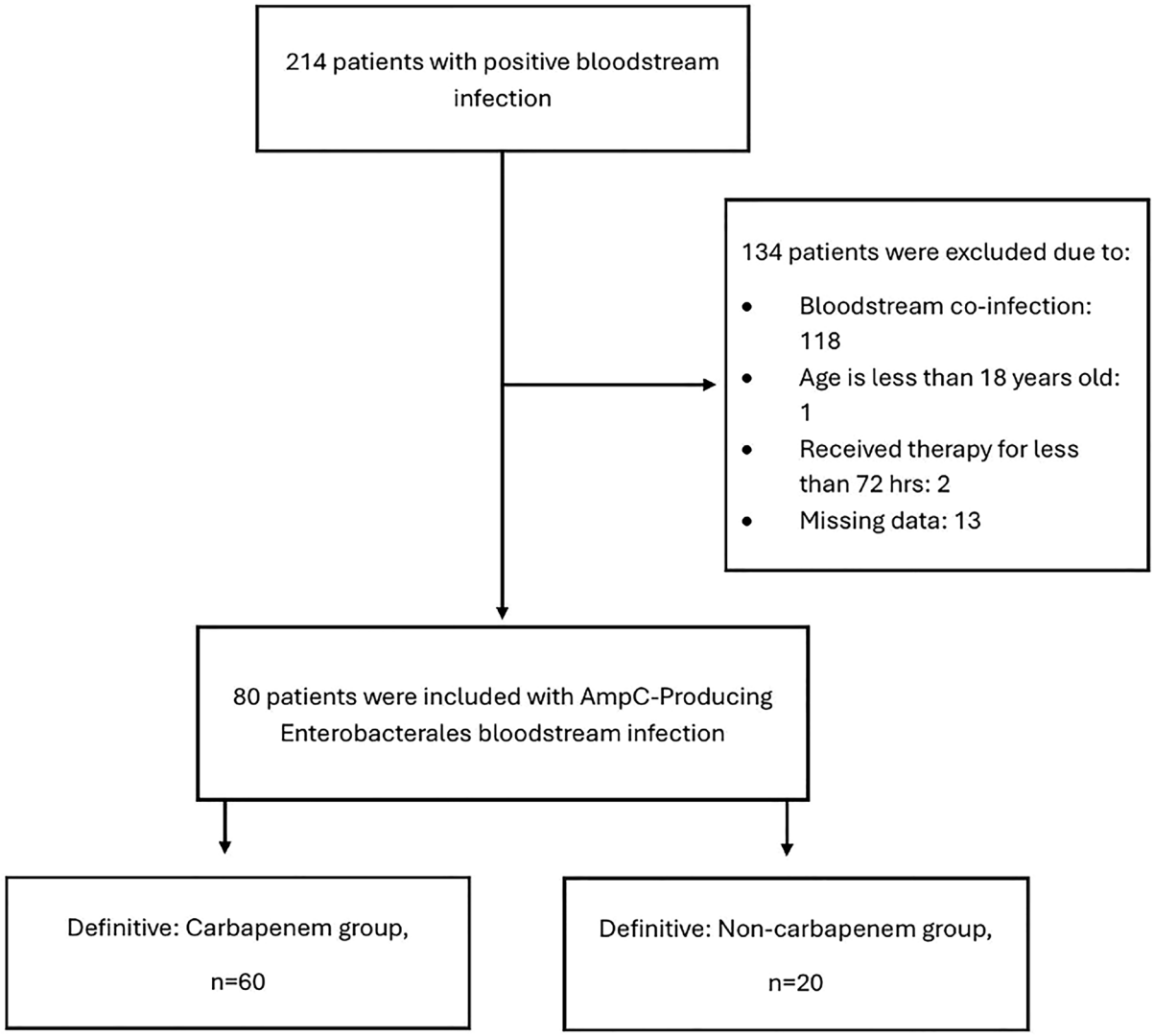

Fig. 1 Flow diagram of inclusion and exclusion

($p=0.13$). Diabetes was more common in the non-carbapenem group (85%) compared with the carbapenem group (60%), though the difference was not statistically significant ($p=0.66$). Cardiovascular disease was present in 46% of patients receiving carbapenems and 30% of those on no-ncarbapenem therapy ($p=0.2$). *E. cloacae* was the most common isolate in the carbapenem group (65% versus 45%; $p<0.05$). Line-related infection was the most common source in both groups (55%). Differences in other infection sources, such as intra-abdominal infections, were seen more frequently in the non-carbapenem group (20% versus 6.6% in the carbapenem group, $p=0.08$), and urinary tract infections were more frequent in the carbapenem group (15% versus 5% in the no-ncarbapenem group, $p=0.24$). However, the differences were not statistically significant. Source control was performed in the majority of patients in both groups (66.6% versus 65%; $p=0.77$) The median Pitt bacteremia score was identical in both groups (2, IQR: 0, 2; $p=0.76$). (Table 3).

Additionally, 55% of patients in the carbapenem definitive group had received carbapenems empirically ($p<0.0003$). Gentamicin use empirically was more frequent in the non-carbapenem group (40% versus 13.3%; $p=0.01$).

Table 1 Baseline characteristics

Characteristics	Overall ($N=80$)
Age, years (IQR)	60 (49.5,72)
Gender	
Men	43 (53.75%)
Weight (kg)	75.9 ± 18.6
Height (m)	1.62 ± 0.103
Body mass index	28.3 ± 6.1
Primary site of admission	
General	79 (98.75%)
Intensive care unit	1 (1.25%)
ICU admission during infection	18 (22.5%)
Comorbidities	
Chronic kidney disease	41 (51.25%)
Diabetes	53 (66.25%)
Cardiovascular disease	33 (41.25%)
Transplant	8 (10%)
Cancer	11 (13.75%)
Liver disease	8 (10%)
Microorganism	
Enterobacter cloacae	48 (60%)
Klebsiella aerogenes	7 (8.75%)
Serratia marcescens	21 (26.25%)
Providencia sturtii	3 (3.75%)
Morganella morganii	2 (2.5%)
Source of bacteremia	
Intra-abdominal	8 (10%)
Bone and joint	2 (2.5%)
Skin soft tissue	5 (6.25%)
Line-related	44 (55%)
Pneumonia	5 (6.25%)
Urinary tract infection	10 (12.5%)
Unknown	4 (5%)
Prosthetic valve endocarditis	1 (1.25%)
Source control	53 (66.25%)
Severity	
Pitt bacteremia score, median (IQR)	2 (0,2)

IQR interquartile range , *kg* kilogram, *m* meter, *ICU* intensive care unit

Ciprofloxacin also showed a higher utilization in the non-carbapenem group (15% versus 1.67%; $p=0.046$). Infectious disease (ID) consultations were more frequent in the carbapenem group (55%) compared with the non-carbapenem group (40%), with a p-value of 0.16.

Mortality within 30 days of infection occurred in six patients (7.5%) in total; 30-day mortality was higher in the non-carbapenem group (20%) compared with the carbapenem group (3.3%). However, this difference did not reach statistical significance ($p=0.08$). Moreover, treatment failure was observed in five patients (6.25%) from the total cohort. It was significantly more common in the non-carbapenem group (20%) compared with the carbapenem group (1.6%), with a p-value of <0.01. Among the patients experiencing treatment failure, two were on piperacillin–tazobactam, one on trimethoprim–sulfamethoxazole (TMP–SMX), and one on gentamicin; all of their definitive therapy was switched to a carbapenem. The fifth patient, who was on meropenem as a definitive therapy, required therapy escalation with ciprofloxacin. The mean hospital length of stay was longer in the carbapenem group (26 ± 38.40 days) compared with the non-carbapenem group (11.15 ± 7.15 days), though it was not statistically significant, with a p-value of 0.87 (Table 3).

The logistic regression analysis assessed the association between mortality and several factors, including age, length of hospitalization, carbapenem use as definitive therapy, carbapenem use as empirical therapy, and source control (Table 4). Carbapenem use as definitive therapy resulted in significantly lower odds of death (OR 0.1, 95% CI −98.41 to −8.18, $p=0.04$). Patients who underwent source control also had lower odds of mortality (OR 0.329, 95% CI 0.65–19.62;

Table 2 Antibiotic choice

Variables	Overall ($N = 80$)
Active empirical antibiotics	
Carbapenems	36 (45%)
Meropenem	35 (43.75%)
Imipenem	1 (1.25%)
Piperacillin–tazobactam	19 (23.75%)
Gentamicin	16 (20.0%)
Trimethoprim–sulfamethoxazole	1 (1.25%)
Ciprofloxacin	4 (5.0%)
Ceftazidime	1 (1.25%)
Ceftriaxone	1 (1.25%)
Amikacin	1 (1.25%)
Colistin	2 (2.5%)
Tigecycline	1 (1.25%)
Active definitive antibiotics	
Carbapenems	60 (75%)
Meropenem	54 (67.5%)
Imipenem	6 (7.5%)
Piperacillin–tazobactam	6 (7.5%)
Gentamicin	13 (16.25%)
Trimethoprim–sulfamethoxazole	1 (1.25%)
Ciprofloxacin	10 (12.5%)
Amikacin	1 (1.25%)
Colistin	1 (1.25%)
Tigecycline	1 (1.25%)
Combination therapy	
Empirical antibiotics	7 (8.75%)
Meropenem and amikacin	1 (1.25%)
Ciprofloxacin and gentamicin	1 (1.25%)
Meropenem and colistin	2 (2.5%)
Ceftazidime and gentamicin	1 (1.25%)
Meropenem and gentamicin	1 (1.25%)
Ciprofloxacin and tigecycline	1 (1.25%)
Definitive antibiotics	12 (15%)
Meropenem and gentamicin	3 (3.75%)
Meropenem and amikacin	1 (1.25%)
Meropenem and ciprofloxacin	1 (1.25%)
Ciprofloxacin and tigecycline	1 (1.25%)
Meropenem, ciprofloxacin, and gentamicin	1 (1.25%)
Ciprofloxacin and gentamicin	3 (3.75%)
Meropenem and colistin	1 (1.25%)
Piperacillin–tazobactam and gentamicin	1 (1.25%)

p 0.15), although this finding was not statistically significant. Older age, however, was significantly associated with higher odds of mortality (OR 1.07, 95% CI 0.98–12.20, $p = 0.015$).

Further analysis showed that consulting the ID team increased the likelihood of prescribing definitive carbapenems with an odds ratio of 1.84 compared with the absence of ID consultation. However, this association did not reach statistical significance (OR 1.84; 95% Cl0.65, 5.13; *p* 0.3). These findings are shown in (Fig. 2).

DISCUSSION

In this study, we assessed the clinical outcomes of adult hospitalized patients treated with various antibiotics versus carbapenems for infections caused by AmpC-producing Enterobacterales blood isolates. Empirical treatment choices showed a preference for carbapenems in the majority of patients. The fact that most patients who started carbapenem therapy continued with it as definitive therapy illustrates how initial antibiotic choices influence subsequent treatment decisions.

Our study found a comparable burden of comorbidities between patients treated with carbapenems and those receiving noncarbapenem

Table 3 Characteristics and outcomes of patients on active definitive noncarbapenems or carbapenems

Characteristics	Definitive carbapenems (*N* = 60)	%	Definitive noncarbapenems (*N* = 20)	%	*p*-Value
Age, years (IQR)	60.433	(47, 72.25)	60.05	(54, 67.75)	0.12
Gender					
Men	30	50	13	65	**0.002**
Primary site of admission					
General	60	100	19	95	> 0.99
Intensive care unit (ICU)	0	0	1	5	0.25
ICU admission during infection	15	25	3	15	0.7
Comorbidities					
Chronic kidney disease	31	51.6	10	50	0.13
Diabetes	36	60	17	85	0.66
Cardiovascular disease	27	46	6	30	0.2
Transplant	7	11.6	1	5	0.32
Cancer	6	10	5	25	0.1
Liver disease	5	8.3	3	15	0.32
Microorganism					
Enterobacter cloacae	39	65	9	45	**< 0.05**
Klebsiella aerogenes	3	5	4	20	0.18
Serratia marcescens	14	23.3	7	35	0.26
Providencia sturtii	3	5	0	0	**0.02**
Morganella morganii	2	3.3	0	0	**0.02**
Source of bacteremia					
Intra-abdominal	4	6.6	4	20	0.08
Bone and joint	2	3.3	0	0	> 0.9
Skin soft tissue	3	5	2	10	0.5
Line-related	33	55	11	55	0.5
Pneumonia	5	8.3	0	0	0.6
Urinary tract infection	9	15	1	5	0.24
Unknown	2	3.3	2	10	0.12
Prosthetic valve endocarditis	1	1.6	0	0	0.2
Source control	40	66.6	13	65	0.77

Table 3 continued

Characteristics	Definitive carbapenems ($N = 60$)	%	Definitive noncarbapenems ($N = 20$)	%	*p*-Value
Severity					
Pitt bacteremia score, median (IQR)	2 (0, 2)		2 (0, 2)		0.76
Antibiotic choice and outcomes					
Empirical antibiotics					
Meropenem	33	55.0	2	10	**< 0.0003**
Imipenem	1	1.75	0	0	> 0.9
Piperacillin–tazobactam	13	16.25	6	30	0.45
Gentamicin	8	13.3	8	40	**0.01**
Trimethoprim–sulfamethoxazole	0	0	1	5	> 0.9
Ciprofloxacin	1	1.67	3	15	**0.046**
Amikacin	1	1.67	0	0.0	> 0.9
Colistin	2	3.33	0	0	0.62
Ceftazidime	0	0	1	5	0.25
Tigecycline	0	0	1	5	0.25
Ceftriaxone	0	0	1	5	0.25
Combination therapy empirical	4	6.67	3	15	0.5
Combination therapy definitive	7	11.67	5	25	0.42
Duration of therapy (in days)	10.28 ± 6.96		28.44 ± 85.89		0.38
Infectious diseases team was consulted	33	55	8	40	0.16
Primary outcome					
30-day mortality	2	3.33	4	20	0.08
Secondary outcome					
Treatment failure	1	1.66	4	20	**< 0.01**
Hospital length of stay (in days)	26 ± 38.40		11.15 ± 7.15		0.87

Bolded p-values indicate statistical significance (P <0.05)

IQR interquartile range, *ICU* intensive care unit

therapy. Chronic kidney disease, diabetes, and cardiovascular disease were prevalent in both groups, with no statistically significant differences observed. However, cancer and liver disease were numerically higher in the noncarbapenem group. These findings suggest that underlying comorbidities may not have been the primary determinant of treatment choice or outcomes and highlight the complexity of managing AmpC-producing Enterobacterales infections in patients with multiple chronic conditions. The high prevalence of diabetes

Table 4 Multiple logistic regression for the odds of mortality

Variable	Odd ratio	95% confidence interval	*p*-Value
Age	1.07	0.98% to 12.20%	**0.015**
Length of hospitalization	1.01	−0.48% to 2.30%	0.16
Carbapenem use as definitive therapy	0.10	−98.41% to −8.18%	**0.04**
Carbapenem use as empirical therapy	2.80	56.43% to 1743.76%	0.27
Source control was done	0.33	−93.57% to 78.63%	0.23

Bolded p-values indicate statistical significance (P <0.05)

and chronic kidney disease, in particular, underscores the importance of careful antibiotic selection and dosing, given the potential impact of these conditions on drug pharmacokinetics and patient outcomes. Additionally, the presence of immunocompromised states, such as cancer and transplant status, further emphasizes the need for individualized treatment strategies and close monitoring to optimize clinical outcomes.

While carbapenems were the most commonly used definitive therapy, aminoglycosides and ciprofloxacin were also being considered as alternative treatment options. Notably, we found an underutilization of cefepime, both as empirical and definitive therapy, despite supporting evidence for its efficacy when the MIC is ≤ 2 mcg/ml. Hoellinger et al. and Coyne et al. demonstrated that cefepime was as effective as carbapenems in terms of 30-day mortality, treatment toxicity, and infection recurrence, particularly when the MIC was ≤ 1 mg/l and in patients with moderate-to-high risk Enterobacterales bacteremia [14, 15]. However, clinicians may be hesitant to use cefepime owing to concerns over extended spectrum β-lactamase (ESBL) infections, which are prevalent in our population, as well as the risk of resistance emerging at higher MIC levels (≥ 4 mcg/ml) [16–18] Additionally, the role of AmpC β-lactamase in resistance mechanisms may further influence prescribing patterns. AmpC enzymes confer resistance to many β-lactams, including cephalosporins, and can contribute to carbapenem resistance when combined with porin loss, limiting the efficacy of alternative therapies in certain cases. [19–21] Moreover, the absence of reported MIC values for cefepime may restrict its clinical utilization and informed decision-making in therapy selection. As a result, broader-spectrum antibiotics such as carbapenems are often prioritized to minimize treatment failure. This underutilization of cefepime points to the need for better integration of cefepime in treatment protocols, potentially as part of antimicrobial stewardship strategies that prioritize more judicious use of broad-spectrum antibiotics.

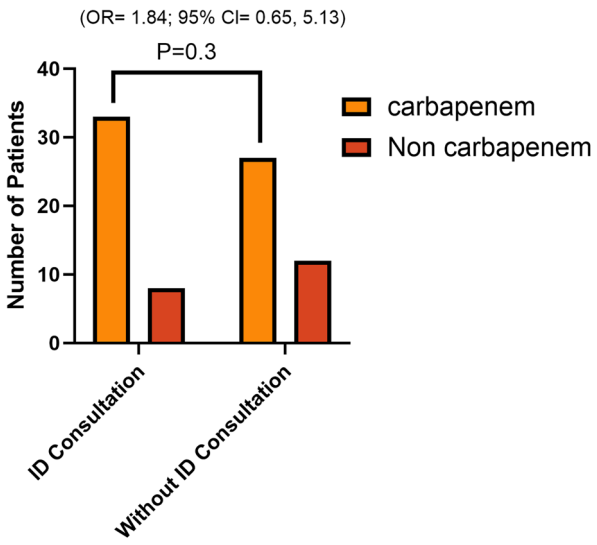

Fig. 2 ID team consultation and choice of definitive antibiotic. *ID* infectious diseases, *OR* odds ratio, *CI* confidence interval

Our results demonstrated that carbapenems were the preferred choice for treating AmpC-producing Enterobacterales infections, aligning with IDSA recommendations for the management of infections caused by AmpC-producing Enterobacterales [2]. *E. cloacae* emerged as the most common pathogen, followed by

S. marcescens. Our results are consistent with prior studies, confirming the prevalence of *E. cloacae* as the predominant pathogen causing AmpC bacteremia [14, 15]. Line-related infections were identified as the primary source of bacteremia. The findings underscore the importance of infection control measures, including source control procedures, in which a significant proportion of our patients underwent source control procedures.

In terms of the primary outcome, 30-day mortality occurred in 7.5% of the total patients, specifically from the noncarbapenem group. Previous studies comparing carbapenems with noncarbapenem antibiotics have shown no significant difference in terms of all-cause 30-day mortality rate. These findings align with other studies, such as those by Drozdinsky et al. and Tan et al., which reported no significant differences in 30-day mortality between carbapenems and other antibiotics, including third-generation cephalosporins and piperacillin–tazobactam [22, 23].

Our results further suggest that treatment failure was significantly higher in the noncarbapenem group (20%), often necessitating escalation to carbapenem therapy, compared with just 1.6% in the carbapenem group. This underscores the efficacy of carbapenems in managing AmpC-producing Enterobacterales infections. Similar trends have been reported in literature. For example, a study evaluated outcomes in patients treated with piperacillin–tazobactam compared with those treated with cefepime and meropenem for bacteremia due to AmpC β-lactamase-producing Enterobacterales. They found treatment escalation in both groups. Specifically, 14% of patients receiving piperacillin–tazobactam required escalation in their antibacterial agents owing to persistent bacteremia compared with 10% of patients in the cefepime or meropenem group, although this difference was not statistically significant ($p=0.63$). Their findings suggest that treatment escalation rates were comparable between the two groups, indicating similar clinical responses to the therapies administered [13]. Similarly, the MERINO-2 trial reported a treatment escalation rate of 11% in the piperacillin–tazobactam group versus 3% in the meropenem group, with a risk difference of 8% (95% CI, – 4% to 19%) [9]. Collectively, these findings indicate that while noncarbapenem therapies may show comparable outcomes in some cases, carbapenems remain a more reliable option, particularly in cases involving treatment failure or persistent bacteremia.

The logistic regression analysis demonstrated lower odds of mortality with carbapenem use as definitive therapy and source control; statistical significance was not reached with source control. Age, on the other hand, was a significant factor, with older patients showing higher odds of death. Our findings are consistent with the general trends observed in the management of AmpC-producing Enterobacterales infections [14, 15].

Our study also examined the role of ID consultations. While the association between ID consultation and carbapenem prescription did not reach statistical significance, a recent study by Tang et al. highlighted the value of ID consultations in reducing mortality risk for bloodstream infections, especially with repeated consultations [24].

Carbapenems remain an effective treatment option for AmpC-producing Enterobacterales bacteremia; however, their use is associated with significant ecological consequences, including the selection of carbapenem-resistant organisms and disruption of the gut microbiota [25]. As antimicrobial resistance continues to escalate, there is increasing interest in alternative therapeutic strategies to mitigate these risks. Emerging approaches such as bacteriophage therapy, antimicrobial peptides, and monoclonal antibody-based therapies have shown promise and warrant further investigation as potential alternative options. [26–28].

This study has several limitations, including its retrospective observational design, which could introduce the risk of selection bias and difficulty in controlling confounding variables. To mitigate this, we applied strict inclusion and exclusion criteria to ensure a consistent cohort and performed statistical analyses, such as logistic regression, to balance covariates between treatment groups. Additionally, the relatively small sample size could have limited the statistical power to detect differences in outcomes between groups. We reported odds ratios to provide context to the

findings, although statistical significance was not reached in some outcomes. However, we acknowledge that larger sample size studies are needed to confirm the findings and to further explore other outcomes. Furthermore, as our study focused on adult patients whose clinical characteristics, antibiotic dosing, and treatment responses differ from those of pediatric populations, future research exploring the effectiveness of carbapenem versus non-carbapenem therapy in pediatric patients would be valuable in addressing this gap.

CONCLUSIONS

This study highlights the preference for carbapenems for both empirical and definitive therapy for AmpC-producing Enterobacterales. Despite its documented efficacy, cefepime remains underutilized, pointing to the need for further research and antimicrobial stewardship initiatives to address this gap. *E. cloacae* was the predominant pathogen causing AmpC bacteremia, primarily originating from line-related infections. Age was identified as a significant factor affecting survival, emphasizing the need for personalized treatment strategies, particularly for older patients who may have higher comorbidities and a more complicated clinical course. Carbapenem use as definitive therapy was significantly associated with improved survival, underscoring its critical role in managing these infections. While source control implementation showed promising trends, it did not reach statistical significance. Larger prospective studies are needed to validate these findings and to refine treatment strategies, especially in optimizing the role of ID consultations in optimizing treatment strategies and cefepime use in managing AmpC infections.

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Declarations

Ethical Approval. This study received institutional review board (IRB) approval from King Abdullah International Medical Research Center (KAIMRC) (approval number: NRC22R/053/01). The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. Informed consent was waived by the IRB.

Conflict of Interest. Shuroug A. Alowais, Atheer Aldairem, Sumaya N. Almohareb, Yara Alsaeed, Rema Aldugiem, Tariq Alqahtani, Rawnd Alamri, Raghad Aied, Hisham A. Badreldin, and Khalid bin Saleh have nothing to disclose.

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