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ORIGINAL RESEARCH

Clinical Characteristics and Risk Factors for Multidrug-Resistant *Enterobacter cloacae* Complex Bacteremia in a Chinese Tertiary Hospital: A Decade Review (2013–2022)

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Objective: This study aimed to analyze the antimicrobial resistance profiles, clinical characteristics and risk factors of bacteremia caused by *Enterobacter cloacae* complex (ECC) strains.

Methods: We retrospectively collected clinical data from patients diagnosed with ECC bacteremia between 2013 and 2022 in a tertiary hospital in Jiangsu. Subgroup analyses were performed based on multidrug resistance (MDR), nosocomial acquisition, polymicrobial bacteremia, and mortality.

Results: Among 188 ECC strains, the highest resistance was to ceftriaxone (39.9%), followed by ceftazidime (36.7%) and aztreonam (31.2%), with low resistance to carbapenems (<8.6%) and amikacin (1.6%). MDR ECC accounted for 30.9% (58/188). Previous antibiotic therapy was an independent risk factor for MDR ECC (OR = 3.193, $P < 0.020$), while appropriate antibiotic therapy significantly reduced the risk (OR = 0.279, $P < 0.001$). ICU admission was an independent risk factor for polymicrobial bacteremia, both endoscopy and blood transfusion were associated with mortality.

Conclusion: Carbapenems and amikacin are the most effective treatments for ECC bacteremia. Previous antibiotic therapy increases the risk of MDR ECC, while appropriate antibiotic therapy reduces it. ICU admission is an independent risk factor for polymicrobial bacteremia, both endoscopy and blood transfusion are linked to higher mortality. Effective control of MDR ECC bacteremia requires comprehensive strategies, including resistance detection, risk factor identification, and infection prevention.

Keywords: *Enterobacter cloacae* complex, bacteremia, multidrug-resistance, clinical characteristics, risk factors

Introduction

The *Enterobacter cloacae* complex (ECC), a member of the *Enterobacter* genus, is widely found in nature. To date, seven ECC species have been identified, including *E. cloacae, E. hormaechei, E. asburiae, E. kobei, E. ludwigii, E. nimipressuralis*, and *E. mori*.[1] ECC is recognized as a significant opportunistic pathogen associated with a broad spectrum of hospital-acquired infections, affecting various organs and systems. These infections often arise from bacteremia, respiratory, urinary tract and wound infections, frequently linked to the use of invasive devices or procedures.[2] Additionally, *Enterobacter* spp. is part of the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp)*, notorious for their ability to "escape" the effects of antimicrobial agents and cause the majority of hospital-acquired infections.[3]

A major concern with ECC is its propensity to develop multidrug resistance (MDR), facilitated by the high expression of AmpC-type cephalosporinase and the acquisition of resistance genes through mobile genetic elements under

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antimicrobial pressure.[1,4] The rise of MDR, including resistance to the carbapenems (meropenem, imipenem, and ertapenem), considered the last line of defense, has heightened worries about these pathogens.[1,5] MDR strains, including those from the *Enterobacterales* family, impose significant clinical and economic burdens,[6–10] making MDR ECC isolates particularly concerning for empiric therapy.[11–13]

In China, the epidemiology of ECC has garnered increasing attention due to the emergence and hospital transmission of MDR ECC strains, which have become a major clinical and public health concern.[14] Recent studies highlight the prevalence of MDR ECC in various hospital settings, driven by factors such as the overuse of antibiotics and the dissemination of mobile genetic elements encoding resistance genes.[14,15] Of great concern, the rise of carbapenem-resistant ECC strains, often considered the last line of defense, has further heightened the need for effective infection control strategies.

Bacteremia is a prevalent hospital-acquired infection that can lead to increased healthcare costs, prolonged hospital stays, and higher mortality rates, especially when associated with MDR or carbapenem resistance.[16–19] Infections due to MDR *Enterobacterales*, including ECC, have been linked to high mortality rates, sometimes as high as 50%.[20] Over recent decades, ECC has become the third most common and lethal *Enterobacterales* species causing bacteremia.[21–24]

Although many studies have assessed risk factors for bacteremia linked to MDR *Enterobacterales*, these recognized risk factors include admission to intensive care units (ICU), extended hospital stays, prior use of broad-spectrum antibiotics, history of resistant strain colonization, indwelling urethral catheterization, and central venous catheterization.[25–27] However, these studies primarily focused on organisms like *Klebsiella pneumoniae* and *Escherichia coli*, less attention has been given to ECC.

This study retrospectively explores the antimicrobial resistance trends of ECC strains causing bacteremia. The risk and prognostic factors for these infections are also identified by reviewing medical records. The findings aim to facilitate the development and implementation of targeted strategies for nosocomial infection prevention and control.

Materials and Methods

Bacterial Identification and Antimicrobial Susceptibility Testing

Blood cultures were conducted using the BacT/ALERT 3D (BioMérieux, Missouri, USA). Identification of bacterial isolates was performed by Vitek 2.0 system (BioMérieux, Marcy- l'Étoile, France) and matrix-associated laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (BioMérieux, Craponne, France). Antimicrobial susceptibility was verified using the Vitek 2.0 system (BioMérieux, Marcy- l'Étoile, France) and Kirby-Bauer disk diffusion method.[28] Results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100, 34th edition.[29]

Definitions and Clinical Data Collection

Patients diagnosed with bacteremia caused by ECC strains were enrolled in this study to collect related information such as demographic details, clinical diagnosis, treatment, and outcome by reviewing patients' medical records and doctor's advice by searching the hospital information system (HIS) and laboratory information system (LIS).

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Nanjing Drum Tower Hospital (2023–390). The requirement for signed informed consent was waived due to the absence of any interventions.

An ECC strain was considered MDR-ECC if it is non-susceptible to three or more classes of antibiotics based on in-vitro sensitivity testing.[30] Bacteremia was defined as the isolation of ECC from one or more blood cultures.[31] Only the first episode of the bacteremia in each patient was considered. The date of onset of bacteremia was defined as the date when the first blood culture was collected from which ECC was isolated. If the positive blood culture was obtained 48h after admission, the bacteremia was considered nosocomial; otherwise, it was considered community acquired.[32]

Invasive procedures during the hospital stay included any therapeutic procedure (eg vascular catheter, urinary catheter, mechanical ventilation) or diagnostic procedure (eg bronchoscopy, colonoscopy) or invasive surgery or blood transfusion that could have caused transient bacteremia if conducted within 10 days before the infection.[31]

Treatments within one month included were chemotherapy or corticosteroid therapy (daily dose of 10 mg or higher for more than 10 days), or antibiotic therapy (receipt of any antibiotics for more than 48 h) performed within one month prior to the onset of bacteremia.[31] Antibiotic therapy was considered as appropriate if the isolate was susceptible to any of the previous administered antibiotics according to the blood culture results.[31]

Statistical Analysis

Univariate analysis was performed using the $\chi 2$-test or the two-tailed Fisher's exact test for categorical variables to identify risk factor. Significant parameters with $P < 0.10$ in univariate analysis were considered candidate predictors and were included in the logistic regression model for multivariate analysis.[33] Differences were considered statistically significant if $P < 0.05$. All the statistical analyses were performed using SPSS software (v27.0).

Results

In total, 188 consecutive and non-duplicate ECC strains isolated from blood were collected from January 2013 to December 2022 within Nanjing Drum Tower Hospital (the affiliated hospital of Nanjing University Medical School), which was a tertiary hospital in Jiangsu with more than 4000 beds. Overall, the ECC strains showed the highest resistant rates to ceftriaxone (39.9%), followed by ceftazidime (36.7%) and aztreonam (31.2%) and low resistant rates to carbapenems (imipenem 8.6%, meropenem 5.0%, ertapenem 8.4%, doripenem 5.3%) and amikacin (1.6%) (Table 1).

Among the isolates, 30.9% (58/188) were identified as MDR ECC strains. The total number of ECC strains and the number of non-MDR strains exhibited a similar trend, while the number of MDR ECC remained relatively stable from 2013 to 2019 (Figure 1A). Notably, the number of MDR ECC detections showed an upward trend from 2019 to 2022. During this period, the number of isolates resistant to ceftazidime (CAZ), aztreonam (ATM), levofloxacin (LVX), and piperacillin-tazobactam (TZP) increased significantly, which may explain the rise in MDR ECC numbers (Figure 1B).

Table 1 Antimicrobial Resistance Rates of Strains Isolated from 188 Patients with *Enterobacter cloacae* Complex Bacteriemia (No. of Isolates Tested)

Antimicrobial Category	Antibiotic	n (%)
3rd and 4th generation cephalosporins	Ceftazidime	69 (36.7%)
	Ceftriaxone	75 (39.9%)
	Cefepime	30 (15.8%)
Monobactams	Aztreonam	59 (31.2%)
Carbapenems	Imipenem	16 (8.6%)
	Meropenem	9 (5.0%)
	Ertapenem	16 (8.4%)
	Doripenem	10 (5.3%)
Aminoglycosides	Amikacin	3 (1.6%)
	Gentamicin	17 (8.8%)
	Tobramycin	27 (14.4%)
Fluoroquinolones	Ciprofloxacin	27 (14.5%)
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	7 (3.7%)
Polymyxins	Colistin	0 (0.0%)
Antipseudomonal penicillins+β-lactamase inhibitors	Piperacillin-tazobactam	36 (19.0%)
Tetracyclines	Minocycline	27 (14.3%)
	Doxycycline	45 (23.8%)

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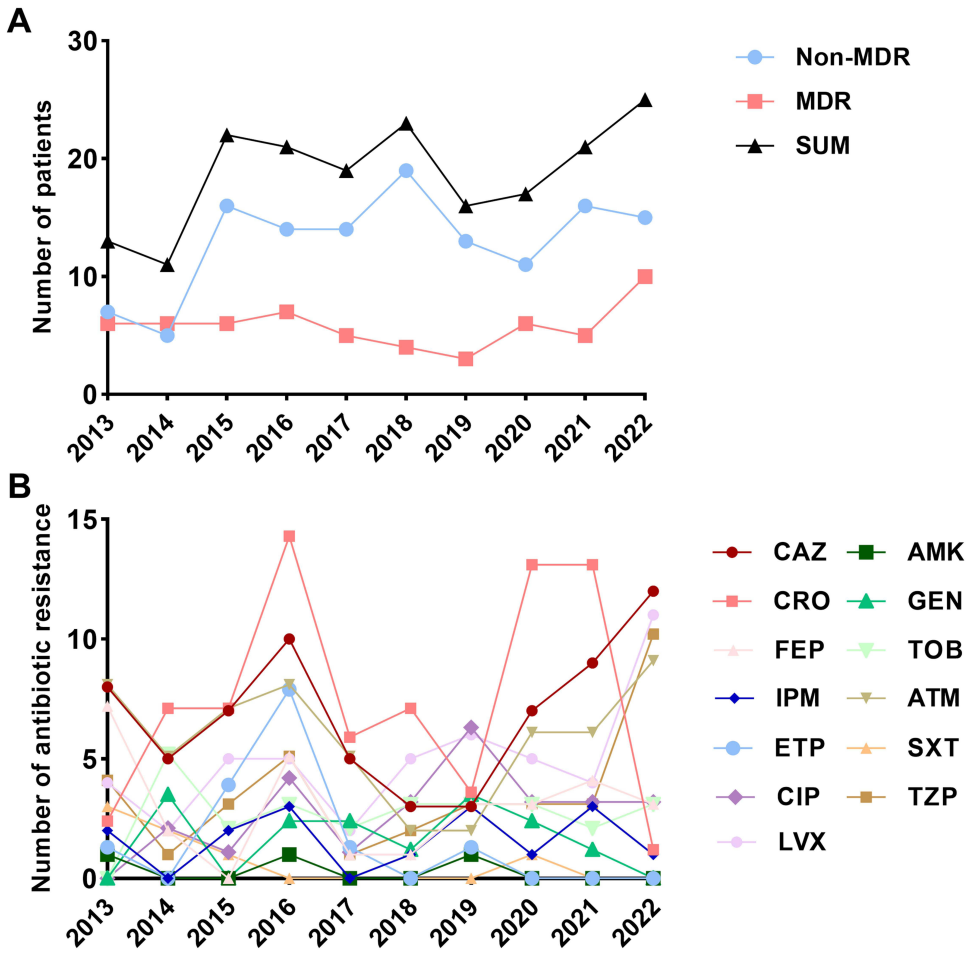

Figure 1 Trends in the numbers of patients with MDR, non-MDR, and total detected *Enterobacter cloacae* complex bacteremia (**A**) and numbers of antibiotic-resistant strains from these patients (**B**) from 2013 to 2022.
Abbreviations: MDR, multidrug-resistant; SUM, summary; CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime; IPM, Imipenem; ETP, Ertapenem; CIP, Ciprofloxacin; LVX, levofloxacin; AMK, Amikacin; GEN, Gentamicin; TOB, Tobramycin; ATM, Aztreonam; SXT, Trimethoprim-sulphamethoxazole; TZP, Piperacillin-tazobactam.

Male patients (58.0%,109/188) were more susceptible to ECC bacteremia. The median age was 60.5 years (range 15–94 years), and the mean age was 60.3 years. Among the patients, 33.0% (62/188) patients had been admitted to the ICU, and 18.6% (35/188) had infections caused by multiple bacteria.

As shown in Figure 2A, 53.2% of the patients with ECC bacteremia were from surgery wards, followed by internal medicine wards (35.1%), ICU (10.6%) and emergency ward (1.1%). Among the internal medicine wards, 34.9% of the patients with ECC bacteremia were from gastroenterology ward, followed by the hematology ward (19.7%), oncology ward (16.6%), geriatric ward (15.2%) (Figure 2B). Among the surgical wards, 34.0% of the patients with ECC bacteremia were from hepatological surgery ward, followed by cardio-thoracic surgery ward (25.0%), and gastrointestinal surgery ward (11.0%) (Figure 2C).

All 188 patients had one or more underlying diseases. The most common were malignant disease (100/188, 53.2%), followed by hypertension (77/188, 41.0%). The most common infection was biliary tract infection, affecting 53 patients (53/188, 28.2%). Invasive procedures had been performed prior to 168 episodes (168/188, 89.4%). Various types of catheters were used in 141 episodes (141/188, 75.0%), with the most common being vascular catheter (117/188, 62.2%), followed by urinary catheter (92/188, 48.9%). There was no significant difference in the use of different types of catheters between patients with MDR and non-MDR ECC bacteremia (Figure 3). A total of 87 patients underwent surgical operations, and 76 patients received recent blood transfusion.

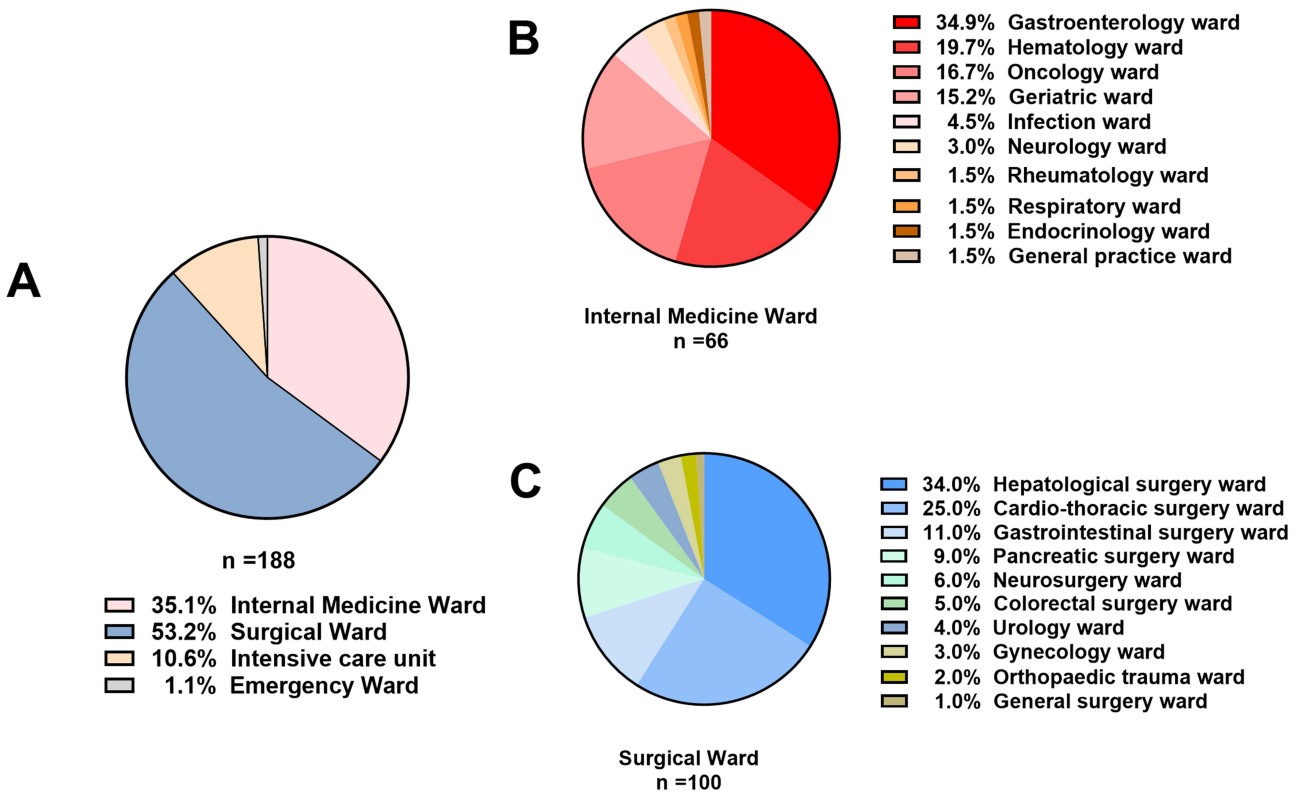

Figure 2 The department distribution of patients with *Enterobacter cloacae* complex bacteremia strains enrolled in this study. (**A**) Department distribution of patients with *Enterobacter cloacae* complex bacteremia; (**B**) Internal medicine department distribution of patients with *Enterobacter cloacae* complex bacteremia; (**C**) Surgical department distribution of patients with *Enterobacter cloacae* complex bacteremia.

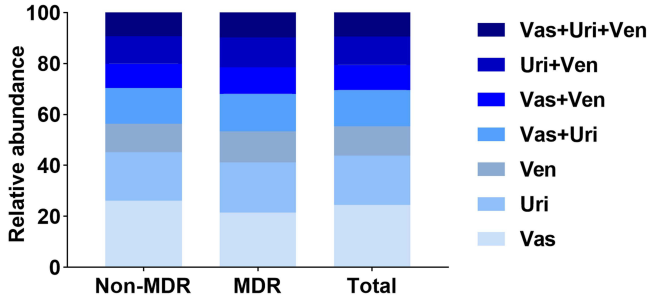

Figure 3 Distribution of vascular catheterization (Vas), urinary catheterization (Uri), mechanical ventilation (Ven), and combined use in patients with *Enterobacter cloacae* complex bacteremia.

Within one-month prior to the onset of bacteremia, 146 (77.7%) patients received antibiotics, 19 (10.1%) underwent chemotherapy, and 18 (9.6%) were administered corticosteroids. The most commonly used antibiotics for previous infections in all patients with ECC bacteremia were carbapenems (31/188), followed by combinations (23/188), first-generation cephalosporins (16/188) and tigecycline (16/188). In patients with MDR bacteremia, carbapenems were the most commonly used antibiotics (11/58), followed by combinations (9/58) and first-generation cephalosporins (7/58). In non-MDR patients, carbapenems (20/130) were also the most commonly used antibiotics followed by combinations (14/130) and tetracyclines (9/130) (Figure 4).

Univariate analysis for bacteremia caused by MDR strains showed statistical differences in age over 60 years, hypertension, pulmonary infection, initial empirical antibiotic therapy, and appropriate therapy (Table 2). Further multivariate analysis revealed that previous antibiotic therapy was a robust and independent risk factor (OR = 3.193, 95% CI 1.203–8.479, $P < 0.020$) (Table 2) of leading to multidrug resistance in the bacteremia pathogens, while appropriate

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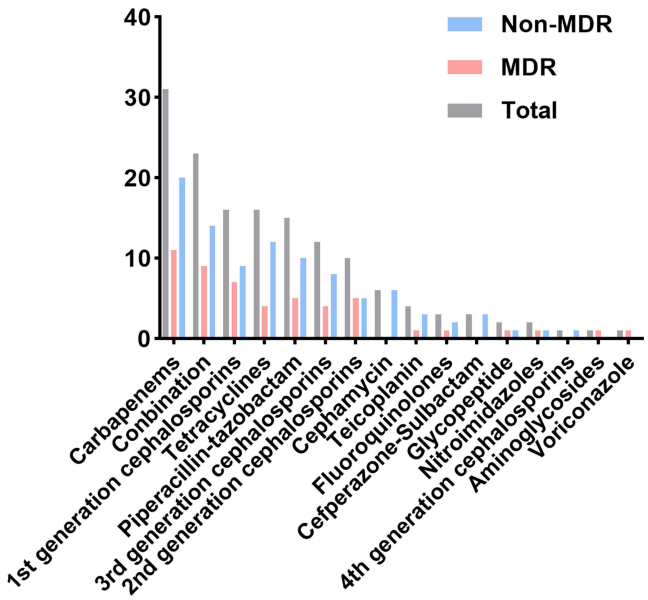

Figure 4 Antibiotic use in the month prior to *Enterobacter cloacae* complex bacteremia.

antibiotic therapy demonstrated a statistically significant impact (OR = 0.279, 95% CI 0.130–0.598, $P < 0.001$) on mitigating this risk.

Univariate analysis for nosocomial acquired bacteremia showed statistical correlation with ICU admission ($P = 0.038$), biliary tract infection ($P < 0.001$), invasive procedures ($P = 0.015$), therapeutic procedure (catheter) ($P < 0.001$), vascular catheter ($P = 0.002$), urinary catheter ($P = 0.003$), diagnostic procedure (endoscopy) ($P = 0.024$), invasive surgery ($P = 0.007$), and blood transfusion ($P = 0.036$) (Table 3). Multivariate analysis showed a statistical difference in biliary tract infection (OR = 0.294, 95% CI 0.086–0.998, $P = 0.050$) (Table 3).

Statistical differences were revealed in ICU admission ($P < 0.001$), malignancy ($P = 0.013$), chronic obstructive pulmonary disease (COPD) ($P = 0.023$), mechanical ventilation ($P = 0.05$), and previous chemotherapy ($P = 0.027$) (Table 4) in the univariate analysis of the risk factors for acquiring polymicrobial bacteremia. Multivariate analysis identified that previous ICU admission was an independent risk factor ($P = 0.009$) (Table 4).

Univariate analysis in the mortality of ECC bacteremia showed a statistically significant association with invasive procedures ($P = 0.048$), urinary catheter ($P = 0.030$), mechanical ventilation ($P = 0.009$), diagnostic procedure (endoscopy) ($P = 0.031$), and blood transfusion ($P < 0.001$) (Table 5). Multivariate analysis indicated that diagnostic procedure (endoscopy) ($P = 0.009$) and blood transfusion ($P = 0.003$) were independent risk factors for mortality (Table 5).

Discussion

The study highlighted notable patterns in antimicrobial resistance among ECC strains and identified significant risk factors for polymicrobial bacteremia, multidrug resistance, nosocomial acquisition and mortality associated with ECC bacteremia.

The resistance rates to ceftazidime and ceftriaxone in our study were obviously higher than those reported in Taiwan[34] and Australian Group on Antimicrobial Resistance (AGAR) Bloodstream Infection Annual Report 2022.[35] In Taiwan, resistance rates to ceftazidime and ceftriaxone were 27.2% and 29.3%, respectively, and in Australia, the resistant rates were 24.6% and 28.4% in order. The differences may come from the use of antimicrobial agents.[36] Whereas, the consistency on the significant resistance to ceftriaxone, ceftazidime, and aztreonam across multiple analyses indicated that ceftriaxone, ceftazidime, and aztreonam consistently pose significant treatment challenges for ECC infections due to the high prevalence of resistant strains. Notably, the upward trend in MDR ECC strains from 2019 to 2022 is alarming, as it indicates a potential escalation in the complexity of clinical management of these cases. The

Table 2 Demographic and Clinical Characteristics of Patients with MDR-Negative and MDR-Positive *Enterobacter cloacae* Complex

Variables	Non-MDR (n = 130)	MDR (n = 58)	OR (95% CI)	P value
Demographics				
Male gender	78 (60.0%)	31 (53.4%)	0.765 (0.410–1.429)	0.401
Age≥60 years	65 (50.0%)	38 (65.5%)	1.900 (1.000–3.608)	0.048
Admission to Intensive care unit (ICU)	39 (30.0%)	23 (40.4%)	1.578 (0.825–3.019)	0.166
Polymicrobial bacteremia	24 (18.5%)	11 (19.0%)	1.034 (0.468–2.282)	0.935
Underlying conditions				
Hypertension	46 (35.4%)	31 (53.4%)	2.097 (1.118–3.932)	0.020
Diabetes mellitus	29 (22.3%)	15 (25.9%)	1.215 (0.592–2.492)	0.595
Autoimmune disease	7 (5.4%)	3 (5.2%)	0.958 (0.239–3.846)	1.000
Malignancy	70 (53.8%)	30 (51.7%)	0.918 (0.494–1.707)	0.788
Agranulocytosis (<0.5*10^9/L)	10 (7.7%)	4 (6.9%)	0.889 (0.267–2.961)	1.000
Cerebrovascular disease	24 (18.5%)	14 (24.1%)	1.405 (0.666–2.966)	0.371
Cardiovascular disease	29 (22.3%)	20 (34.5%)	1.833 (0.928–3.622)	0.079
Presence of chronic renal failure (CRF)	5 (3.8%)	3 (5.2%)	1.364 (0.315–5.907)	0.980
Chronic obstructive pulmonary disease (COPD)	2 (1.5%)	2 (3.4%)	2.286 (0.314–16.637)	0.771
Pulmonary infection	22 (16.9%)	22 (37.9%)	3.000 (1.488–6.048)	0.002
Urinary tract infection	11 (8.5%)	6 (10.3%)	1.248 (0.438–3.555)	0.678
Biliary tract infection	34 (26.2%)	19 (32.8%)	1.376 (0.701–2.698)	0.353
Invasive procedures during hospital stay				
Invasive procedures	118 (90.8%)	50 (86.2%)	0.636 (0.245–1.65)	0.349
Therapeutic procedure (catheter)	98 (75.4%)	43 (74.1%)	0.936 (0.46–1.905)	0.855
1.Vascular catheter	82 (63.1%)	35 (60.3%)	0.891 (0.472–1.681)	0.721
2.Urinary catheter	60 (46.2%)	32 (55.2%)	1.436 (0.771–2.674)	0.253
3.Mechanical ventilation	35 (26.9%)	20 (34.5%)	1.429 (0.734–2.78)	0.293
Diagnostic procedure (scopy)	30 (23.1%)	14 (24.1%)	1.061 (0.513–2.194)	0.874
Invasive surgery	59 (45.4%)	28 (48.3%)	1.123 (0.604–2.088)	0.713
Blood transfusion	47 (36.2%)	29 (50.0%)	1.766 (0.943–3.305)	0.074
Treatments within one month				
Previous chemotherapy	13 (10.0%)	6 (10.3%)	1.038 (0.374–2.883)	0.942
Previous corticosteroid therapy	15 (11.5%)	3 (5.2%)	0.418 (0.116–1.505)	0.271
Previous antibiotic therapy	95 (73.1%)	51 (87.9%)	2.684 (1.113–6.471)	0.024
Appropriate antibiotic therapy	57 (44.2%)	16 (27.6%)	0.481 (0.246–0.943)	0.031
Multivariate analysis				
Age≥60 years			1.705 (0.822–3.534)	0.152
Hypertension			1.482 (0.726–3.024)	0.280
Cardiovascular disease			1.265 (0.586–2.730)	0.550
Pulmonary infection			2.157 (0.963–4.834)	0.062
Blood transfusion			1.681 (0.815–3.468)	0.160
Previous antibiotic therapy			3.193 (1.203–8.479)	0.020
Appropriate antibiotic therapy			0.279 (0.130–0.598)	0.001

Notes: A strain was considered MDR if it is non-susceptible to three or more classes of antibiotics based on in-vitro sensitivity testing.
Abbreviation: MDR, multidrug resistant.

stable prevalence of MDR strains prior to 2019 suggests that existing infection control measures and antimicrobial stewardship programs were initially effective, but the recent increase may signal a need for renewed strategies to prevent the spread of resistant strains. Notably, 30.9% of MDR ECC strains underscores the growing issue of MDR in clinical settings. This provided evidence to the reports that patients infected with third-generation or broad-spectrum cephalosporin-resistant isolates experience worse clinical response, longer hospital stay, poorer outcomes, and higher mortality

Table 3 Demographic and Clinical Characteristics of Patients with Community and Nosocomial Acquired *Enterobacter cloacae* Complex

Variables	Community (n = 24)	Nosocomial (n = 164)	OR (95% CI)	P value
Demographics				
Male gender	16 (66.7%)	93 (56.7%)	0.655 (0.265–1.616)	0.356
Age≥60 years	13 (54.2%)	90 (54.9%)	1.029 (0.436–2.432)	0.948
Admission to Intensive care unit (ICU)	3 (12.5%)	59 (36.0%)	3.971 (1.136–13.877)	0.038
Underlying conditions				
Hypertension	8 (33.3%)	69 (42.1%)	1.453 (0.589–3.586)	0.416
Diabetes mellitus	2 (8.3%)	42 (25.6%)	3.787 (0.854–16.793)	0.108
Autoimmune disease	0 (0.0%)	10 (6.1%)	0.865 (0.816–0.917)	0.366
Malignancy	14 (58.3%)	86 (52.4%)	0.788 (0.331–1.875)	0.589
Agranulocytosis (<0.5*10^9/L)	1 (4.2%)	13 (7.9%)	1.980 (0.247–15.861)	0.811
Cerebrovascular disease	4 (16.7%)	34 (20.7%)	1.308 (0.419–4.081)	0.848
Cardiovascular disease	2 (8.3%)	47 (28.7%)	4.419 (0.999–19.54)	0.062
Presence of chronic renal failure (CRF)	1 (4.2%)	7 (4.3%)	1.025 (0.121–8.720)	1.000
Chronic obstructive pulmonary disease (COPD)	0 (0.0%)	4 (2.4%)	0.870 (0.822–0.920)	1.000
Pulmonary infection	2 (8.3%)	42 (25.6%)	3.787 (0.854–16.793)	0.108
Urinary tract infection	2 (8.3%)	15 (9.1%)	1.107 (0.237–5.175)	1.000
Biliary tract infection	15 (62.5%)	38 (23.2%)	0.181 (0.073–0.446)	<0.001
Invasive procedures during hospital stay				
Invasive procedures	18 (75.0%)	150 (91.5%)	3.571 (1.220–10.455)	0.015
Therapeutic procedure (catheter)	10 (41.7%)	131 (79.9%)	5.558 (2.267–13.626)	<0.001
1.Vascular catheter	8 (33.3%)	109 (66.5%)	3.964 (1.598–9.832)	0.002
2.Urinary catheter	5 (20.8%)	87 (53.0%)	4.294 (1.530–12.048)	0.003
3.Mechanical ventilation	3 (12.5%)	52 (31.7%)	3.250 (0.928–11.385)	0.091
Diagnostic procedure (scopy)	10 (41.7%)	34 (20.7%)	0.366 (0.150–0.896)	0.024
Invasive surgery	5 (20.8%)	82 (50.0%)	3.800 (1.354–10.661)	0.007
Blood transfusion	5 (20.8%)	71 (43.3%)	2.901 (1.033–8.146)	0.036
Treatments within one month				
Previous chemotherapy	2 (8.3%)	17 (10.4%)	1.272 (0.275–5.887)	1.000
Previous corticosteroid therapy	1 (4.2%)	17 (10.4%)	2.660 (0.338–20.955)	0.553
Previous antibiotic therapy	20 (83.3%)	126 (76.8%)	0.663 (0.214–2.059)	0.651
Appropriate antibiotic therapy	7 (29.2%)	66 (40.2%)	1.652 (0.649–4.205)	0.288
Multivariate analysis				
Previous ICU admission			2.416 (0.501–11.665)	0.272
Biliary tract infection			0.294 (0.086–0.998)	0.050
1.Vascular catheter			2.053 (0.630–6.686)	0.232
2.Urinary catheter			1.328 (0.575–3.063)	0.507
3.Mechanical ventilation			0.748 (0.393–1.425)	0.377
Diagnostic procedure (scopy)			1.325 (0.398–4.408)	0.646
Previous surgery			1.971 (0.486–7.999)	0.342
Blood transfusion			1.270 (0.361–4.470)	0.709
Cardiovascular disease			3.254 (0.679–15.59)	0.140

rates.[34] Furthermore, the finding that carbapenems and amikacin were the most effective antimicrobial agents against ECC in this study is in accordance with results from the China Antimicrobial Resistance Surveillance Trial (CARST) Program, 2011–2020,[16] which suggests that carbapenems and amikacin may be considered primary options for empiric

Table 4 Demographic and Clinical Characteristics of Patients with Non-Polymicrobial and Polymicrobial Bacteremia

Variables	Non-Polymicrobial (n = 153)	Polymicrobial (n = 35)	OR (95% CI)	P value
Demographics				
Male gender	84 (54.9%)	25 (71.4%)	2.054 (0.923–4.568)	0.074
Age≥60 years	80 (52.3%)	23 (65.7%)	1.749 (0.812–3.765)	0.150
Admission to Intensive care unit (ICU)	42 (27.5%)	20 (57.1%)	3.492 (1.636–7.452)	<0.001
Underlying conditions				
Hypertension	61 (39.9%)	16 (45.7%)	1.27 (0.606–2.661)	0.526
Diabetes mellitus	35 (22.9%)	9 (25.7%)	1.167 (0.500–2.721)	0.720
Autoimmune disease	9 (5.9%)	1 (2.9%)	0.471 (0.058–3.841)	0.763
Malignancy	88 (57.5%)	12 (34.3%)	0.385 (0.179–0.831)	0.013
Agranulocytosis (<0.5*10^9/L)	13 (8.5%)	1 (2.9%)	0.317 (0.040–2.506)	0.430
Cerebrovascular disease	27 (17.6%)	11 (31.4%)	2.139 (0.937–4.885)	0.067
Cardiovascular disease	36 (23.5%)	13 (37.1%)	1.920 (0.880–4.193)	0.098
Presence of chronic renal failure (CRF)	6 (3.9%)	2 (5.7%)	1.485 (0.287–7.687)	0.992
Chronic obstructive pulmonary disease (COPD)	1 (0.7%)	3 (8.6%)	14.25 (1.436–141.431)	0.023
Pulmonary infection	33 (21.6%)	11 (31.4%)	1.667 (0.741–3.750)	0.214
Urinary tract infection	13 (8.5%)	4 (11.4%)	1.390 (0.424–4.551)	0.827
Biliary tract infection	40 (26.1%)	13 (37.1%)	1.669 (0.769–3.622)	0.192
Invasive procedures during hospital stay				
Invasive procedures	137 (89.5%)	31 (88.6%)	0.905 (0.283–2.896)	1.000
Therapeutic procedure (catheter)				
1.Vascular catheter	97 (63.4%)	20 (57.1%)	0.770 (0.365–1.623)	0.491
2.Urinary catheter	71 (46.4%)	21 (60.0%)	1.732 (0.821–3.657)	0.147
3.Mechanical ventilation	40 (26.1%)	15 (42.9%)	2.119 (0.990–4.532)	0.050
Diagnostic procedure (scopy)	36 (23.5%)	8 (22.9%)	0.963 (0.402–2.305)	0.932
Invasive surgery	69 (45.1%)	18 (51.4%)	1.289 (0.618–2.689)	0.498
Blood transfusion	61 (39.9%)	15 (42.9%)	1.131 (0.538–2.379)	0.745
Treatments within one month				
Previous chemotherapy	19 (12.4%)	0 (0.0%)	0.793 (0.734–0.856)	0.027
Previous corticosteroid therapy	15 (9.8%)	3 (8.6%)	0.863 (0.236–3.158)	1.000
Previous antibiotic therapy	118 (77.1%)	28 (80.0%)	1.186 (0.478–2.948)	0.713
Appropriate antibiotic therapy	55 (35.9%)	18 (51.4%)	1.867 (0.890–3.917)	0.096
Multivariate analysis				
Male gender			1.824 (0.760–4.375)	0.178
Previous ICU admission			3.527 (1.377–9.034)	0.009
Malignancy			0.507 (0.216–1.187)	0.117
Cerebrovascular disease			1.600 (0.631–4.058)	0.322
Cardiovascular disease			1.228 (0.496–3.037)	0.657
Chronic obstructive pulmonary disease (COPD)			6.556 (0.482–89.236)	0.158
3.Mechanical ventilation			0.920 (0.661–1.280)	0.622
Appropriate antibiotic therapy			1.378 (0.597–3.181)	0.453

therapy in severe ECC infections with known resistance issues. However, clinicians must balance the need for effective immediate treatment with the long-term goal of preserving antibiotic efficacy.

Further, our study shows that male elderly patients are more susceptible to ECC bacteremia, suggesting a possible gender-related difference in susceptibility to ECC infections, which could be influenced by various biological and behavioral factors. Moreover, the high proportion of patients admitted to the ICU indicates the severity of the infections.

Table 5 Risk Factor Analysis for Survival and Mortality in Patients with *Enterobacter cloacae* Complex Bacteremia

	Survival (n = 160)	Mortality (n = 28)	OR (95% CI)	P value
Demographics				
Male gender	90 (56.3%)	19 (67.9%)	1.642 (0.700–3.851)	0.251
Age≥60 years	92 (57.5%)	11 (39.3%)	0.478 (0.211–1.087)	0.074
Admission to Intensive care unit (ICU)	50 (31.3%)	12 (42.9%)	1.635 (0.720–3.712)	0.237
Underlying conditions				
Hypertension	67 (41.9%)	10 (35.7%)	0.771 (0.335–1.776)	0.541
Diabetes mellitus	38 (23.8%)	6 (21.4%)	0.876 (0.331–2.318)	0.789
Autoimmune disease	8 (5.0%)	2 (7.1%)	1.462 (0.294–7.271)	0.992
Malignancy	88 (55.0%)	12 (42.9%)	0.614 (0.273–1.380)	0.235
Agranulocytosis (<0.5*10^9/L)	13 (8.1%)	1 (3.6%)	0.419 (0.053–3.335)	0.648
Cerebrovascular disease	31 (19.4%)	7 (25.0%)	1.387 (0.541–3.554)	0.494
Cardiovascular disease	43 (26.9%)	6 (21.4%)	0.742 (0.282–1.954)	0.545
Presence of chronic renal failure (CRF)	5 (3.1%)	3 (10.7%)	3.720 (0.836–16.545)	0.184
Chronic obstructive pulmonary disease (COPD)	4 (2.5%)	0 (0.0%)	0.848 (0.797–0.901)	1.000
Pulmonary infection	34 (21.3%)	10 (35.7%)	2.059 (0.870–4.869)	0.095
Urinary tract infection	14 (8.8%)	3 (10.7%)	1.251 (0.335–4.671)	1.000
Biliary tract infection	44 (27.5%)	9 (32.1%)	1.249 (0.525–2.968)	0.614
Invasive procedures during hospital stay				
Invasive procedures	140 (87.5%)	28 (100.0%)	1.200 (1.122–1.284)	0.048
Therapeutic procedure (catheter)	116 (72.5%)	25 (89.3%)	3.161 (0.909–10.998)	0.058
1.Vascular catheter	95 (59.4%)	22 (78.6%)	2.509 (0.964–6.528)	0.053
2.Urinary catheter	73 (45.6%)	19 (67.9%)	2.516 (1.073–5.898)	0.030
3.Mechanical ventilation	41 (25.6%)	14 (50.0%)	2.902 (1.276–6.599)	0.009
Diagnostic procedure (scopy)	33 (20.6%)	11 (39.3%)	2.490 (1.065–5.824)	0.031
Invasive surgery	70 (43.8%)	17 (60.7%)	1.987 (0.875–4.512)	0.097
Blood transfusion	54 (33.8%)	22 (78.6%)	7.198 (2.755–18.804)	<0.001
Treatments within one month				
Previous chemotherapy	18 (11.3%)	1 (3.6%)	0.292 (0.037–2.282)	0.366
Previous corticosteroid therapy	15 (9.4%)	3 (10.7%)	0.292 (0.037–2.282)	1.000
Previous antibiotic therapy	122 (76.3%)	24 (85.7%)	1.869 (0.610–5.724)	0.388
Appropriate antibiotic therapy	59 (36.9%)	14 (50.0%)	1.695 (0.756–3.801)	0.197
Multivariate analysis				
Age≥60 years			0.449 (0.176–1.144)	0.093
Pulmonary infection			1.475 (0.503–4.33)	0.479
1.Vascular catheter			1.564 (0.453–5.398)	0.479
2.Urinary catheter			1.235 (0.577–2.644)	0.587
3.Mechanical ventilation			0.993 (0.65–1.517)	0.973
Diagnostic procedure (scopy)			5.706 (1.928–16.889)	0.002
Previous surgery			1.339 (0.317–5.662)	0.692
Blood transfusion			6.091 (1.845–20.112)	0.003

In addition, the presence of underlying diseases in all patients highlights the vulnerability of these individuals to ECC bacteremia, and patients with compromised immune systems or chronic illnesses are at a higher risk. Lastly, the use of various types of catheters in 75.0% of the cases may indicate that medical interventions, particularly the use of various types of catheters are significant risk factors for infections. And the presence of these devices is a general risk factor for

ECC bacteremia regardless of resistance status, since no significant difference in catheter use between MDR and non-MDR ECC bacteremia was observed.

MDR ECC is closely associated with prolonging hospitalization duration and worsening clinical outcome.[11,12] Therefore, it is crucial to continuously monitor susceptibility profiles, clinical features and risk factors for MDR-ECC bacteremia to guide the formulation and implementation of effective infection control measures. Up to date, risk factors for MDR ECC bacteremia have not been extensively studied. Most studies focused on MDR *Enterobacterales* or *Enterobacter* bacteremia.[7,31,37,38] For example, factors such as ICU admission, length of hospital stay, prior use of broad-spectrum antibiotics (eg, quinolones and cephalosporins), history of resistant strain colonization, indwelling urethral catheterization, and central venous catheterization are considered independent risk factors for bacteremia with MDR *Enterobacterales*.[27] Previous third-generation cephalosporins therapy and prolonged perioperative prophylaxis are strong, independent risk factors for MDR *Enterobacter* bacteremia.[31] ICU admission, drainage tube use, central venous catheterization, and carbapenem exposure are independent risk factors for carbapenem-resistant *Enterobacter cloacae* infection.[33] Consistent with this study, the selective pressure of antibiotics leads to MDR ECC bacteremia, as patients receiving antibiotic therapy within one month were more likely to suppress sensitive bacteria while promoting the proliferation and spread of resistant strains.[39] Notably, carbapenems were the most widely used antibiotic in this study. However, initial therapy with a carbapenem appears to be associated with improved clinical outcome in BSI due to ESBL-producing *E. cloacae*.[20] Despite the improvement in clinical outcomes, the use of carbapenem antibiotics will inevitably select for carbapenem-resistant strains, resulting in the extensive proliferation of various resistant bacteria, and complicating subsequent antibiotic selection.

Multivariate analysis showed a statistical association between biliary tract infections and nosocomial ECC bacteremia. Interestingly, the data revealed that patients with community-acquired biliary tract infections accounted for 62.5% (15/24) of the cases, significantly higher than the 23.2% (38/164) observed for nosocomial-acquired infections. This suggests that patients with prior biliary tract infections, particularly those acquired in the community, may be predisposed to ECC bacteremia. This predisposition could be attributed to several factors. Patients with community-acquired biliary tract infections may already be colonized with ECC, which can translocate to the bloodstream during or after the infection due to disruption of the biliary tract barrier, potentially exacerbated by delayed diagnosis or incomplete treatment.[40] Additionally, community-acquired infections may occur in patients with underlying conditions such as gallstones or biliary strictures, which increase their susceptibility to recurrent infections or prolonged colonization.[40] In contrast, nosocomial ECC bacteremia may arise from diverse sources, such as indwelling devices or invasive procedures,[41] thereby reducing the relative contribution of biliary tract infections in these cases.

ICU admission was identified as an independent risk factor for polymicrobial bacteremia. This could be due to several reasons. Firstly, patients in the ICU are usually in an immunocompromised state and exposed to multiple antimicrobial agents and undergo frequent invasive procedures, increasing the probability of polymicrobial bacteremia.[33,42] Secondly, repeated exposure of ECC to antimicrobial agents more easily suppresses susceptible strains, facilitating the proliferation of resistant strains and promoting the dissemination of MDR ECC strains.[32] Therefore, preventive and control measures for nosocomial infections should be implemented, and guidelines for invasive procedures should be strictly followed to mitigate the spread of MDR ECC.

Nosocomial infection has been independently associated with mortality of *Enterobacter* bacteremia.[31] Solid tumors, septic shock and mechanical ventilation are significant predictors for 28-day mortality in carbapenem-resistant *Enterobacter cloacae* causing nosocomial infections.[33] Lung infections, abdominal infections, central venous catheterization, and hormone use within 30 days increased the mortality rate of *Enterobacterales* BSIs.[27] Both endoscopy and blood transfusion are associated with significant risks due to their invasive nature and the underlying conditions of the patients requiring these interventions. As we know that the resulted disruption of mucosal barriers, potential procedural contamination, immune modulation, and the severity of the underlying illness all contribute to the increased risk of mortality in patients with *Enterobacter* bacteremia undergoing these procedures. Understanding these risks underscores the importance of stringent infection control measures and careful patient monitoring during and after these interventions to mitigate the risk of adverse outcomes.

This study has several limitations. The study was conducted in a single center, and the prevalence of resistance found here might not be applicable to the entire region. As in any observational study, our analysis of clinical information in subject to confounding biases. However, it provides the foundation for future national research related to cooperative surveillance on resistance and risk factors to control further infection spread.

In conclusion, carbapenems and amikacin are the most effective treatments for ECC bacteremia. Previous antibiotic therapy was an independent risk factor, and appropriate therapy was a protective factor for patients with MDR ECC bacteremia. ICU admission was an independent risk factor for polymicrobial bacteremia. Both endoscopy and blood transfusion are associated with mortality of ECC Bacteremia. Control of MDR ECC bacteremia requires a cooperative and comprehensive approach, including strategies for improving the rate of pathogenic bacteria testing for antibiotic therapy in hospitalized patients, using antibiotics rationally based on susceptibility test results, risk factor detection and implementation strategies of infection-control and prevention.

Data Sharing Statement

The authors confirm that the data and material supporting the findings of this study are available within the article.

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Disclosure

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

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