Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Comparative in vitro Activity and Clinical Outcomes of Eravacycline, Tigecycline, and Omadacycline Against Carbapenem-Resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*

Diandian Chen[1,*], He Lan[1,*], Wenshuo Yang[1,*], Dequan Tian[1], Yunyi Liu[1], Leyang Ju[1], Qiao Song[1], Rong Min[1], Yan Wang[1], Ying Li[1], Peichang Wang[1,2], Jingrong Cao[1,2]

[1]Department of Clinical Laboratory, Xuanwu Hospital Capital Medical University, National Gerontic Disease Clinical Research Center, Beijing, 100053, People's Republic of China; [2]Department of Clinical Laboratory, Xiong'an Xuanwu Hospital, Xiong'an New Area, Hebei Province, 070001, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jingrong Cao; Peichang Wang, Department of Clinical Laboratory, Xuanwu Hospital Capital Medical University, National Gerontic Disease Clinical Research Center, No. 45 Changchun Street, Xicheng District, Beijing, 100053, People's Republic of China, Email 13683581168@126.com; pcw1905@126.com

Purpose: Carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Klebsiella pneumoniae* (CRKP) pose a serious public health threat, underscoring the urgent need for novel therapeutic options. This study compared the in vitro antimicrobial activity and associated clinical outcomes of three tetracycline-class antibiotics—eravacycline (ERV), tigecycline (TGC), and omadacycline (OMC)—against regional carbapenem-resistant isolates.

Patients and Methods: A total of 106 CRKP and 117 CRAB non-duplicate clinical isolates were collected from Xuanwu Hospital (Beijing) between December 2024 and June 2025. Minimum inhibitory concentrations (MICs) were determined using broth microdilution (CLSI M07 guidelines). Time-kill assays (0–48 h) were used to evaluate bactericidal activity, and clinical outcomes were analyzed in patients treated with TGC or ERV.

Results: ERV demonstrated superior in vitro activity: its MIC_{90} against CRKP (0.5 μg/mL) was 4-fold lower than TGC (2 μg/mL) and 8-fold lower than OMC (4 μg/mL). For CRAB, ERV's MIC_{90} (0.25 μg/mL) was 4-fold lower than TGC (1 μg/mL). ERV maintained sustained bactericidal activity (≥3-$\log_{10}$ CFU/mL reduction) for 24–36 h against CRAB—2.3-fold longer than TGC and 3.1-fold longer than OMC. ERV-treated patients (n = 20) showed a 5% mortality rate (6.7% for CRAB and 0% for CRKP), compared with 18.9% (CRAB) and 16.7% (CRKP) in TGC-treated patients.

Conclusion: Current evidence indicates that ERV exhibits strong in vitro bactericidal activity and demonstrates more favorable clinical efficacy comparable to that of TGC against CRKP and CRAB infections, as observed in our retrospective clinical cohort.

Plain Language Summary: Faced with the increasing threat of CRAB and CRKP, this study evaluated effectiveness of three tetracycline-class antibiotics against these resistant bacteria. ERV showed superior in vitro potency than TGC and OMC, with lower concentrations needed to inhibit bacterial growth. ERV also killed CRAB more effectively and for a longer duration than the other two antibiotics. In clinical settings, patients treated with ERV had a 5% mortality rate, compared with 18.9% for CRAB patients treated with TGC. Although limited by a small number of patients, the results suggest that ERV could be a promising treatment option for CRAB and CRKP infections, warranting further multi-center validation.

Keywords: carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Klebsiella pneumoniae*, broth microdilution, time-kill assays, tetracycline-class antibiotics

https://doi.org/10.2147/IDR.S583973
Received: 27 November 2025
Accepted: 5 February 2026
Published: 13 February 2026

Introduction

Carbapenem-resistant Gram-negative organisms (CROs), particularly CRAB and CRKP, represent a critical public health threat. According to China's CHINET 2024 surveillance data, the prevalence of CRKP and CRAB in clinical settings is 26.4% and 66.5%, respectively, with CRAB rates reaching 78.3% in intensive care units (ICUs).[1,2] These pathogens evade conventional therapies primarily through the production of carbapenemase-encoding genes (eg, bla_{KPC}, bla_{NDM}, $bla_{OXA-48/23}$),[3] leading to 30-day mortality rates of 35% for CRKP and 48% for CRAB.[4,5]

The transmission of CRKP and CRAB within healthcare facilities further complicates clinical management, as they spread through interpatient contact, contaminated medical devices, and environmental reservoirs. The global proliferation of these highly resistant organisms underscores the urgent need for novel therapeutic strategies and enhanced infection control protocols.

Current guidelines recommend ERV and TGC as alternative therapies for CRKP and CRAB infections. However, TGC exhibits limitations such as suboptimal serum concentrations, poor alveolar penetration (one-third of serum levels), and elevated coagulation risks at high doses. In contrast, ERV offers superior tissue penetration (8-fold higher alveolar fluid levels than serum) and fewer coagulation-related adverse events.[6] OMC, with its oral bioavailability, is useful for community-acquired infections but has limited data on CRKP and CRAB.

Time-kill assays are pivotal for pharmacodynamic evaluation, offering insights into bacterial killing kinetics and regrowth potential that static MIC testing cannot capture.[7] Although individual studies[8] have reported in vitro susceptibility data for ERV, TGC, and OMC, comparative data for all three agents remain scarce. This study is the first tertiary hospital-based comparison of these three agents against clinical CRAB and CRKP isolates, with concurrent analysis of clinical outcomes in patients treated with ERV or TGC.

Materials and Methods

Clinical Isolates

Non-duplicate clinical isolates of CRKP (n = 106) and CRAB (n = 117) were retrospectively collected from Xuanwu Hospital of Capital Medical University between December 2024 and June 2025. Isolates were excluded if they had insufficient clinical data (particularly missing outpatient records), failed to resuscitate from cryopreservation, were misidentified taxonomically, or showed phenotypic-genotypic discordance (eg, absence of carbapenemase genes despite phenotypic resistance). Random exclusion was applied to specific subsets to minimize statistical bias and balance cohort sizes. All qualifying strains were cryopreserved at −80°C in 15–20% glycerol broth, and species identification was confirmed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Germany).

Mass Spectrometry Cluster Analysis

Principal Component Analysis (PCA) and hierarchical clustering (HC) were performed to visualize the population structure. A dual-threshold strategy was applied to dendrograms: a distance level of 1.0 delineated major spectral clusters, while a stricter cutoff of 0.4 excluded clonally related strains, ensuring only spectrally distinct isolates (distance > 0.4) were retained for downstream experiments.

Genotyping

Carbapenemase genes in CRKP isolates were detected using immunochromatographic colloidal gold assays (Beijing Jinshanchuan Technology Development Co., Ltd.) and fluorescent PCR (Shanghai BioGerm Medical Technology), with targets including bla_{KPC}, bla_{NDM}, bla_{IMP}, and bla_{OXA-48}. For CRAB isolates, bla_{OXA-23} was detected using fluorescent PCR (Shanghai BioGerm Medical Technology). Positive results were defined as the presence of both test (T) and control (C) lines for colloidal gold assays and a fluorescence signal with Ct ≤37 for PCR.

Fluorescence PCR amplification results of carbapenemase genes are detailed in Supplementary Figure 1.

Antimicrobial Susceptibility Test (AST)

MICs for TGC, ERV, and OMC were determined using broth microdilution (CLSI M07-A11).[9] *E. coli* ATCC 25922 served as the negative control, and CRKP strains resistant to all three antibiotics (verified by E-test) served as positive controls. Assays were conducted in 96-well plates and antibiotics were serially diluted to final concentrations ranging from 32 μg/mL to 0.064 μg/mL. Breakpoints followed Food and Drug Administration (FDA) criteria for TGC (≤2 μg/mL susceptible [S], 4 μg/mL intermediate [I], ≥ 8 μg/mL resistant [R]) and OMC (≤4 μg/mL S, 8 μg/mL I, ≥ 16 μg/mL R), and ChinaCAST for ERV (≤1 μg/mL S).[10]

Time-Kill Assays

Time-kill assays were conducted on non-clonal clinical isolates selected via the cluster analysis, which included all positive resistant genes. Reference strains included KPC-producing *K. pneumoniae* ATCC BAA-1705 and OXA-23-producing *A. baumannii* ATCC 19606. Negative blank controls containing only culture medium were included. Antibiotics were tested at concentrations corresponding to their MIC_{90} values. Bacterial growth was monitored via OD_{600} absorbance at hourly intervals for the first 24 h, every 2 hours from 24 to 48 h, and every 6 hours thereafter. Log_{10} CFU/mL values were calculated using pre-validated standard curves.[11]

Clinical Efficacy Analysis

For the clinical analysis, patients were selected from the in-vitro isolate collection. Demographic and clinical outcome data were analyzed for those infected with CRKP or CRAB who received treatment with either TGC or ERV (OMC data were unavailable). This study adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of Xuanwu Hospital (XA[KS2024]039–002). Informed consent was obtained from all patients.

Statistical Analysis

The results were compiled using Microsoft Excel and statistical analyses were performed using SPSS 26.0. Categorical variables were analyzed using the chi-square (χ^2) test. Statistical significance was defined as a two-tailed *p-value* < 0.05.

Results

Collection, Distribution, and Molecular Characteristics of Clinical Isolates

A total of 223 non-duplicate isolates (106 CRKP and 117 CRAB) were collected. The workflow encompassing strain screening, exclusion, and patient enrollment is summarized in Figure 1. CRKP and CRAB were most frequently isolated from respiratory samples (sputum: 57.8% vs 63.7%, bronchoalveolar lavage fluid: 8.4% vs 8.5%), followed by urine (16.0% vs 8.5%), blood (9.4% vs 5.1%), and drainage fluid (8.4% vs 5.1%) (Figure 2a). The positive detection rates of KPC, NDM, and OXA-48 carbapenemase genes in CRKP were 85.8%, 14.2% and 1.9%, respectively. In CRAB, OXA-23-producing and non-OXA-23-producing strains each accounted for 92.3% and 7.7% (Figure 2b).

PCA-Based Hierarchical Clustering and Population Structure Analysis

PCA-based hierarchical clustering revealed distinct population structure for CRKP (clusters A–C) and CRAB (clusters D–F), with internal heterogeneity at sub-lineage levels (eg, A1 vs A2; D1 vs D2) (Figure 3). Using a cutoff value of 0.4, 33 non-clonal isolates (16 CRKP and 17 CRAB) were selected for downstream experiments.

Antimicrobial Susceptibility Test (AST)

For CRKP (n = 106), ERV susceptibility (94.3%) was significantly higher than TGC (19.8%, EUCAST: $\chi^2 = 28.41$, $p < 0.001$; 77.3%, FDA: $\chi^2 = 9.56$, $p = 0.002$) and OMC (16.9%, FDA: $\chi^2 = 34.17$, $p < 0.001$) (Table 1). EUCAST's revised TGC breakpoints (≤0.5 μg/mL S) reduced TGC susceptibility to 52.1%, highlighting breakpoint variability. MIC_{50} /MIC_{90} values were 0.5/1 μg/mL for ERV, 2/4 μg/mL for TGC, and 16/32 μg/mL for OMC. For CRAB (n = 117), ERV susceptibility was 99.1%, with MIC_{50}/MIC_{90} values (0.125/0.25 μg/mL) lower than TGC (0.5/1 μg/mL) and OMC (1/2 μg/mL). OMC demonstrated species-dependent activity, with an 8-fold lower MIC_{90} against CRAB than CRKP (8 vs

https://doi.org/10.2147/IDR.S583973

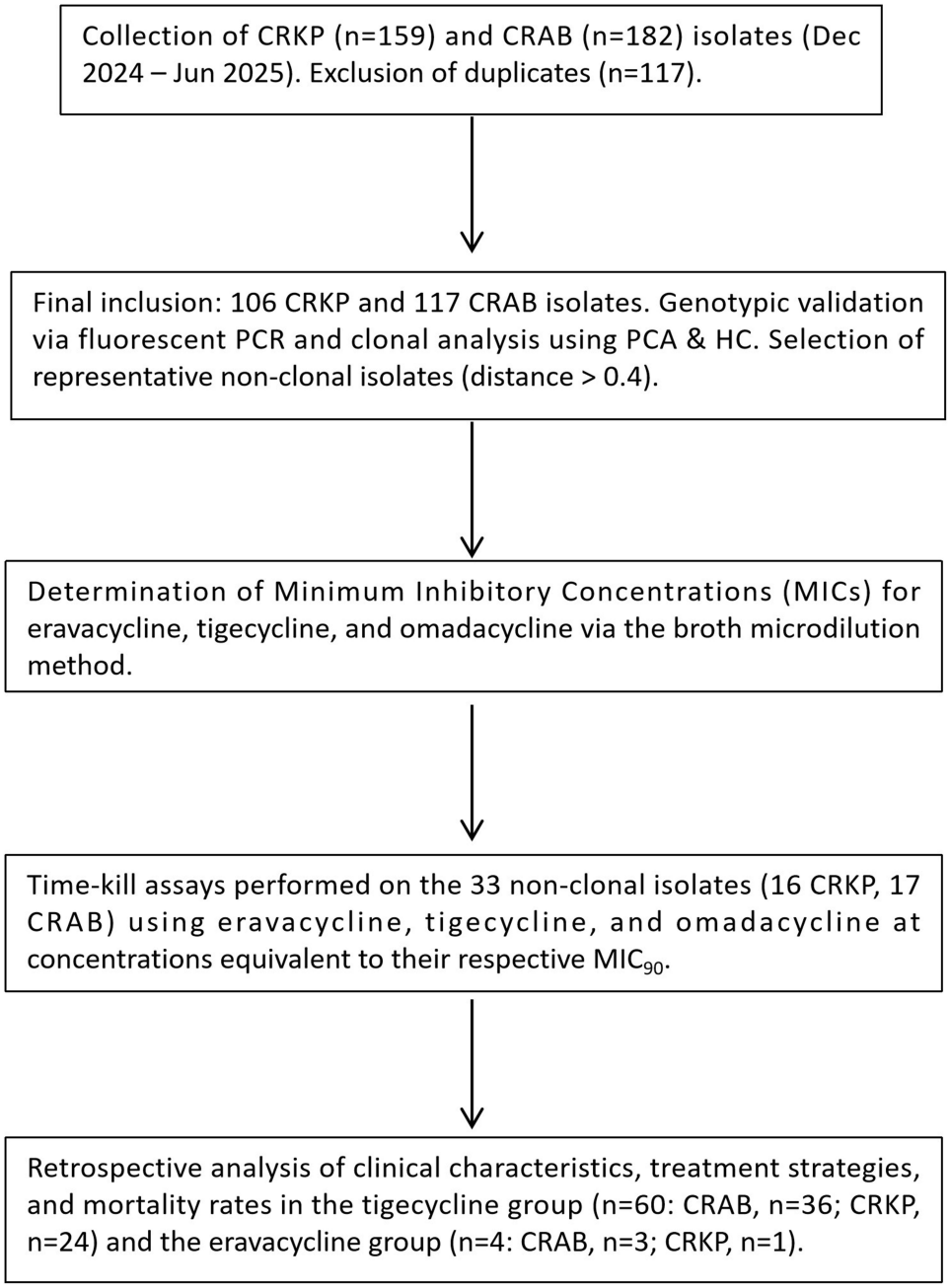

Figure 1 Experimental Workflow.

64 μg/mL) (Table 2). Specimen sources, resistance genotypes, and antimicrobial susceptibility profiles of CRKP and CRAB are detailed in Supplementary Tables 1 and 2.

Subgroup Analysis

Subgroup analysis based on carbapenemase type confirmed ERV's superiority in KPC-producing and metallo-β-lactamase (MBL)-producing CRKP strains (Figure 4). For KPC-producing CRKP (n = 91), ERV exhibited a significantly higher susceptibility rate (94%) than TGC (EUCAST breakpoints ≤ 0.5 mg/L: 52.1%, $\chi^2 = 31.09$, $p < 0.001$; FDA breakpoints ≤ 2 mg/L: 77%, $\chi^2 = 10.24$, $p = 0.001$). ERV also showed significantly higher susceptibility than OMC (17%, FDA breakpoints ≤ 4 mg/L: $\chi^2 = 72.35$, $p < 0.001$). For MBL-producing CRKP (n = 15), ERV demonstrated

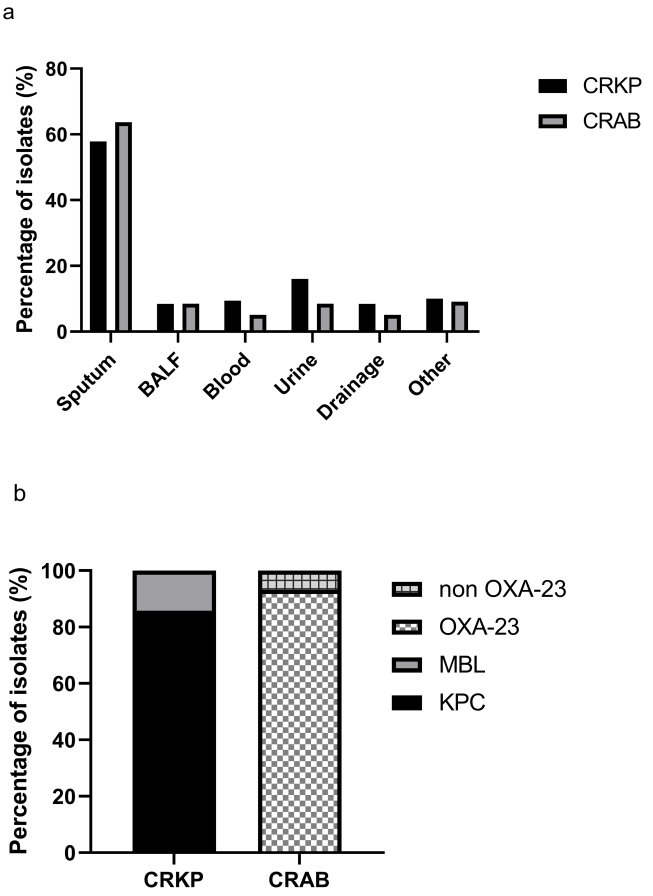

Figure 2 Specimen Sources and Genotyping Characteristics of the Collected Isolates. (**a**) Distribution of specimen types for CRKP and CRAB. (**b**) Distribution of carbapenemase genes.
Abbreviations: BALF, bronchoalveolar lavage fluid; MBL, metallo-β-lactamase; non-OXA-23, isolates negative for bla_{OXA-23}.

significantly superior activity compared to OMC (FDA breakpoints ≤ 4 mg/L: $\chi^2 = 19.83$, $p < 0.001$) and TGC (EUCAST breakpoints ≤ 0.5 mg/L: $\chi^2 = 8.94$, $p = 0.003$). No significant differences in susceptibility rates were observed for OXA-23/non-OXA-23-producing CRAB (ERV: 99.1% vs 100%; TGC and OMC: 100%).

Time-Kill Assays

Time-kill assays were conducted with 33 non-clonal isolates, including 16 CRKP strains (10 KPC producers and 6 MBL producers) and 17 CRAB strains (15 OXA-23 producers and 2 non-OXA-23 isolates). The MIC_{90} values determined for the time-kill curve experiments were as follows: 1/4/32 mg/L (ERV/TGC/OMC) for CRKP isolates and 0.25/1/2 mg/L for CRAB. Both CRAB and CRKP carbapenemase-producing strains showed robust antibacterial activity compared to the negative controls, with bacteriostatic effects lasting up to 12 h. ERV maintained bactericidal activity (≥3-$\log_{10}$ CFU/mL reduction) for 36 hours against CRAB and for 24 hours against CRKP, whereas TGC and OMC showed bacterial regrowth after 12 hours (Figure 5). ERV at 4–8×MIC completely suppressed regrowth, demonstrating concentration-dependent activity. Bacterial counts (log10 CFU/mL) in time-kill assays of ERV/TGC/OMC against CRKP or CRAB are detailed in Supplementary Tables 3–5.

Clinical Outcomes

We analyzed 36 CRKP and 24 CRAB isolates that were exposed to targeted antibiotics. The CRAB isolates were derived from 36 patients (26 male, 10 female; median age 68 years, range 27–93), of whom 33 (91.7%) were treated in the ICU and 3 were from the Geriatric Rehabilitation Department. Similarly, 24 CRKP isolates were obtained from patients of 21 males and 3 females (age range 17~92 years), 91.7% (22/24) were in ICUs, and 2 from Hematology Department and

https://doi.org/10.2147/IDR.S583973

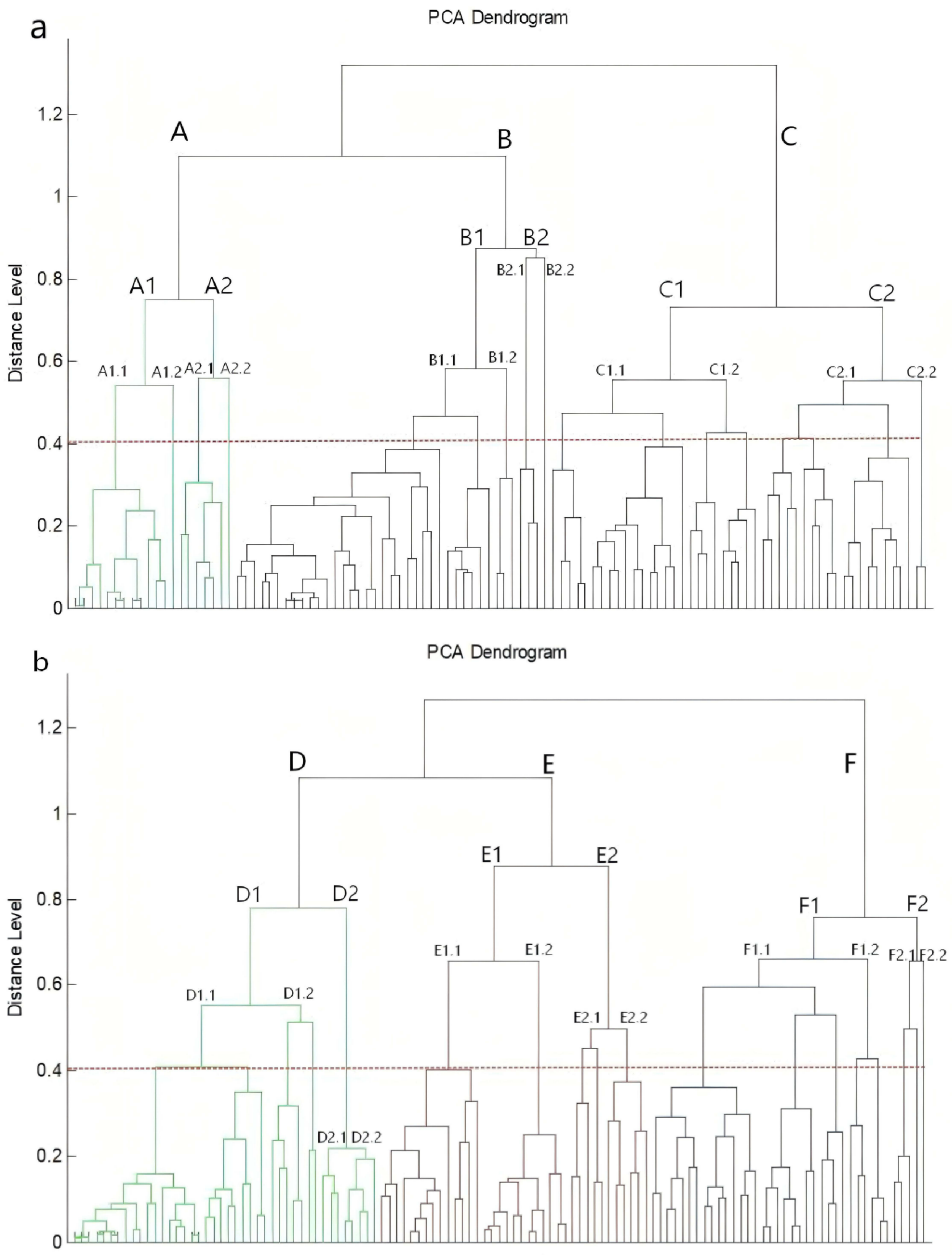

Figure 3 Hierarchical Clustering Dendrograms for CRKP and CRAB Isolates. (**a**) Clustering dendrograms of CRKP isolates. (**b**) Clustering dendrograms of CRAB isolates. The red dashed line indicates the cut-off value (distance level = 0.4) used to define clonal relatedness; isolates clustered below this line were considered to be of the same clone. Major clusters and sub-clusters are labeled with capital letters and numbers (eg, A, A1, B, B1).

General Medicine Department; ERV-treated patients (n = 20, 15 CRAB and 5 CRKP) had a 5% mortality rate (6.7% for CRAB and 0% for CRKP), compared with rates of 18.9% (CRAB) and 16.7% (CRKP) in TGC-treated patients (n = 60, 36 CRAB and 24 CRKP) (Table 3). This disparity aligns with ERV's superior in vitro activity and tissue penetration.

Discussion

This study evaluated in vitro activity of three tetracycline-class agents against 223 CRKP and CRAB isolates and analyzed clinical outcomes in patients treated with ERV or TGC. Key findings demonstrate the potent in vitro activity of ERV against CRKP and CRAB, exhibiting favorable profiles compared to TGC and OMC. This conclusion is supported by three key observations: (a) MIC profiles: ERV demonstrated 4-fold lower MIC values than TGC and 8-fold lower than OMC against CRKP, consistent with previous in vitro studies.[12,13] For CRAB, ERV's MIC_{90} was 4-fold lower than TGC,

Table 1 Antimicrobial Susceptibility Profiles of CRKP and CRAB

	Eravacycline	Tigecycline		Omadacycline
AST (n) (S%)	**ChinaCAST**	**FDA**	**EUCAST**	**FDA**
***K. pneumoniae* (n=106)**	100 (94.3)	82 (77.3)	21 (19.8)	18 (16.9)
bla$_{KPC}$ (n=91)	86 (94.5)	70 (77.0)	13 (14.2)	16 (17.6)
bla$_{NDM}$ (n=5)	4 (80.0)	3 (60.0)	2 (40.0)	0 (0)
bla$_{KPC}$+*bla*$_{NDM}$ (n=7)	7 (100)	6 (85.7)	1 (14.3)	0 (0)
bla$_{KPC}$+*bla*$_{IMP}$ (n=1)	1 (100)	1 (100)	1 (100)	0 (0)
bla$_{KPC}$+*bla*$_{NDM}$+*bla*$_{OXA-48}$ (n=2)	2 (100)	2 (100)	0 (0)	1 (50)
Metallo-β-lactamase* (n=15)	14 (92.9)	12 (80)	4 (28.6)	1 (6.7)
***A. Baumannii* (n=117)**	116 (99.1)	117 (100)	—	117 (100)
bla$_{OXA-23}$ (n=108)	107 (99.1)	108 (100)	—	108 (100)
Non-bla$_{OXA-23}$ (n=9)	9 (100)	9 (100)	—	9 (100)
MIC$_{50}$ (μg/mL)				
A. baumannii	0.125	0.5		1
K. pneumoniae	0.5	2		16
bla$_{KPC}$	0.5	2		16
Metallo-β-lactamase*	0.5	1		16
MIC$_{90}$ (μg/mL)				
A. baumannii	0.25	1		2
K. pneumoniae	1	4		32
bla$_{KPC}$	1	4		32
Metallo-β-lactamase*	1	4		32
MIC Range (μg/mL)				
A. baumannii	0.064–2	0.125–2		0.125–4
K. pneumoniae	0.064–4	0.125–8		0.25–32
bla$_{KPC}$	0.064–4	0.125–8		0.25–32
Metallo-β-lactamase*	0.125–4	0.25–8		4–32

Note:*Metallo-β-lactamase includes *bla*$_{NDM}$ and *bla*$_{IMP}$.
Abbreviations: MIC$_{50}$: Minimum inhibitory concentration required to inhibit 50% of isolates; MIC$_{90}$: Minimum inhibitory concentration required to inhibit 90% of isolates.

Table 2 MIC Distribution of Eravacycline and Tigecycline Against CRKP and CRAB

CRKP (CRAB) (MIC μg/mL)		**Eravacycline (n)**						
Tigecycline (n)	0.125	1 (3)	0 (1)					
	0.25	0 (6)	1 (2)	1 (0)				
	0.5	4 (28)	5 (24)		3 (0)	1 (0)		
	1	0 (21)	2 (28)	13 (6)	6 (2)	1 (0)		0 (1)
	2	0 (1)	0 (2)	2 (2)	12 (1)	16 (0)	1 (0)	
	4					16 (0)	1 (0)	
	8					1 (0)	1 (0)	2 (0)

though all three agents showed high susceptibility. (b) Although the CRAB isolates displayed in vitro susceptibility to all tested agents, ERV demonstrated a distinct advantage in maintaining bacterial suppression. Specifically, ERV exerted bactericidal effects against CRAB for 36 hours, significantly surpassing the 12-hour duration observed for TGC and OMC. This finding highlights the superior durability of ERV's antimicrobial activity against CRAB compared to other tetracycline-class agents. (c) Clinical correlation: ERV-treated patients showed a 5% mortality rate, compared with

https://doi.org/10.2147/IDR.S583973

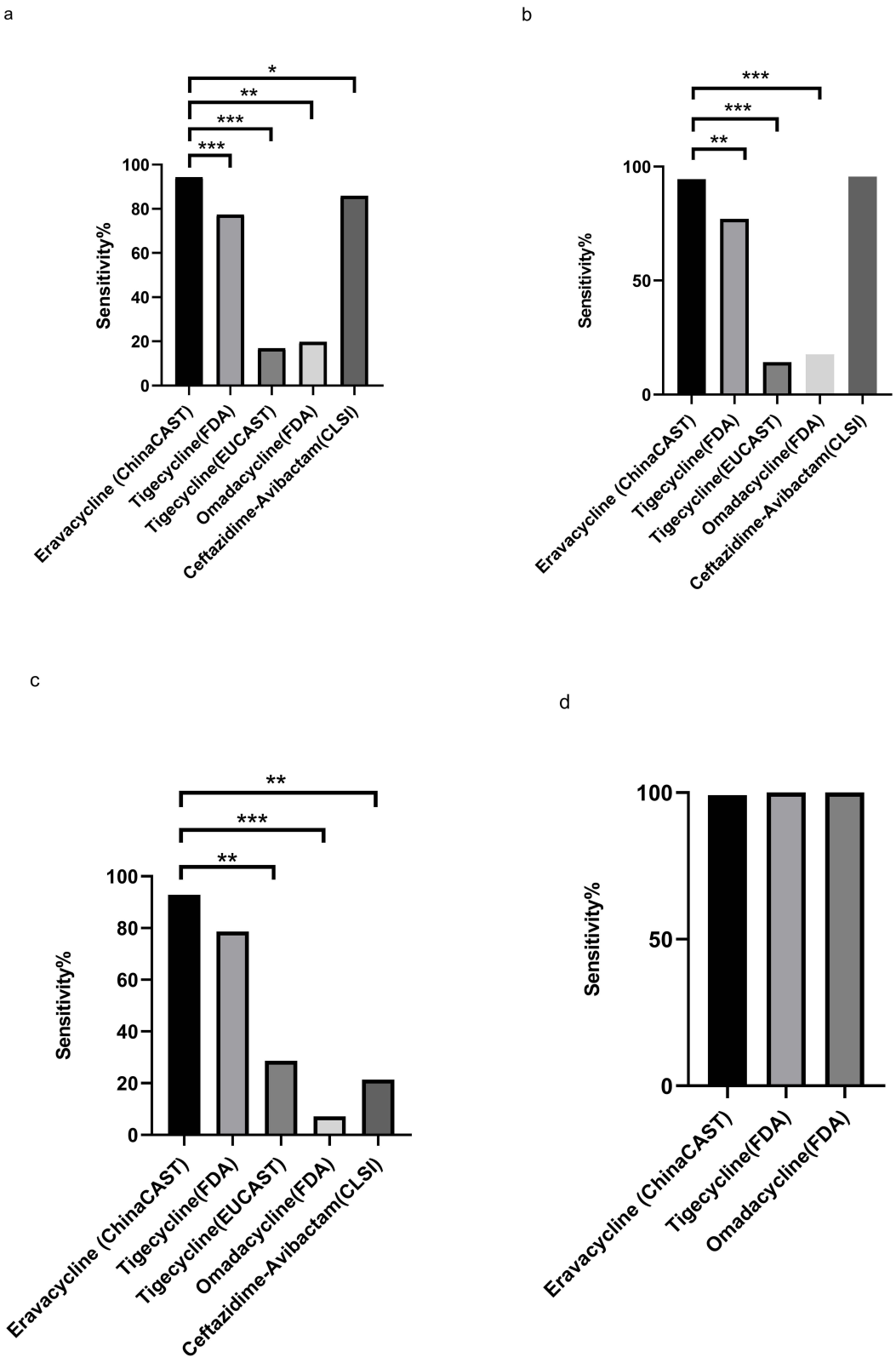

Figure 4 Susceptibility Rates of Eravacycline, Tigecycline, and Omadacycline against Carbapenem-resistant Isolates. (**a**) Total CRKP strains. (**b**) KPC-producing CRKP strains. (**c**) MBL-producing CRKP strains. (**d**) CRAB strains. Statistical significance is indicated by asterisks: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The number of strains for each genotype is listed in Table 1.

Abbreviation: MBL, metallo-β-lactamase.

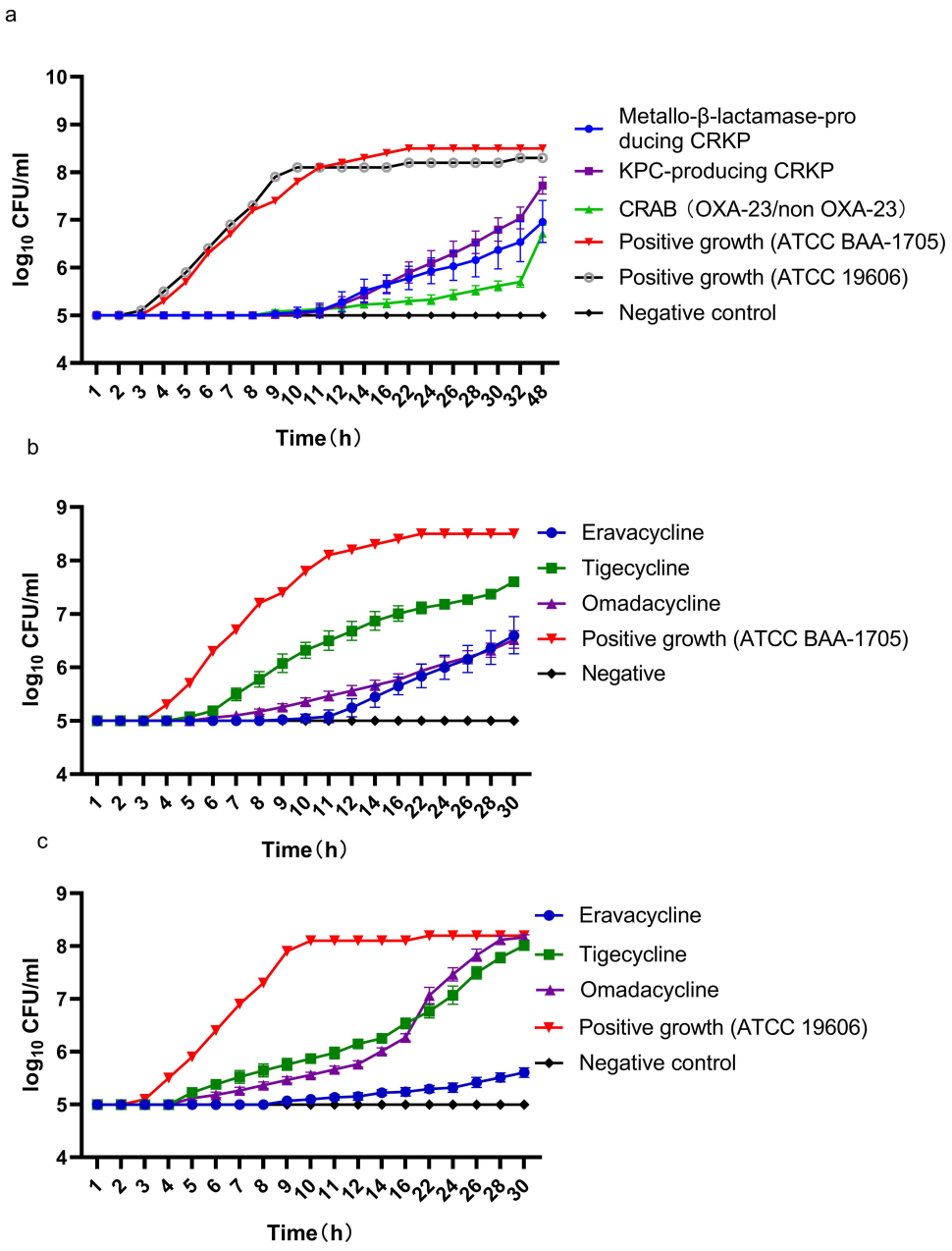

Figure 5 Time-kill Curves for Eravacycline, Tigecycline, and Omadacycline against CRKP and CRAB. (**a**) Eravacycline susceptibility of CRKP and CRAB strains with diverse resistance phenotypes. (**b**) Comparison of eravacycline, tigecycline, and omadacycline against CRKP. (**c**) Comparison of the three tetracyclines against CRAB. *K. pneumoniae* ATCC BAA-1705 and *A. baumannii* ATCC 19606 served as positive growth controls for CRKP and CRAB, respectively. The time-kill assays were performed at concentrations corresponding to the MIC_{90} values determined for the clinical isolates: 1/4/32 mg/L (ERV/TGC/OMC) for CRKP and 0.25/1/2 mg/L (ERV/TGC/OMC) for CRAB. Bactericidal activity was defined as a ≥ 3-$\log_{10}$ CFU/mL reduction under the tested conditions (initial inoculum: 10^5 CFU/mL; temperature: 37°C).

16.7–19.4% for TGC-treated patients, despite the smaller ERV cohort. This aligns with ERV's superior tissue penetration and in vitro activity.

CRKP and CRAB are most prevalent in respiratory samples but also detected in blood/urine/cerebrospinal fluid, underscoring the need for vigilance across infection types. Using CLSI-standardized broth microdilution (M07-A11), we found: For CRKP, ERV (94% susceptibility) outperformed TGC (77%) and OMC (17%). EUCAST's revised TGC breakpoints (≤0.5 μg/mL) reduced its susceptibility to 52.1%, highlighting breakpoint variability impacts. For CRAB, all three agents showed high activity (ERV: 99.1%, TGC/OMC: 100%), though EUCAST lacks Acinetobacter-specific breakpoints for global comparisons.

https://doi.org/10.2147/IDR.S583973

Table 3 Therapeutic Regimens and Clinical Outcomes of Tigecycline Vs Eravacycline for CRAB and CRKP Infections

	NO.	ICU (n)	Antimicrobial Therapy (n)	MIC Range (μg/mL)	Case Fatality Rate
Tigecycline					
A. baumannii	36	33			19.4%
			TGC+SCF (20)	0.5–2	10%
			TGC+MEM (5)	1–2	60%
			TGC+IPM (1)	2	100%
			TGC+MEM+SCF (3)	1–2	0%
			TGC+FEP (2)	1–2	0%
			TGC+MEM+PB (1)	1–2	0%
			TGC+SCF+CZA (1)	1–2	0%
			TGC+CIP (1)	2	100%
RTI	26	25			23.1%
			TGC+SCF (17)	0.5–2	11.7%
			TGC+MEM (3)	1–2	66.7%
			TGC+IPM (1)	2	100%
			TGC+FEP (2)	1–2	100%
			TGC+MEM+SCF (1)	1	0%
			TGC+SCF+CZA (1)	1	0%
			TGC+CIP (1)	2	100%
BSI	5	4			0%
			TGC+SCF (3)	1–2	0%
			TGC+MEM (1)	1	0%
			TGC+MEM+SCF (1)	1	0%
IAI	4	3			20%
			TGC+SCF (2)	1–2	0%
			TGC+MEM (1)	2	100%
			TGC+MEM+SCF (1)	1	0%
			TGC+MEM+PB (1)	1	0%
K. *pneumoniae*	24	22			16.7%
			TGC+SCF (4)	0.5–8	0%
			TGC+MEM (1)	2	0%
			TGC+IPM (4)	2–4	0%
			TGC+IPM (2)	2	0%
			TGC+CZA (6)	1–8	16.7%
			TGC+SCF+AK (1)	1	0%
			TGC+SCF+CZA (1)	1	0%
			TGC+IPM+CSF (3)	4–8	100%
			TGC+PB (2)	4	0%
RTI	12	10			8.3%
			TGC+SCF (3)	0.5–4	0%
			TGC+MEM (1)	2	0%
			TGC+IPM (2)	2–4	0%
			TGC+IPM (1)	2	0%
			TGC+CZA (3)	2–8	0%
			TGC+IPM+CZA (1)	4	0%
			TGC+SCF+IPM (1)	8	100%
BSI	2	2			50%
			TGC+CZA (1)	2	0%
			TGC+IPM (+CZA (1)	8	100%
CNSI	1	1			14.3%
UTI	2	2	TGC+PB (1)	4	0%

(*Continued*)

Table 3 (Continued).

	NO.	ICU (n)	Antimicrobial Therapy (n)	MIC Range (μg/mL)	Case Fatality Rate
IAI	7	7	TGC+CZA (2)	1–4	50%
			TGC+SCF (1)	1	0%
			TGC+IPM (2)	2–4	0%
			TGC+IPM (1)	2	0%
			TGC+SCF+AMK (1)	1	0%
			TGC+IPM (+CZA (1)	4	100%
			TGC+PB (1)	2	0%
Eravacycline					
A. baumannii	15	15	ERV+SCF (15)	1	6.7%
RTI	15	15	ERV+SCF (15)	1	6.7%
K. pneumoniae	5	5	ERV+SCF (5)	1	0%
RTI	5	5	ERV+SCF (5)	1	0%

Abbreviations: TGC, Tigecycline; ERV, Eravacycline; SCF, ceftriaxone sulbactam; MEM, meropenem; IPM, imipenem; BIMP, biapenem; CZA, ceftazidime-avibactam; AMK, amikacin; CIP, ciprofloxacin; PB, polymyxin B; RTI, respiratory tract infection; BSI, bloodstream infection; UTI, urinary tract infection; CNSI, central nervous system infection; IAI, intra-abdominal infection.

ERV's enhanced activity is explained by its stability against tetracycline resistance mechanisms (efflux pumps, ribosomal protection).[14,15] Notably, we detected ERV-resistant strains, consistent with international reports.[16] OMC showed species-dependent activity, with higher susceptibility against CRAB than CRKP (8-fold lower MIC_{90} against CRAB vs CRKP), suggesting potential utility for mild-to-moderate CRAB infections in outpatient settings.[17] However, its 16.9% susceptibility against CRKP limits its clinical utility. TGC's suboptimal tissue penetration and higher mortality may be attributed to AcrAB-TolC overexpression in CRKP and OprD deficiency in CRAB.[18] Two OXA-48-coharboring isolates showed partial OMC susceptibility, but small sample size prevents definitive conclusions.[19]

Time-kill assays revealed ERV's concentration-dependent bactericidal effects: 4–8×MIC suppressed regrowth for 36 hours (unlike TGC/OMC at 2×MIC). Its superior tissue penetration (2.3-fold vs TGC, 3.1-fold vs OMC in alveolar fluid)[20] further supports in vivo efficacy. The lower mortality rate observed in ERV-treated patients (5%) compared to TGC-treated patients (16.7–19.4%) suggests a potential link between its superior laboratory potency and improved clinical outcomes. This mortality disparity aligns with our in vitro findings of ERV's superior bactericidal activity and documented enhanced tissue penetration. However, the small ERV cohort warrants caution—prospective, balanced multicenter studies are needed to confirm findings and elucidate pharmacokinetic/pharmacodynamic (PK/PD) drivers and solidify ERV's role in future treatment paradigms for carbapenem-resistant Gram-negative infections.

This study has several limitations, including its single-center design, small ERV cohort, and inability to adjust for confounding factors (eg, baseline comorbidities). Future multicenter studies with larger cohorts and multivariate analyses are needed to validate ERV's role in CRKP and CRAB treatment paradigms.

In summary, this work positions ERV as a promising therapeutic alternative for CRKP and CRAB infections, especially where sustained bactericidal activity is critical, though widespread multicenter prospective validation is still required. Based on current literature, OMC may be suitable for mild-to-moderate infections and outpatient management, while TGC's utility in severe infections may be compromised by tissue penetration and dosing issues. However, these findings must be interpreted with caution, given the small ERV sample size (n=20) and the lack of adjustment for disease severity and infection site.

Conclusion

ERV demonstrates superior in vitro bactericidal activity compared to both of TGC and OMC, alongside favorable clinical outcomes relative to TGC for CRKP and CRAB infections from our retrospective clinical cohort. Its potential as a core therapeutic agent warrants validation in large-scale, multicenter studies.

Data Sharing Statement

De-identified datasets supporting the findings of this study are available from the corresponding author (*E-mail: 13683581168@126.com)* on reasonable request.

Ethical Approval

The research protocol was approved by the Medical Ethics Committee of Xuanwu Hospital, Capital Medical University (XA[KS2024] 039-002 and [2025] 411-002). All methods were performed in accordance with the relevant guidelines and regulations.

Acknowledgments

We thank Xuanwu Hospital for providing isolates, data, and all study participants.

Author Contributions

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

Funding

This work was supported by the Hebei Provincial Department of Science and Technology (244X7703D and XA202401102002K), Beijing Municipal Health Commission (Discipline Backbone-01-023), and Beijing Natural Science Foundation (L256081).

Disclosure

The authors declare that they have no conflicts of interest. This paper has been uploaded to Research Square as a preprint: https://doi.org/10.21203/rs.3.rs-7052797/v1

References

1. Jean S, Harnod D, Hsueh P. Global threat of carbapenem-resistant gram-negative bacteria. *Front Cell Infect Microbiol*. 2022;12:823684. doi:10.3389/fcimb.2022.823684
2. Lawandi A, Yek C, Kadri SS. IDSA guidance and ESCMID guidelines: complementary approaches toward a care standard for MDR Gram-negative infections. *Clin Microbiol Infect*. 2022;28(4):465–469. doi:10.1016/j.cmi.2022.01.030
3. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-lactam-β-lactamase inhibitor combinations. *Clin Microbiol Rev*. 2020;34(1):e115–e120. doi:10.1128/CMR.00115-20
4. Jin X, Chen Q, Shen F, et al. Resistance evolution of hypervirulent carbapenem-resistant *Klebsiella pneumoniae* ST11 during treatment with tigecycline and polymyxin. *Emerg Microbes Infect*. 2021;10(1):1129–1136. doi:10.1080/22221751.2021.1937327
5. Zhou C, Huang F, Zhang J, Zhuang Y. Population pharmacokinetics of tigecycline: a systematic review. *Drug Des Devel Ther*. 2022;16:1885–1896. doi:10.2147/DDDT.S365512
6. Chen Z, Sun W, Chi Y, Liang B, Cai Y. Efficacy and safety of eravacycline (ERV) in treating infections caused by gram-negative pathogens: a systematic review and meta-analysis. *Expert Rev Anti Infect Ther*. 2024;22(10):867–875. doi:10.1080/14787210.2024.2397663
7. Balouiri M, Sadiki M, Ibnsouda SK. Methods for *in vitro* evaluating antimicrobial activity: a review. *J Pharm Anal*. 2016;6(2):71–79. doi:10.1016/j.jpha.2015.11.005
8. Zhang S, Di L, Qi Y, Qian X, Wang S. Treatment of infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Front Cell Infect Microbiol*. 2024;14:1395260. doi:10.3389/fcimb.2024.1395260
9. Chen X, Liu X, Ren W, Li H, Yang S. Distribution patterns and evolution of antimicrobial resistance in gram-negative bacteria within the intensive care unit of a tertiary hospital from 2019 to 2024. *Front Microbiol*. 2025;16:1587132. doi:10.3389/fmicb.2025.1587132
10. Gong Y, Liu Y, Zhu Y, et al. Antibacterial activity of eravacycline against *Klebsiella pneumoniae* isolates: an in vitro study. *Microbiol Spectr*. 2025;13(7):e256424. doi:10.1128/spectrum.02564-24
11. Filimonova AV, Golikova MV, Strukova EN, Portnoy YA, Kuznetsova AA, Zinner SH. Predicting the effects of carbapenem/carbapenemase inhibitor combinations against KPC-producing *Klebsiella pneumoniae* in time-kill experiments: alternative versus traditional approaches to MIC determination. *Antibiotics*. 2021;10(12):1520. doi:10.3390/antibiotics10121520
12. LaPlante KL, Dhand A, Wright K, Lauterio M. Re-establishing the utility of tetracycline-class antibiotics for current challenges with antibiotic resistance. *Ann Med*. 2022;54(1):1686–1700. doi:10.1080/07853890.2022.2085881

13. Kounatidis D, Dalamaga M, Grivakou E, et al. Third-generation tetracyclines: current knowledge and therapeutic potential. *Biomolecules*. 2024;14 (7):783. doi:10.3390/biom14070783
14. Luo Q, Lu P, Chen Y, et al. ESKAPE in China: epidemiology and characteristics of antibiotic resistance. *Emerg Microbes Infect*. 2024;13 (1):2317915. doi:10.1080/22221751.2024.2317915
15. Ji X, Mak WY, Xue F, et al. Population pharmacokinetics and pulmonary modeling of eravacycline and the determination of microbiological breakpoint and cutoff of PK/PD. *Antimicrob Agents Chemother*. 2025;69(3):e106524. doi:10.1128/aac.01065-24
16. Zhang Y, Liu D, Liu Y, et al. Detection and characterization of eravacycline heteroresistance in clinical bacterial isolates. *Front Microbiol*. 2024;15:1332458. doi:10.3389/fmicb.2024.1332458
17. Morrisette T, Alosaimy S, Lagnf AM, et al. Real-world, multicenter case series of patients treated with oral omadacycline for resistant gram-negative pathogens. *Infect Dis Ther*. 2022;11(4):1715–1723. doi:10.1007/s40121-022-00645-5
18. Du Y, Liu Y, Liu T, et al. The in vitro activity of omadacycline alone and in combination against carbapenem-resistant *Klebsiella pneumoniae*. *Infect Drug Resist*. 2024;17:5785–5794. doi:10.2147/IDR.S473546
19. Talsma DT, Monteiro R, Flores-Vallejo RDC, et al. Nosocomial transmission of tet(x3), bla (NDM-1) and bla (OXA-97)-carrying *Acinetobacter baumannii* conferring resistance to eravacycline and omadacycline, the Netherlands, March to August 2021. *Euro Surveillance*. 2024;29 (28):2400019. doi:10.2807/1560-7917.ES.2024.29.28.2400019
20. Connors KP, Housman ST, Pope JS, et al. Phase I, open-label, safety and pharmacokinetic study to assess bronchopulmonary disposition of intravenous eravacycline in healthy men and women. *Antimicrob Agents Chemother*. 2014;58(4):2113–2118. doi:10.1128/AAC.02036-13