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Comparative efficacy of eravacycline and tigecycline in addressing multidrug-resistant Gram-negative bacteria

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Abstract

The rise in antibiotic resistance among Gram-negative bacteria poses significant challenges to global health. This study evaluates the in vitro efficacy of tigecycline, omadacycline, and eravacycline against clinical isolates harboring the mobile tigecycline resistance genes *tet*(X4) and *tet*(A). A total of 175 clinical strains collected between 1999 and 2023 were analyzed. Resistance genes, including *tet*(X4) and *tet*(A), were determined using Polymerase chain reaction (PCR). Minimum inhibitory concentrations (MICs) were determined using the broth microdilution method. Eravacycline exhibited significantly lower MIC values than those of tigecycline for *Escherichia coli* carrying *tet*(X4) ($P < 0.0001$), despite similar resistance rates. Omadacycline consistently displayed the highest MIC values, indicating reduced potency. In contrast, *Klebsiella pneumoniae* carrying *tet*(A) showed higher MIC values for eravacycline than tigecycline. Universal resistance was observed in *Enterobacter cloacae* carrying *tet*(A). Eravacycline demonstrated superior in vitro efficacy, particularly against *E. coli* carrying *tet*(X4), underscoring its potential as a therapeutic option for multidrug-resistant infections. MIC values should complement resistance rates in clinical decision-making, and further studies are warranted to validate eravacycline's clinical utility.

Keywords Eravacycline, Tigecycline, Antibiotic resistance, *Tet*(X4), *Escherichia coli*, *Klebsiella pneumoniae*

Introduction

The rise in antibiotic resistance represents a formidable challenge to global health, with the World Health Organization designating antibiotic resistance as a principal threat to human health [1]. Multidrug resistance refers to bacteria that are not susceptible to three or more classes of clinically used antimicrobials [2]. The increasing prevalence of antibiotic resistance in Gram-negative bacteria, particularly through mobile resistance genes such as *tet*(X4) and *tet*(A), presents a major global health challenge. These genes, associated with tetracycline resistance, are especially concerning because of their ability to spread rapidly across bacterial populations.

Tetracyclines are natural products of actinomycetes that were first reported in 1948 [3]. In the late 1980s, structural optimization of tetracycline led to the development of several semisynthetic derivatives such as

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doxycycline and minocycline, which are second-generation tetracyclines [4]. Subsequent modifications to the tetracycline side chain resulted in the production of the third-generation tetracycline tigecycline in 1993. To date, fourth-generation tetracyclines, such as omadacycline and eravacycline, have been developed. The structural and physicochemical components pivotal in the discovery of modern tetracycline have been explored [5].

Tigecycline is a semisynthetic glycylcycline, a derivative of minocycline, which overcomes resistance mediated by efflux pumps and ribosomal protective proteins, resulting in broader and more effective antimicrobial activity than that of other tetracyclines [6]. Owing to its broad-spectrum antibacterial activity, it was approved by the U.S. Food and Drug Administration (FDA) in 2005 and is used to treat complicated intra-abdominal infections [7]. It was subsequently approved for the treatment of community-acquired bacterial pneumonia (CABP) in 2008 [8] and was approved for marketing in China in 2010 [9]. Currently, tigecycline is approved as adult monotherapy for the treatment of complicated skin and soft structure infections (cSSTIs), complicated intra-abdominal infections (cIAIs), and CABP [10].

Eravacycline is structurally similar to tigecycline but has two changes in the D-ring of the tetracycline core and, like other tetracyclines, it inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit [11]. Eravacycline, approved by the FDA for marketing in 2018 and available in China since 2023, has received FDA approval for the treatment of cIAIs [12]. Eravacycline has been used to treat serious bacterial infections caused by a broad spectrum of Gram-negative, Gram-positive, aerobic, and anaerobic pathogens, including multidrug-resistant microorganisms [13]. Eravacycline exhibited a superior gastrointestinal safety profile among the tetracycline-glycylcycline class [14]. The use of eravacycline presents a promising approach for the management of infections caused by multidrug-resistant organisms, particularly in cases where traditional antibiotics fail [14].

Omadacycline was FDA-approved for marketing in 2018 and has been available in China since 2023 for the treatment of acute bacterial cSSTIs and CABP and can be administered intravenously or orally [15]. Omadacycline was the first aminomethyl tetracycline to enter the clinical use [16]. This antibiotic is structurally based on minocycline, with an aminomethyl group at the C9 position [17]. Omadacycline resists efflux pumps and ribosomal protection mechanisms [18].

Resistance to tigecycline involves several mechanisms, including the overexpression of efflux pumps, mutations in ribosomal protein genes, and the production of tigecycline-inactivating enzymes. Specifically, genes encoding efflux pumps, such as *tet*(A), *OqxAB*, and *AcrAB*-TolC [19–21], confer resistance by actively expelling tetracycline molecules from bacterial cells, thereby mediating high levels of tigecycline resistance [22]. Mutations in regulatory genes, such as *ramR, marR*, and other genes, can affect the expression of efflux pumps, which can indirectly lead to tigecycline resistance [23, 24]. In contrast, the *tet*(X4) gene family encodes tigecycline-inactivating enzymes, which significantly increase the minimum inhibitory concentration (MIC) values for tigecycline in bacteria harboring this gene [25]. Among these, plasmid-borne genes encoding transferable tigecycline resistance, including *tet*(X) variants (particularly *tet*(X3) and *tet*(X4)) [26] and *tet*(A) variants, are particularly concerning [26, 27].

The current understanding of the efficacy of third- and fourth-generation tetracyclines in combatting clinical strains is limited. To address this issue, we evaluated the in vitro antimicrobial effects of tigecycline, omadacycline, and eravacycline against clinical isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp., and *Enterobacter cloacae* harboring mobile tigecycline resistance genes, including *tet*(X4) and *tet*(A). This study seeks not only to underscore the therapeutic potential of these novel antibiotics but also to chart a course toward reclaiming the upper hand in our ongoing battle against antibiotic resistance.

Results

A total of 175 Gram-negative clinical strains were collected, including 97 *E. coli*, 26 *K. pneumoniae*, 34 *Acinetobacter* spp., and 18 *E. cloacae*. The PCR results indicated that each strain harbored either the wild-type *tet*(X4) or the wild-type *tet*(A) or lacked mobile tigecycline resistance genes entirely. Among the 175 Gram-negative strains, the resistance rates to tigecycline, omadacycline, and eravacycline were comparable across species, with *E. coli* showing resistance rates of 55.7%, 52.6%, and 58.8%, respectively. Resistance was strongly associated with the presence of *tet*(X4) and *tet*(A), as carriers of these genes exhibited significantly higher resistance rates than those of noncarriers.

The MIC_{50} and MIC_{90} values of tigecycline, omadacycline, and eravacycline were determined to assess their potencies against the tested bacterial isolates (Table 1). Omadacycline exhibited significantly higher MIC values than tigecycline and eravacycline. Specifically, eravacycline exhibited significantly lower MIC values (3.81 ± 1.63 μg/mL) than tigecycline (9.68 ± 5.63 μg/mL) in *E. coli* harboring *tet*(X4) ($P < 0.0001$) (Fig. 1A), indicating a potential advantage in treating these resistant strains. In contrast, omadacycline consistently displayed the highest MIC values across all species, suggesting reduced efficacy relative to the other two antibiotics.

Table 1 Characteristics of the four bacteria species and the resistance rates to the three antibiotics (total $n = 175$)

Species	Mobile resistance gene	Number of strains	Tigecycline			Omadacycline			Eravacyclin		
			MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	R (%)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	R (%)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	R (%)
Escherichia coli	*tet*(X4)	52	8	16	98.1	32	> 32	94.2	4	4	100
	none	45	< 0.25	0.5	6.7	2	8	4.4	0.25	1	11.1
	all	97	2	16	55.7	16	> 32	52.6	2	4	58.8
Klebsiella pneumoniae	*tet*(A)	22	2	4	77.3	> 32	> 32	90.9	2	8	95.45
	none	4	< 0.25	4	50	4	32	25	0.5	2	50
	all	26	1	4	73.1	32	> 32	80.8	2	8	88.5
Enterobacter cloacae	*tet*(A)	5	4	4	100	32	> 32	100	4	8	100
	none	13	0.25	0.5	0	4	16	15.4	0.5	1	23.1
	all	18	0.5	4	27.8	4	> 32	38.9	0.5	4	44.4
Acinetobacter spp.	none/all	34	1	4	-	8	32	-	2	4	-

Resistance rate not applicable because of the lack of a documented breakpoint for *Acinetobacter* spp

Abbreviations: MIC_{50} The concentration of an antibiotic that inhibits the growth of 50% of the bacteria, MIC_{90} The concentration of an antibiotic that inhibits the growth of 90% of the bacteria, *R (%)* Resistance rate of the bacteria based on breakpoints

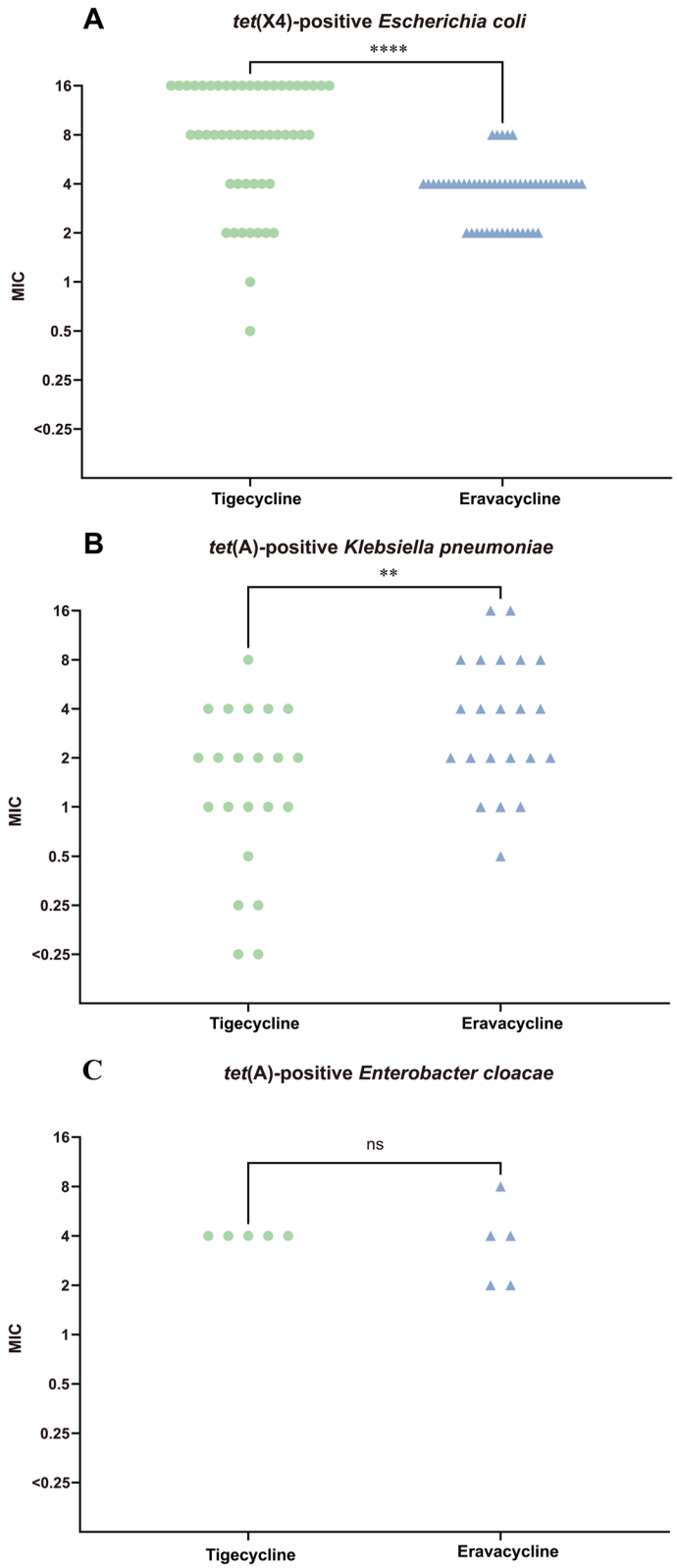

Fig. 1 Minimum inhibitory concentration (MIC) distribution of tigecycline and eravacycline in strains carrying mobile tigecycline resistance genes: **A** *Escherichia coli*, **B** *Klebsiella pneumoniae*, and **C** *Enterobacter cloacae*. Statistical significance was determined using the Mann–Whitney test, with a significance threshold of $P < 0.05$. For P values, ns (not significant) indicates $P > 0.05$; **, $P \leq 0.01$; ****, $P \leq 0.0001$

Notably, *K. pneumoniae* carrying *tet*(A) showed higher MIC values for eravacycline (4.89 ± 4.34 μg/mL) than for tigecycline (3.81 ± 1.63 μg/mL) ($P = 0.0097$) (Fig. 1B), underscoring the influence of resistance genes on antibiotic potency.

For *E. cloacae* strains carrying *tet*(A), the resistance rates to all three antibiotics were universally high (100%), with no significant difference in the MIC values between eravacycline (4 ± 2.19 μg/mL) and tigecycline (4 ± 0 μg/mL) ($P = 0.222$) (Fig. 1C). *Acinetobacter* spp., which lacked mobile tigecycline resistance genes, exhibited comparable MIC values for eravacycline (2.52 ± 1.73 μg/mL) and tigecycline (1.89 ± 1.53 μg/mL) ($P = 0.352$), further supporting the role of resistance genes in determining antibiotic susceptibility.

Further analysis was conducted on four species that lacked mobile tigecycline resistance genes (Fig. 2). Among *E. coli* without *tet*(X4), the resistance rates to tigecycline, eravacycline, and omadacycline did not significantly differ ($P = 0.604$). However, the MIC values varied significantly ($P < 0.0001$), with omadacycline (4.06 ± 4.99 μg/mL) exhibiting the highest MIC values, followed by eravacycline (0.47 ± 0.39 μg/mL) and tigecycline (0.2 ± 0.23 μg/mL). For *K. pneumoniae* and *E. cloacae* without resistance genes, no significant differences were observed in either the resistance rates or the MIC values between tigecycline and eravacycline ($P > 0.05$). In contrast, the MIC values for omadacycline in *Acinetobacter* spp. (13.94 ± 11.43 μg/mL) and *E. cloacae* (5.08 ± 4.98 μg/mL) were significantly higher ($P < 0.05$), indicating reduced efficacy.

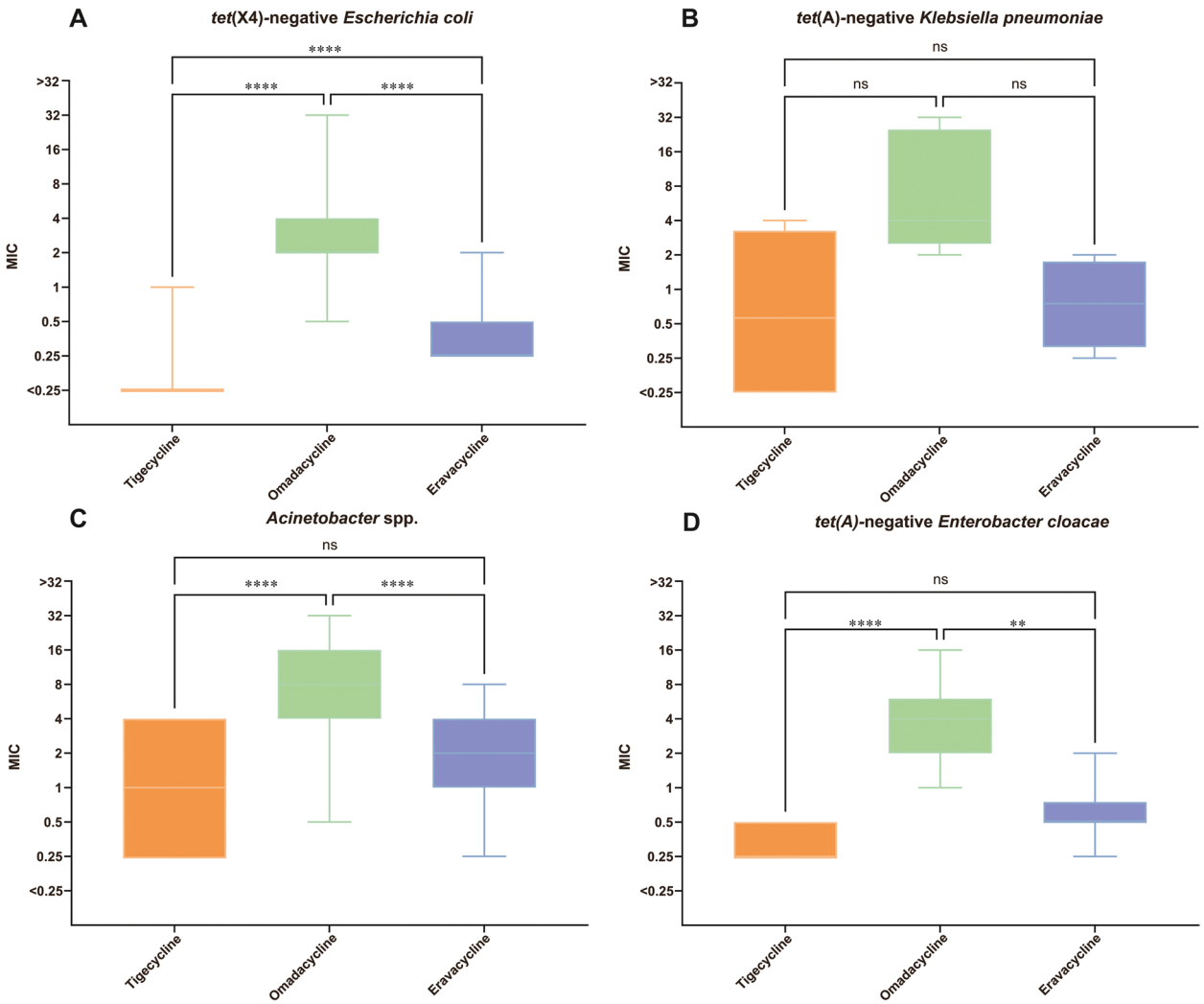

Fig. 2 MIC distribution of tigecycline, omadacycline, and eravacycline in strains carrying no mobile tigecycline resistance genes: **A** *Escherichia coli*, **B** *Klebsiella pneumoniae*, **C** *Acinetobacter* spp., and **D** *Enterobacter cloacae*. Statistical significance was determined using the Kruskal–Wallis test, with statistical significance set at $P < 0.05$. For P values, ns (not significant) indicates $P > 0.05$; **, $P \leq 0.01$; ****, $P \leq 0.0001$

Across all species, omadacycline exhibited significantly higher MIC values than tigecycline and eravacycline ($P < 0.05$), implying reduced in vitro potency. In contrast, the resistance rates among species were comparable across antibiotics ($P = 0.701$ for *E. coli*, $P = 0.428$ for *K. pneumoniae*, and $P = 0.701$ for *E. cloacae*). This finding suggests that resistance rates alone may not fully capture the differences in antibiotic efficacy. While resistance rates provide a population-level perspective on susceptibility, MIC values offer a more precise measure of antibiotic potency, particularly for strains with borderline susceptibility or resistance. The lower MIC values observed for eravacycline suggest that it may require lower doses to achieve therapeutic efficacy than omadacycline, highlighting its potential as a more potent treatment option despite the similar resistance profiles.

While the resistance rates did not significantly differ across antibiotics ($P = 0.500$ for *E. coli*), the MIC values provided important insights into the relative potency of each drug. Eravacycline's lower MIC values in *tet*(X4)-positive *E. coli* suggest a clinical advantage in targeting these resistant strains. While resistance rates provide a useful overview of antibiotic susceptibility in a population, MIC values enable a more granular understanding of the antibiotic's efficacy, particularly in strains with specific resistance genes such as *tet*(X4). For example, eravacycline demonstrated lower MIC values than tigecycline in *E. coli* harboring *tet*(X4), highlighting its potential clinical utility despite the comparable resistance rates.

Discussion

Initially, tetracyclines were widely used in human and animal therapy for their broad-spectrum antimicrobial activity and were recommended as first-line therapeutic options for a variety of indications. However, with the increase in drug resistance, tetracyclines have been continuously updated and optimized. Currently, three third-generation tetracyclines (tigecycline, eravacycline, and omadacycline) have been developed to effectively overcome the most common resistance mechanisms. This study provides a comprehensive analysis of the antimicrobial efficacy of tigecycline, omadacycline, and eravacycline against multidrug-resistant Gram-negative bacteria. While the resistance rates across antibiotics were similar, eravacycline exhibited consistently lower MIC values, particularly in *E. coli* strains harboring *tet*(X4). These findings underscore eravacycline's potential as a potent therapeutic option for treating infections caused by multidrug-resistant bacteria.

In a previous global study, *Enterobacteriaceae* showed a high susceptibility to eravacycline, with rates of 98.8% in *E. coli*, 90.6% in *Klebsiella* spp., 94.6% in *Citrobacter* spp., and 89.6% in *Enterobacter* spp. [28]. Another study from France investigated the in vitro antimicrobial activity of tigecycline, with susceptibility rates of 99.4% for *E. coli* and 87.4% for *K. pneumoniae* [29]. An in vitro antimicrobial activity study suggested that the susceptibility rate to omadacycline was 87.3% for *E. coli* and 61.8% for *K. pneumoniae* at a breakpoint of MIC ≤ 4 μg/mL [30].

The MIC range observed for omadacycline was significantly higher than those for tigecycline and eravacycline, suggesting reduced in vitro potency compared with the potencies of the other two antibiotics. While omadacycline is a fourth-generation tetracycline, these findings align with previous studies, such as a study conducted in Taiwan [31]. In contrast, eravacycline's consistently lower MIC values reinforce its potential as a preferred option for multidrug-resistant infections, particularly in strains carrying resistance genes.

Although the resistance rates between tigecycline and eravacycline were similar, eravacycline's consistently lower MIC values, particularly in *E. coli* strains harboring *tet*(X4), highlight its potential as a more potent therapeutic option. The lower MIC values suggest that eravacycline can achieve bacterial inhibition at lower concentrations, reducing the likelihood of resistance development and minimizing the need for higher dosing. However, the clinical utility of MIC values should be assessed alongside pharmacokinetic and pharmacodynamic data to inform treatment decisions.

Animal studies have demonstrated that eravacycline achieves higher tissue penetration than tigecycline, supporting its potential utility in treating resistant infections [32, 33]. In clinical settings, tigecycline often requires dose doubling to achieve adequate tissue concentrations, particularly in the lungs, which increases the risk of gastrointestinal side effects [34]. In contrast, eravacycline maintains effective concentrations at standard doses with fewer adverse effects. These pharmacokinetic advantages, combined with eravacycline's consistently lower MIC values, suggest its potential as a safer and more effective option for multidrug-resistant infections. Additionally, eravacycline has shown synergistic effects with other antibiotics, making it suitable for managing complex infections commonly encountered in intensive care unit patients [35].

Therefore, the absence of a significant difference in the resistance rates between eravacycline and tigecycline did not diminish the clinical relevance of the MIC values. The lower MIC values for eravacycline suggest that it may be a more potent therapeutic option in certain cases, particularly for *tet*(X4)-positive *E. coli*, in which a lower dose of eravacycline may achieve better outcomes than those with higher doses of tigecycline.

Resistance genes play a critical role in determining antibiotic efficacy. For example, the presence of *tet*(X4) in *E. coli* was associated with high resistance rates to all antibiotics; however, eravacycline consistently maintained lower MIC values than those of tigecycline, suggesting it may partially overcome certain resistance mechanisms. Conversely, in *K. pneumoniae* carrying *tet*(A), eravacycline displayed higher MIC values than those of tigecycline, emphasizing the complexity of gene–drug interactions and the importance of genetic profiling in guiding therapy.

The universal resistance observed in *E. cloacae* carrying *tet*(A) toward all three antibiotics is alarming, highlighting the urgent need for novel antimicrobial strategies. This resistance pattern underscores the broader challenges of antibiotic resistance, which transcends clinical practice and requires a unified approach.

Integrating a One Health perspective, it is evident that the fight against antibiotic resistance requires a unified approach that spans the human, animal, and environmental health sectors [36]. The spread of antibiotic resistance does not recognize the boundaries between these domains, necessitating comprehensive strategies that address antibiotic use and microbial ecosystems as a whole [37]. Collaborative efforts under the One Health umbrella can lead to more sustainable antibiotic use practices and the development of policies that mitigate the risk of resistance spreading across different environments and populations [37, 38].

While the introduction of newer antibiotics such as omadacycline and eravacycline represents a significant investment in combating resistance, their cost-effectiveness depends on clinical efficacy. The distinct efficacy profile of eravacycline, particularly against *tet*(X4)-positive *E. coli*, suggests that it could play a crucial role in managing resistant infections if its cost remains reasonable.

While this study provides valuable insights into the comparative efficacy of eravacycline and tigecycline, several limitations must be acknowledged. First, this study is based on in vitro data, and the results may not fully reflect the in vivo activity of these antibiotics. Additionally, this study focuses on MIC values as an important measure of antibiotic efficacy; however, resistance rates, which provide a population-level perspective, were not thoroughly analyzed in the context of clinical decision-making. MIC values offer strain-specific insights, while resistance rates are critical for understanding broader trends. Future studies should explore the integration of these two metrics to better guide therapeutic decisions.

Conclusion

In conclusion, this study highlights that eravacycline has superior efficacy compared with tigecycline and omadacycline, particularly against *E. coli* strains harboring the *tet*(X4) gene. While the resistance rates were comparable between tigecycline and eravacycline, the consistently lower MIC values for eravacycline underscore its potential as a potent therapeutic option for multidrug-resistant infections. In contrast, omadacycline's higher MIC values suggest limited utility in severe infections caused by resistant pathogens.

These findings emphasize the importance of incorporating MIC data alongside resistance rates to guide clinical decisions. However, the high level of resistance observed in *E. cloacae* carrying *tet*(A) highlights the urgent need for novel therapeutic strategies and ongoing surveillance of resistance patterns.

Future research should validate eravacycline's efficacy in clinical settings and assess its cost-effectiveness to ensure accessible treatment options for managing multidrug-resistant infections.

Materials and methods

Strain collection and tigecycline resistance gene identification

Strains were randomly selected from those retained in the Second Hospital of Zhejiang University School of Medicine between 1999 and 2023. Species identification was performed by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany). Mobile tigecycline resistance genes were identified by PCR targeting *tet*(X4) and *tet*(A), using the following primers: *tet*(X4)-F primer 5'-TGAACCTGGTAAGAAGAAGTG-3', *tet*(X4)-R primer 5'-CAGACAATATCAAAGCATCCA-3'; *tet*(A)-F primer 5'-GTCAGCTACCTTCTCGGCAC-3', *tet*(A)-R primer 5'-GATGATTAACGCACTCGCCG-3'. The PCR products were validated by Sanger sequencing.

Antimicrobial susceptibility testing

The MICs of tigecycline, omadacycline, and eravacycline were determined by the broth microdilution method. The medium used was Mueller–Hinton broth (Hangzhou Binhe Microorganism Reagent Co. Ltd., Hangzhou, China), incubated at 37 °C for 18–24 h. *E. coli* ATCC 25922 was used as the quality control strain. The interpretation breakpoints were based on the European Committee on Antimicrobial Susceptibility Testing (eravacycline and tigecycline) [39] and the U.S. FDA (omadacycline) [40].

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (International Business Machines Corporation, Armonk, New York, USA) with normality and log-normality tests, Mann–Whitney tests, and the Kruskal–Wallis test, and statistical significance was set at $P < 0.05$. GraphPad Prism 9.5 (GraphPad Software, Boston, MA, USA) was used for figure illustration.

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Authors' contributions
Conceptualization, K.L.; methodology, N.D.; data Curation: H.Z.; formal Analysis, J.Z., A.C.; investigation, H.Z.; writing – original draft preparation, J.Z., H.W.; writing – review & editing, J.Z., H.W.; visualization, J.Z., H.W.; supervision, K.L.; project administration, K.L., H.Z. All authors have read and agreed to the final version of the manuscript.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
All samples were obtained from patients as part of routine hospital procedure and were stored. Ethical permission for this study was provided by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine (2023–0611).

Consent for publication
Not applicable.

Competing interests
The author(s) report no conflicts of interest in this work.

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