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Original Article

Comparing the activity of novel antibiotic agents against carbapenem-resistant Enterobacterales clinical isolates

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Abstract

Objective: We compared the activity of 8 novel β-lactam and tetracycline-derivative antibiotics against a cohort of clinical carbapenem-resistant Enterobacterales (CRE) isolates and investigated the incremental susceptibility benefit of the addition of an aminoglycoside, fluoroquinolone, or polymyxin to the β-lactam agents to assist with empiric antibiotic decision making.

Methods: A collection of consecutive CRE clinical isolates from unique patients at 3 US hospitals (2016–2021) was assembled. Broth microdilution was performed to obtain antimicrobial susceptibility testing results. Mechanisms of carbapenem resistance were investigated through short-read and long-read whole-genome sequencing.

Results: Of the 603 CRE isolates, 276 (46%) were carbapenemase producing and 327 (54%) were non–carbapenemase producing, respectively. The organisms most frequently identified were *Klebsiella pneumoniae* (38%), *Enterobacter cloacae* complex (26%), and *Escherichia coli* (16%). We obtained the following percent susceptibility to novel β-lactam agents: ceftazidime-avibactam (95%), meropenem-vaborbactam (92%), imipenem-relebactam (84%), and cefiderocol (92%). Aminoglycosides and the polymyxins provided greater incremental coverage as second agents, compared to fluoroquinolones. Amikacin and plazomicin exhibited the greatest additive value. Ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol were active against 94% of the 220 KPC-producing isolates. Cefiderocol was active against 83% of the 29 NDM-producing isolates. Ceftazidime-avibactam had 100% activity against the 9 OXA-48-like–producing isolates. Tigecycline had the highest activity compared to other tetracyclines against KPC, NDM, or OXA-48-like–producing isolates.

Conclusion: Selection among novel agents requires a nuanced understanding of the molecular epidemiology of CRE. This work provides insights into the comparative activity of novel agents and the additive value of a second antibiotic for empiric antibiotic decision making.

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Within the past decade, 3 novel β-lactam-β-lactamase inhibitor combinations with activity against carbapenem-resistant Enterobacterales (CRE) have received US Food and Drug Administration (FDA) approval: ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam.[1–3] Furthermore, a novel siderophore-cephalosporin conjugate (ie, cefiderocol),[4] aminoglycoside (ie, plazomicin),[5] and tetracycline derivatives (ie, eravacycline and omadacycline)[6,7] have also been introduced into the clinical arena in recent years. Understanding the comparative activity of these novel antibiotics is critical to avoiding unnecessary delays in effective therapy, particularly because CRE tend to infect vulnerable medical populations at high risk of mortality. Moreover, the introduction of rapid molecular diagnostics capable of identifying carbapenemase genes prior to antimicrobial susceptibility testing (AST) results further underscores the importance of understanding the likelihood of each novel agent's activity against specific carbapenemase families.

Comprehensive investigations into the relative activity percentages of various novel agents against CRE are limited. Studies funded by pharmaceutical companies often limit evaluation to novel agents they have developed and marketed, and generally select traditional agents as comparators, rather than other novel ones. We evaluated the activity of 8 novel antibiotics against a cohort of consecutive CRE clinical isolates and investigated the incremental benefit in susceptibility percentage with the addition of a second agent (ie, aminoglycosides, fluoroquinolones, or polymyxins) to novel β-lactam agents to assist with empiric antibiotic decision making.

Methods

Description of isolates

From June 1, 2016, to June 30, 2021, a cohort of consecutive CRE clinical isolates was assembled. CRE were defined as isolates

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(1) exhibiting resistance to at least 1 carbapenem agent or (2) carrying at least 1 carbapenemase gene.[8] CRE isolates were obtained from clinical specimens collected from patients receiving medical care at The Johns Hopkins Hospital, Bayview Medical Center, and Howard County General Hospital, all located in Maryland. Only the first isolate was included for patients who had multiple cultures growing the same species (eg, carbapenem-resistant *Escherichia coli* recovered in multiple specimens from the same patient). However, if different carbapenem-resistant species were recovered from the same patient (eg, *E. coli* and *Klebsiella pneumoniae*), the first isolate of each species was included.

Bacterial genus and species were identified using matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Billerica, MA). Antimicrobial susceptibility testing (AST) results were determined using the BD Phoenix Automated System (BD Diagnostics, Sparks, MD) and interpreted following Clinical Laboratory and Standards Institute (CLSI) guidelines.[9] All CRE isolates were stored at −80°C in glycerol until further testing was performed.

Antimicrobial susceptibility testing

Frozen isolates were subcultured twice to tryptic soy agar with 5% sheep blood. AST was performed using lyophilized Sensititer broth microdilution (BMD) GN7F and MDRGNX2F panels (Thermo Fisher Scientific, Waltham, MA). For all AST studies, quality control organisms were prepared each day of testing, as recommended by the manufacturer. Susceptibility criteria were interpreted using CLSI or FDA criteria, if CLSI criteria were not available. The following susceptibility criteria were applied to the results: ceftazidime-avibactam, ≤8/4 μg/mL (CLSI); meropenem-vaborbactam, ≤4/8 μg/mL (CLSI); imipenem-relebactam, ≤1/4 μg/mL (FDA); cefiderocol, ≤4 μg/mL (CLSI); tigecycline, ≤2 μg/mL (FDA); minocycline, ≤4 μg/mL (CLSI); eravacycline, ≤0.5 μg/mL (FDA); omadacycline, ≤4 μg/mL (FDA); gentamicin, ≤4 μg/mL (CLSI); tobramycin, ≤4 μg/mL (CLSI); amikacin, ≤16 μg/mL (CLSI); plazomicin, ≤2 μg/mL (FDA); ciprofloxacin, ≤0.25 μg/mL (CLSI); levofloxacin, ≤0.5 μg/mL (CLSI); and colistin intermediate, ≤2 μg/mL (CLSI).[9,10]

Whole-genome sequencing

CRE isolates underwent whole-genome sequencing (WGS) using short-read Illumina sequencing (MiSeq or HiSeq). Carbapenemase-producing CRE (CP-CRE) underwent additional sequencing using long-read nanopore sequencing. Genomic DNA was extracted from pure cultures using the DNeasy PowerSoil Pro Kit (Qiagen, Hilden, Germany). WGS and analyses were performed as previously described.[11] Assemblies were deposited to the National Institutes of Health Sequence Read Archive (PRJNA496461 and PRJNA686978).

Statistical analysis

The χ^2 test was used to evaluate differences between susceptibility proportions across drug–organism combinations for each of the 4 novel β-lactams and 4 tetracycline derivatives, followed by post-hoc tests of pairwise comparisons between agents. Bonferroni corrections of *P* values were applied for the 4 β-lactams (group 1) and for the 4 tetracycline-derivatives (group 2), separately. The χ^2 test was also used to compare susceptibilities between CP-CRE and non–carbapenemase-producing CRE (non-CP-CRE). Statistical analyses were performed using R version 4.1.1 software (R Foundation for Statistical Learning, Vienna, Austria).

Results

Overall results

In total, 603 consecutive CRE clinical isolates collected from sterile sources were identified. Isolates were collected from the following specimen sources: urine (n = 189), respiratory (n = 133), intra-abdominal fluid (n = 132), blood (n = 88), skin and soft tissue (n = 40), osteoarticular (n = 16), and biliary (n = 5). Table 1 lists the species recovered and the percent susceptibility to 8 last-resort antibiotic agents. The most frequently identified organisms were *Klebsiella pneumoniae* (n = 229, 38%), *Enterobacter cloacae* complex (n = 158, 26%), and *Escherichia coli* (n = 95, 16%). No association between year of isolate and susceptibility percentages were observed for any of the 8 antibiotic agents.

Susceptibility to the novel β-lactam agents across the 603 CRE clinical isolates was as follows: ceftazidime-avibactam (95%), meropenem-vaborbactam (92%), imipenem-relebactam (84%), and cefiderocol (92%). Of note, as imipenem-relebactam susceptibility criteria do not apply to *Morganella* spp., *Proteus* spp., and *Providencia* spp. these organisms were not included in the imipenem-relebactam analysis. Pairwise comparisons indicated significant differences in overall susceptibilities between other novel β-lactam agents and imipenem-relebactam ($P < .002$).

The following susceptibility percentages to tetracycline derivatives were obtained: tigecycline (94%), minocycline (56%), eravacycline (74%), and omadacycline (69%). Pairwise comparisons indicated that there were significant differences in overall susceptibilities between tigecycline and all other agents ($P < .001$) as well as between all other agents and minocycline ($P < .001$).

CP-CRE and non–CP-CRE

Of the 603 CRE isolates, 276 (46%) and 327 (54%) were CP-CRE and non–CP-CRE, respectively. Of the 327 non–CP-CRE isolates, the most common identified resistance mechanisms included the presence of extended-spectrum β-lactamase (ESBL) genes and/or *ampC* genes in conjunction with porin mutations or loss (eg, *ompK35* and *ompK36*), which were identified in 249 (76%) of non–CP-CRE isolates.

Table 1 describes the species recovered categorized by the presence of carbapenemase production and the percent susceptibility to 8 last-resort antibiotic agents. No significant differences were detected between susceptibilities in CP-CRE and non–CP-CRE across any of the 8 β-lactam or tetracycline-derivative antibiotics.

Activity against specific carbapenemase genes

Table 2 lists the susceptibility of the 8 β-lactam and tetracycline antibiotics against specific carbapenemases. Of β-lactam agents, ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol had activity against KPC-producing isolates, all exhibiting 94% activity against the 220 KPC-producing CRE isolates (excluding those that contained additional carbapenemase genes). Imipenem-relebactam was active against 88% of the KPC-producing isolates. Cefiderocol was active against 83% of the 29 NDM-producing isolates. Ceftazidime-avibactam had 100% activity against the 9 isolates producing OXA-48–like carbapenemases. Tigecycline had the highest activity among the tetracycline-derivates against isolates producing KPC, NDM, or OXA-48–like enzymes. Isolates

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Table 1. Activity of 8 Last-Resort Antibiotics Against 603 Consecutive Carbapenem-Resistant Enterobacterales (CRE) Clinical Isolates Obtained From Unique Patients

Organism	Isolates Tested. No.	% Susceptible							
		Ceftazidime-Avibactam	Meropenem-Vaborbactam	Imipenem-Relebactam	Cefiderocol	Tigecycline	Minocycline	Eravacycline	Omadacycline
All CRE									
Citrobacter amalonaticus	1	0	0	100	100	100	0	100	100
C. freundii complex	26	96	96	77	89	100	62	73	69
C. koseri	1	100	100	100	100	100	100	0	0
Enterobacter cloacae complex	158	96	96	88	91	92	56	75	72
Escherichia coli	95	94	88	84	86	85	65	78	73
Hafnei alvei	7	86	57	86	100	100	43	86	57
Klebsiella aerogenes	30	90	90	83	97	100	53	77	77
K. oxytoca	23	83	87	87	91	100	61	87	78
K. pneumoniae	229	97	93	87	93	97	53	69	64
Morganella morganii	3	100	100	. . .	100	100	0	33	67
Pantoea agglomerans	2	100	100	100	100	100	50	50	50
Proteus mirabilis	6	100	100	. . .	83	100	50	83	100
P. vulgaris	2	100	100	. . .	100	100	50	50	50
Providencia spp	3	100	100	. . .	100	100	100	67	100
Serratia marcescens	17	88	77	65	100	77	59	100	65
Overall	603	95	92	84	92	94	56	74	69
Carbapenemase-producing CRE (CP-CRE)									
Citrobacter amalonaticus	1	0	0	100	100	100	0	100	100
C. freundii	18	100	100	89	89	100	56	72	72
Enterobacter cloacae complex	46	87	91	87	86	87	57	73	71
Escherichia coli	36	94	83	81	86	89	56	67	61
Klebsiella aerogenes	4	50	50	50	75	100	75	100	100
K. oxytoca	18	83	89	83	100	100	56	83	78
K. pneumoniae	140	96	92	88	94	99	53	69	62
Pantoea agglomerans	1	100	100	100	100	100	100	100	100
Proteus vulgaris	1	100	100	. . .	100	100	0	0	0
Providencia spp	2	100	100	. . .	100	100	100	50	100
Serratia marcescens	9	89	67	67	100	78	56	78	67
Overall CP-CRE	276	93	89	85	92	96	55	71	66
Non–carbapenemase-producing CRE (Non-CP-CRE)									
Citrobacter freundii	8	88	88	50	88	100	75	75	63
C. koseri	1	100	100	100	100	100	100	0	0
Enterobacter cloacae complex	112	98	97	88	92	93	56	76	73
Escherichia coli	59	93	92	87	86	83	71	85	80
Hafnei alvei	7	86	57	86	100	100	43	86	57
Klebsiella aerogenes	26	96	96	89	100	100	50	73	73
K. oxytoca	5	80	80	100	60	100	80	100	80
K. pneumoniae	89	98	94	87	91	94	52	69	66
Morganella morganii	3	100	100	. . .	100	100	0	33	67
Pantoea agglomerans	1	100	100	100	100	100	0	0	0

(*Continued*)

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Table 1. (*Continued*)

Organism	Isolates Tested. No.	% Susceptible							
		Ceftazidime-Avibactam	Meropenem-Vaborbactam	Imipenem-Relebactam	Cefiderocol	Tigecycline	Minocycline	Eravacycline	Omadacycline
Proteus mirabilis	6	100	100	. . .	83	100	0.5	83	100
P. vulgaris	1	100	100	. . .	100	100	100	100	100
Providencia species	1	100	100	. . .	100	100	100	100	100
Serratia marcescens	8	88	88	63	100	75	63	50	63
Overall Non–CP-CRE	327	96	94	83	91	92	57	75	72

Table 2. Activity of 8 Last-Resort Antibiotics Against 276 Consecutive Carbapenemase-Producing Enterobacterales Clinical Isolates Obtained From Unique Patients

Carbapenemase Gene (No. of Isolates)	Organisms Involved, Species (No.)	% Susceptible							
		Ceftazidime-Avibactam	Meropenem-Vaborbactam	Imipenem-Relebactam	Cefiderocol	Tigecycline	Minocycline	Eravacycline	Omadacycline
bla_{KPC} alone (220)	*C. amalonaticus* (1), *C. freundii* (17), *E. cloacae* complex (38), *E. coli* (15), *K. aerogenes* (3), *K. oxytoca* (17), *K. pneumoniae* (122), *P. agglomerans* (1), *P. vulgaris* (1), *S. marcescens* (5)	94	94	88	94	96	54	70	65
bla_{NDM} alone (29)	*C. freundii* (1), *E. cloacae* complex (6), *E. coli* (13), *K. oxytoca* (1), *K. pneumoniae* (7), *P. stuartii* (1)	. . .	. . .	. . .	83	90	62	83	76
$bla_{OXA-48-like}$ alone (9)	*E. coli* (5), *K. pneumoniae* (4)	100	. . .	. . .	78	100	44	67	44
bla_{SME} alone (4)	*S. marcescens* (4)	100	100	25	100	75	75	75	75
bla_{KPC} & bla_{NDM} (2)	*E. coli* (1), *K. pneumoniae* (1)	. . .	. . .	. . .	0	100	0	0	0
bla_{KPC} & $bla_{OXA-48-like}$ (2)	*K. pneumoniae* (2)	50	. . .	. . .	0	50	0	0	0
bla_{NDM} & $bla_{OXA-48-like}$ (9)	*E. coli* (2), *K. aerogenes* (1), *K. pneumoniae* (5), *P. rettgeri* (1)	. . .	. . .	. . .	100	100	63	63	75
bla_{KPC}, bla_{NDM} & $bla_{OXA-48-like}$ (1)	*K. pneumoniae* (1)	. . .	. . .	. . .	100	100	100	100	100

producing >1 carbapenemase enzyme generally had reduced activity to both β-lactam and tetracycline-derivative agents.

Additive value of combination therapy

The incremental benefit of agents frequently combined as components of combination therapy (ie, aminoglycosides, fluoroquinolones, or polymyxins) when added to a novel β-lactam agent was investigated (Fig. 1). The calculations displayed in Figure 1 reflect isolates with in vitro susceptibility to either the β-lactam or the additive agent. Organisms known to be intrinsically resistant to the polymyxins were removed from the analysis, including *Morganella* spp, *Proteus* spp, *Providencia* spp, and *Serratia* spp. Generally, aminoglycosides and polymyxins provided greater incremental benefit as second agents compared to the fluoroquinolones. The percentages of susceptibility to ciprofloxacin and levofloxacin were identical, and neither agent provided substantial additive value to any of the β-lactam agents. Of aminoglycosides, plazomicin, and amikacin provided the greatest additive value, providing nearly identical incremental benefits ranging from an additional 4%–11% compared to β-lactam therapy alone (all *P* values <.001). The β-lactam that benefitted the most from the addition of a second agent was imipenem-relebactam.

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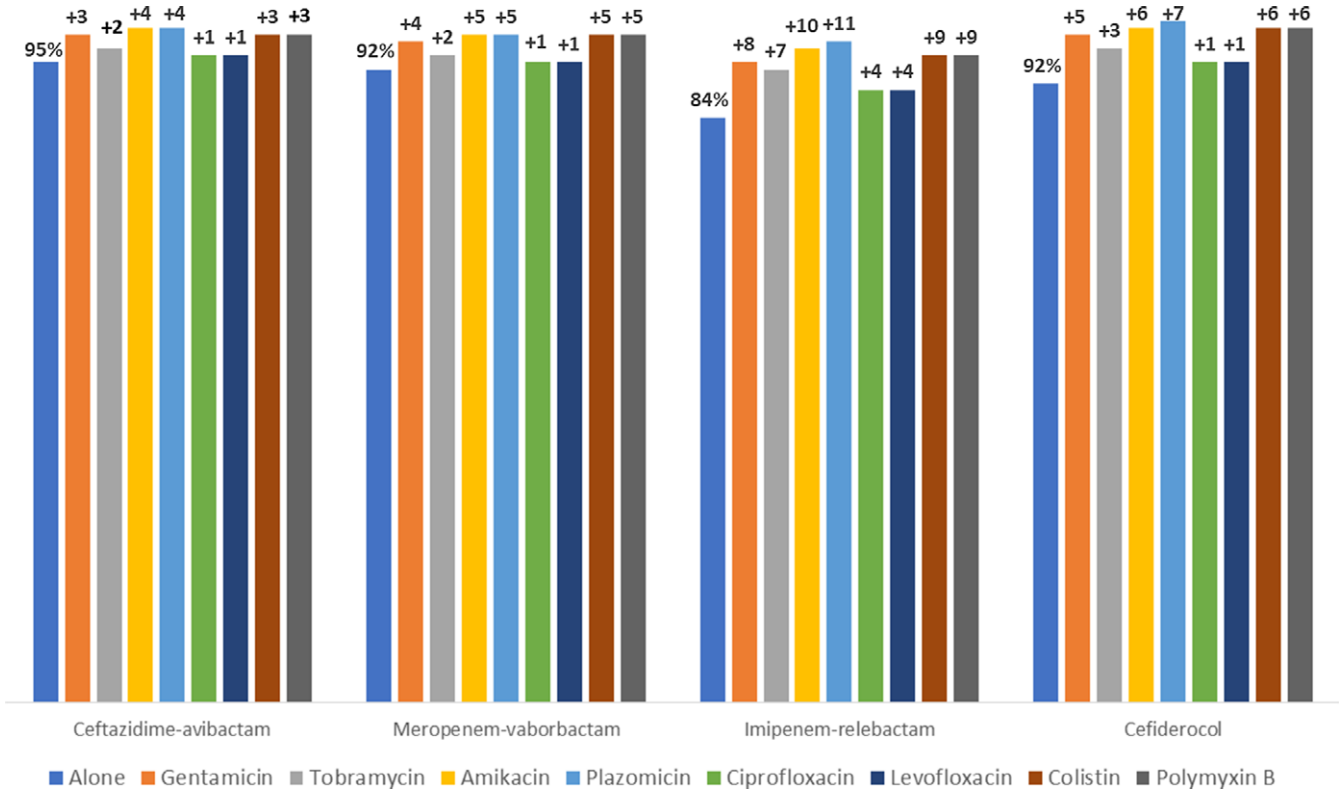

Fig. 1. Additional percentage coverage provided by novel β-lactam agents in combination with aminoglycosides, fluoroquinolones, or polymyxins, compared to novel β-lactam monotherapy.

Discussion

Evaluating a cohort of 603 consecutive clinical CRE isolates, ceftazidime-avibactam and tigecycline were the β-lactam and tetracycline-derivatives, respectively, with the highest likelihood of activity, regardless of whether organisms were carbapenemase producing or not. When specific carbapenemase genes were identified, the following β-lactams had the highest activity: KPC-producing (ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol at 94%), NDM-producing (cefiderocol, 83%), and OXA-48-like–producing (ceftazidime-avibactam, 100%). These findings underscore the important role of carbapenemase gene identification in guiding antibiotic decision making.[12]

Moreover, we investigated the incremental benefit of adding an aminoglycoside, fluoroquinolone, or polymyxin to each of the novel β-lactams to determine whether they substantively increased the likelihood of activity against CRE isolates for empiric antibiotic decision making. Clinical trial data comparing the outcomes of patients with CRE infections treated with combination therapy (eg, ceftazidime-avibactam and amikacin) versus β-lactam monotherapy (eg, ceftazidime-avibactam) are not available. An observational study comparing the outcomes of 577 patients receiving ceftazidime-avibactam or ceftazidime-avibactam plus a second agent for the treatment of KPC-producing infections did not identify a mortality benefit with this approach.[13] However, for ill-appearing patients known to be colonized with CRE or in regions of high CRE endemicity, the addition of a second agent to a novel β-lactam may still have a role to increase the likelihood that at least 1 active antibiotic agent is being administered while awaiting AST results. In our cohort, while the addition of a fluoroquinolone to a novel β-lactam was generally of limited additive value, the addition of an aminoglycoside to a β-lactam, particularly amikacin or plazomicin, increased the likelihood of activity across all β-lactams.

Our study had several limitations. Our cohort consisted of isolates from patients in the mid-Atlantic United States and may not be reflective of other regions of the United States or other regions of the world. Region-specific antibiograms are necessary to understand local susceptibility data. Moreover, for regions with a high prevalence of CRE clinical isolates, the development of regional combination antibiograms specific for CRE organisms can provide data on the combinations of antibiotics associated with the highest likelihood of adequate coverage when novel agents need to be administered on an empiric basis.[14–16]

We included the first CRE species isolated from unique patients. Therefore, our results do not reflect the potential emergence of resistance in subsequent isolates after exposure to novel agents. As an example, >90% of all KPC-producing isolates were susceptible to ceftazidime-avibactam and meropenem-vaborbactam. Estimates of the emergence of resistance after clinical exposure of CRE isolates to ceftazidime-avibactam and meropenem-vaborbactam have been described to be ~20%[13,17–21] and 5%,[21–23] respectively. With the inclusion of subsequent isolates, susceptibility percentages would likely be lowered, particularly to ceftazidime-avibactam, in which acquired resistance due to amino acid substitutions in the KPC carbapenemase are not rare events.[24] Notably, Sensititer MDRGNX2F panels were used to generate cefiderocol MICs for the current study. In early 2022, an investigation from the manufacturer found that these panels may produce lower cefiderocol MICs compared to reference BMD for *E. coli* and *Klebsiella* isolates.

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Importantly, in vitro susceptibility does not necessarily translate into improved clinical outcomes. Factors such as adequate and sustained antibiotic penetration to the site of infection and drug-specific toxicities need to be considered when selecting amongst antibiotics. For example, colistin enhanced CRE coverage by 4%–9% across novel β-lactam agents in our cohort. However, colistin is administered as a prodrug, leading to unreliable plasma concentrations.[25] Additionally, its associated nephrotoxicity often precludes its use for patients with existing renal disease.[26] As a second example, although tigecycline exhibited 94% activity against CRE isolates, tetracycline-derivatives achieve rapid tissue distribution following administration, resulting in limited concentrations in urine and poor serum concentrations,[27] limiting their effectiveness for certain sites of infection.

In conclusion, selecting among novel agents can be challenging because it requires a nuanced understanding of the molecular epidemiology of gram-negative resistance mechanisms. This research provides insights into the comparative activity of novel β-lactam and tetracycline-derivate agents against CRE isolates and the additive value of a second agent as empiric therapy. However, *in vitro* activity is just one component of the complex decision-making process of selecting the most effective antibiotic or combination of antibiotic agents.

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