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Ertapenem (MK-0826) Potency and Spectrum Tested Alone and in Combinations Against 902 Drug-Resistant Isolates

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ABSTRACT

Background: Emerging resistances, especially directed against β-lactams limit continued use of newer cephalosporins and penicillins ± enzyme inhibitors. Carbapenems have remained wider in spectrum, but compromised by PK/PD characteristics. Ertapenem (ETP) offers long-acting PK features and was tested here against a world-wide challenge of resistant (R) isolates.

Methods: NCCLS reference MIC tests were used to compare ETP, imipenem (IMP), meropenem (MER), ceftazidime (CAZ) and ≥7 other drugs. Strains (902) were selected for R to CAZ (ESBLs [93], amp C [93]); IMP and MER; penicillins (drug-R pneumococci) and glycopeptides (VRE). Synergy was assessed by checkerboard and kill curves.

Results: ETP was active against a variety of Gram-negative (G-) pathogens, with high potency versus *E. coli* and *K. pneumoniae* (MIC_{90}s, ≤0.015-0.5 µg/ml) including ESBL-producing strains. ETP MIC results for ESBL strains were modestly elevated compared to wild-types of the same species. Less ETP activity was noted for *P. aeruginosa*, especially CAZ-R strains (MIC_{50}, 16 µg/ml). Except for enterococci (MIC_{90}, >32 µg/ml) and OXA-R staphylococci, ETP was active against G+ species, including β-haemolytic streptococci (MIC_{90}, 0.03 µg/ml; 100% susceptible [S]), viridans gr. streptococci (MIC_{90}, 2 µg/ml; 98.1% S), and pen-S *S. pneumoniae* (MIC_{90}, ≤0.015 µg/ml; 100% S). ETP was also potent against *H. influenzae* (MIC_{90}, 0.25 µg/ml; 100% S). Bactericidal action was observed versus G+ species and enteric bacilli, and at least an additive effect was seen against the majority of strains when combined with ciprofloxacin or gentamicin.

Conclusions: These results from testing 902 recently isolated clinical R strains indicate that ETP, like IPM and MER appears to be a promising broad-spectrum carbapenem with an expanding role against emerging R species. Carbapenem spectrum rank was: MER > IMP > ETP, and all were wider than CAZ.

INTRODUCTION

Considered one of the most potent classes of antimicrobial agents, carbapenems (imipenem, meropenem) are usually reserved for the treatment of serious infections, or multiply-resistant pathogens. Carbapenems display a remarkably broad-spectrum of activity against Gram-negative, Gram-positive, and anaerobic species. Further, these β-lactams typically are stable against hydrolysis by most chromosomal- and plasmid-mediated β-lactamases, including the evolving extended spectrum β-lactamases (ESBL).

Ertapenem (MK-0826) is a novel, long-acting parenteral 1-β-methyl carbapenem. This agent was selected for clinical development partially based on its favorable pharmacokinetics. *In vivo* studies have shown that ertapenem's serum half-life (3.2 hours) and ability to persist in the circulation support the possibility a once-daily dosing. The purpose of this study was to examine the antimicrobial activity of ertapenem tested against a collection of multiply -resistant strains of Gram-positive and -negative bacteria from diverse locations worldwide identified through numerous surveillance studies. In addition, this study examined the bactericidal activity of ertapenem against selected organisms and explored the potential for antimicrobial synergy with ertapenem when combined with a fluoroquinolone (ciprofloxacin) or an aminoglycoside (gentamicin).

MATERIALS AND METHODS

Antimicrobial susceptibility testing was performed using the broth microdilution method as described by the National Committee for Clinical Laboratory Standards (NCCLS). Isolates with increased MICs (≥2 µg/mL) for ceftazidime and/or ceftriaxone (cefotaxime) and/or aztreonam were characterized for the production of extended spectrum β-lactamases (ESBL) and genotyped. The ESBL production was determined based on the susceptibility to ceftazidime, cefuroxime, cefotaxime, ceftriaxone, and cefepime, with and without clavulanic acid using Etest® (AB BIODISK, Solna, Sweden) strips. A reduction of β-lactam MIC in the presence of clavulanate by >2 $\log_2$ dilutions indicated probable ESBL production.

The studies of the ESBL-producing enteric bacilli by isoelectric focusing were performed using crude β-lactamase extracts prepared by freeze-thaw lysis of bacterial cultures grown in tryptic soy broth.

Synergy using the broth microdilution checkerboard method was performed against *Staphylococcus aureus* (10 strains), CoNS (10 strains), *Escherichia coli* (10 strains, with 5 producing ESBL), and *Klebsiella pneumoniae* (10 strains, with 5 producing ESBL) isolates. Synergy was defined as a four-fold or more decrease in the MIC of both drugs; partial synergy was a four-fold or more decrease in the MIC of one drug and a two-fold decrease in the other; and additive was a two-fold decrease in the MIC of both drugs. Indifference was defined as no significant change in the MIC of either drug; antagonism as an increase of four-fold in the MIC of both drugs; and indeterminate as MICs above the dilution schedules used in the tests with one or both drugs having MIC results indicating that even after combining drugs, there would be no clinical utility as a co-drug. Bactericidal testing was performed as described in the NCCLS document.

The 902 strains were selected from the collection at the University of Iowa College of Medicine (Iowa City, IA), many derived from national and international surveillance programs. The selection criteria were designed to severely challenge ertapenem with strains observed to be resistant to other parenteral β-lactams and also sample species likely to be treated by carbapenems.

All strains were examined to minimize duplication from clonal dissemination within surveillance samples by: 1) antibiogram analysis; 2) PFGE testing; and 3) automated ribotyping. The strains used for the bactericidal assays and synergy studies were chosen from the strains listed in Tables 1, and are described in the footnotes to Tables 4 and 5.

RESULTS

- Ertapenem was active against *E. coli* (MIC_{90}, ≤0.015-0.5 µg/mL) and *K. pneumoniae* (MIC_{90}, ≤0.015-0.5 µg/mL), but demonstrated more elevated MICs when tested against some ESBL-producing isolates. However, all ertapenem MICs were ≤1 µg/mL for *E. coli* and ≤4 µg/mL for 96.7% of ESBL-producing K. pneumoniae (Table 2).
- All but three *Enterobacter* spp or *Citrobacter* spp.(93 of 113 strains resistant to ceftazidime) were susceptible to ertapenem (MIC_{90}, ≤4 µg/mL). MIC_{90}s of 0.12 and 1 µg/mL for ertapenem were observed for the ceftazidime-susceptible and ceftazidime-resistant strains, respectively.
- Ertapenem was marginally active (MIC_{50}, 4 µg/mL) versus ceftazidime-susceptible *P. aeruginosa*, but relatively inactive against ceftazidime-resistant strains (only 14.3% susceptible at ≤4 µg/mL).
- Ertapenem also was active against *H. influenzae* (MIC_{90}, 0.06 µg/mL), with a potency 32-fold greater than that of cefuroxime.
- Although ertapenem was not active against the enterococci (MIC_{90}, >32 µg/mL), it was very potent versus other Gram-positive cocci (Table 3), especially β-haemolytic streptococci (MIC_{90}, 0.03 µg/mL; 100.0% susceptible), and other penicillin-susceptible streptococci. Ertapenem was also very potent against a variety of *S. pneumoniae* isolates, including penicillin-susceptible (MIC_{90}, ≤0.015 µg/mL; 100.0% susceptible) and penicillin-intermediate (MIC_{90}, 0.5 µg/mL; 77.1% susceptible) strains. Penicillin-resistant (MIC_{90}, 2 µg/mL; 5.7% susceptible at ≤0.25 µg/mL - the criteria used for meropenem) *S. pneumoniae* and viridans group streptococci (MIC_{90}, 2 µg/ml) were less susceptible to ertapenem.
- Oxacillin-susceptible staphylococci were ertapenem-susceptible with all MICs ≤0.5 µg/mL, as were *Bacillus* spp. (MICs ≤1 µg/mL). Corynebacteria, however, were less inhibited by ertapenem.
- Ertapenem generally demonstrated bactericidal action versus staphylococci, *E. coli*, and *K. pneumoniae* (Table 4).
- Synergy analyses revealed enhanced inhibition with partial synergy or additive effects for the majority of strains tested when ertapenem was combined with ciprofloxacin or gentamicin (Table 5). Indifference was more common among the ertapenem-gentamicin combinations, but no antagonism was observed in the 80 tests conducted.

Table 1.

Strains tested in each study phase (902 total organisms).

Pathogens	No. Strains/Characteristics
E. coli	79 strains; 32 with ESBL phenotypes
K. pneumoniae	99 strains; 61 with ESBL phenotypes
C. freundii and *Enterobacter* spp.	113 strains; 93 with ceftazidime resistance
P. aeruginosa	39 strains; 14 resistant to ceftazidime
H. influenzae	97 strains; 39 having a β-lactamase or ampicillin resistance
Enterococci	56 strains; 28 vancomycin-resistant
β-haemolytic streptococci	99 strains; 5 serogroups
Viridans group streptococci	108 strains; ≥10 species
S. pneumoniae	114 strains; 44 penicillin-susceptible
Coagulase-negative staphylococci	16 strains; all oxacillin-susceptible
S. aureus	51 strains; all oxacillin-susceptible
Bacillus spp.	12 strains
Corynebacterium jeikeium	8 strains
Corynebacterium spp.	11 strains

Table 2.

Comparative antimicrobial activity of ertapenem tested against 427 strains of Gram-negative organisms including strains resistant to other β-lactams.

Organism/resistance Phenotype (no. tested)	Antimicrobial Agent	MIC (µg/mL) 50%	90%	Range	% Susceptible[a]
E. coli Wild-type (47)	Ertapenem	≤0.015	≤0.015	≤0.015-0.06	100.0
	Imipenem	0.12	0.25	≤0.06-1	100.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25-1	100.0
	Ceftazidime	0.25	0.25	≤0.12-1	100.0
	Cefepime	≤0.12	≤0.12	≤0.12-2	100.0
	Ciprofloxacin	≤0.25	>2	≤0.25->2	85.1
	Gentamicin	≤1	2	≤1->8	93.6
	Tobramycin	0.5	2	0.25-16	93.6
	Ampicillin	4	>16	1->16	53.2
	Piperacillin/Tazobactam	2	16	0.5->128	91.5
	Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	72.3
ESBLs (32)[a]	Ertapenem	0.06	0.5	≤0.015-1	100.0
	Imipenem	0.12	0.5	≤0.06-0.5	100.0
	Meropenem	≤0.06	0.12	≤0.06-0.12	100.0
	Ceftriaxone	>32	>32	2->32	12.5
	Ceftazidime	16	>16	1->16	46.9
	Cefepime	16	>16	0.25->16	40.6
	Ciprofloxacin	≤0.25	>2	≤0.25->2	50.0
	Gentamicin	>8	>8	≤1->8	31.3
	Tobramycin	>16	>16	0.5->16	25.0
	Ampicillin	>16	>16	>16	0.0
	Piperacillin/Tazobactam	128	>128	1->128	34.4
	Trimethoprim/Sulfamethoxazole	>2	>2	≤0.5->2	31.3
K. pneumoniae Wild-type (38)	Ertapenem	≤0.015	≤0.015	≤0.015-0.5	100.0
	Imipenem	0.12	0.25	≤0.06-0.5	100.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0
	Ceftazidime	≤0.12	0.5	≤0.12-1	100.0
	Cefepime	≤0.12	≤0.12	≤0.12-0.25	100.0
	Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	97.4
	Gentamicin	≤1	≤1	≤1->8	92.1
	Tobramycin	0.5	1	0.25->16	92.1
	Ampicillin	>16	>16	4->16	13.2
	Piperacillin/Tazobactam	4	16	0.12-128	94.7
	Trimethoprim/Sulfamethoxazole	≤0.5	>1	≤0.5->1	89.5
ESBLs (61)[a]	Ertapenem	0.06	0.5	≤0.015-16	96.7
	Imipenem	0.25	0.5	≤0.06-2	100.0
	Meropenem	≤0.06	0.12	≤0.06-2	100.0
	Ceftriaxone	>32	>32	≤0.25->32	18.0
	Ceftazidime	>16	>16	2->16	21.3
	Cefepime	8	>16	0.25->16	57.4
	Ciprofloxacin	≤0.25	>2	≤0.25->2	80.3
	Gentamicin	>8	>8	≤1->8	29.5
	Tobramycin	>16	>16	0.25->16	16.4
	Ampicillin	>16	>16	>16	0.0
	Piperacillin/Tazobactam	>128	>128	4->128	19.7
	Trimethoprim/Sulfamethoxazole	2	>2	≤0.5->2	60.7
Amp C species Wild-type (20)[b]	Ertapenem	≤0.015	0.12	≤0.015-8	95.0
	Imipenem	0.5	1	0.12-2	100.0
	Meropenem	≤0.06	≤0.06	≤0.06-2	100.0
	Ceftriaxone	≤0.25	16	≤0.25->32	80.0
	Ceftazidime	0.25	8	≤0.12-8	100.0
	Cefepime	≤0.12	2	≤0.12->16	95.0
	Ciprofloxacin	≤0.25	0.5	≤0.25->2	90.0
	Gentamicin	≤1	>8	≤1->8	85.0
	Tobramycin	0.5	16	0.25->16	75.0
	Amikacin	1	32	1->32	85.0
	Ampicillin	>16	>16	8->16	10.0
	Piperacillin/Tazobactam	2	>128	1->128	75.0
	Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	80.0
SD Amp C (93)[b]	Ertapenem	0.25	1	≤0.015-32	97.8
	Imipenem	0.5	1	0.12-8	98.9
	Meropenem	≤0.06	0.25	≤0.6-4	100.0
	Ceftriaxone	32	>32	4->32	16.1
	Ceftazidime	>16	>16	16->16	0.0
	Cefepime	2	8	≤0.12->16	90.3
	Ciprofloxacin	≤0.25	>2	≤0.25->2	66.7
	Gentamicin	≤1	>8	≤1->8	72.0
	Tobramycin	1	>16	0.25->16	58.1
	Amikacin	2	16	0.5->32	90.3
	Ampicillin	>16	>16	>16	0.0
	Piperacillin/Tazobactam	128	>128	0.5->128	14.0
	Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	58.1
P. aeruginosa Ceftazidime-susc (25)	Ertapenem	4	>32	0.5->32	60.0
	Imipenem	1	8	0.5->8	76.0
	Meropenem	0.5	8	≤0.06->8	88.0
	Ceftriaxone	>32	>32	8->32	4.0
	Cefepime	2	8	1-16	92.0
	Ciprofloxacin	≤0.25	>2	≤0.25->2	72.0
	Gentamicin	2	>8	≤1->8	80.0
	Tobramycin	0.5	>16	≤0.12->16	84.0
	Ampicillin	>16	>16	>16	0.0
	Piperacillin/Tazobactam	4	32	0.5-128	96.0
	Trimethoprim/Sulfamethoxazole	>1	>1	≤0.5->1	4.0
Ceftazidime-resist. (14)	Ertapenem	16	>32	4->32	14.3
	Imipenem	>8	>8	0.5->8	42.9
	Meropenem	4	>8	0.25->8	50.0
	Ceftriaxone	>32	>32	>32	0.0
	Cefepime	>16	>16	8->16	14.3
	Ciprofloxacin	>2	>2	≤0.25->2	35.7
	Gentamicin	>8	>8	≤1->8	35.7
	Tobramycin	2	>16	0.5->16	57.1
	Ampicillin	>16	>16	>16	0.0
	Piperacillin/Tazobactam	64	>128	2->128	50.0
	Trimethoprim/Sulfamethoxazole	>1	>1	1->1	0.0
H. influenzae (97)[c]	Ertapenem	≤0.015	0.06	≤0.015-0.25	100.0
	Cefuroxime	1	2	0.12-4	92.8
	Ceftriaxone	≤0.008	≤0.008	≤0.008-0.015	100.0
	Ceftazidime	≤0.25	≤0.25	≤0.25	100.0
	Cefepime	≤0.06	0.12	≤0.06-0.25	100.0
	Ampicillin	≤0.5	>4	≤0.5->4	60.8
	Piperacillin/Tazobactam	≤0.06	≤0.06	≤0.06-0.25	100.0
	Azithromycin	1	2	≤0.12-4	100.0
	Ciprofloxacin	≤0.015	≤0.015	≤0.015	100.0
	Levofloxacin	≤0.03	≤0.03	≤0.03	100.0
	Chloramphenicol	≤2	≤2	≤2	100.0
	Tetracycline	≤2	≤2	≤2->16	97.9
	Trimethoprim/Sulfamethoxazole	≤0.5	>4	≤0.5->4	79.4

a. Breakpoints for susceptibility as defined by the NCCLS [2000] or as follows: ertapenem-susceptible at ≤4 µg/mL and ESBL-positive strains at ≥2 µg/mL for ceftazidime or ceftriaxone or aztreonam.
b. Wild-type = susceptible to ceftazidime and many other "third-generation" cephalosporins; and SD Amp C = stably derepressed expression of Amp C cephalosporinase (ceftazidime-resistant; MIC at ≥16 µg/mL). Includes: *C. freundii* (30 strains) and *Enterobacter* spp. (83).
c. Includes 39.2% ampicillin-resistant strains (β-lactamase-positive).

Table 3.

Comparative antimicrobial activity of ertapenem tested against 475 strains of Gram-positive cocci and bacilli.

Organism/resistance Phenotype (no. tested)	Antimicrobial Agent	MIC (µg/mL) 50%	90%	Range	% Susceptible[a]
Enterococci Vancomycin-susc. (28)	Ertapenem	8	>32	0.12->32	17.9
	Imipenem	2	>8	≤0.06->8	82.1
	Ceftriaxone	>32	>32	≤0.25->32	-
	Ceftazidime	>16	>16	4->16	-
	Cefepime	>16	>16	v0.12->16	-
	Ciprofloxacin	2	>2	≤0.25->2	46.4
	Gentamicin	≤500	>1000	≤500->1000	67.9
	Ampicillin	2	>16	≤0.12->16	85.7
	Piperacillin/Tazobactam	4	>128	1->128	78.6
	Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	75.0
Vancomycin-resist. (28)	Ertapenem	>32	>32	8->32	0.0
	Imipenem	>8	>8	2->8	21.4
	Ceftriaxone	>32	>32	>32	-
	Ceftazidime	>16	>16	>16	-
	Cefepime	>16	>16	>16	-
	Ciprofloxacin	>2	>2	0.5->2	3.6
	Gentamicin	>1000	>1000	≤500->1000	35.7
	Ampicillin	>16	>16	1->16	21.4
	Piperacillin/Tazobactam	>128	>128	2->128	21.4
	Trimethoprim/Sulfamethoxazole	>2	>2	≤0.5->2	28.9
β-*haemolytic streptococci* (99)[b]	Ertapenem	≤0.015	0.03	≤0.015-0.5	100.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0
	Ceftazidime	0.25	1	≤0.25-4	-
	Cefepime	≤0.12	≤0.12	≤0.12-1	98.0
	Levofloxacin	0.5	1	0.25-2	100.0
	Gentamicin	4	>8	≤1->8	-
	Penicillin	≤0.015	0.06	≤0.015-0.12	100.0
	Ampicillin	≤0.12	≤0.12	≤0.12-0.25	100.0
	Piperacillin/Tazobactam	≤0.06	0.25	≤0.06-0.25	-
	Erythromycin	≤0.06	>8	≤0.06->8	83.8
	Clindamycin	≤0.06	0.5	≤0.06->8	89.9
	Vancomycin	0.5	0.5	0.25-1	100.0
	Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5	-
viridans group streptococci (108)[c]	Ertapenem	0.12	2	≤0.015-8	98.1
	Imipenem	≤0.06	0.25	≤0.06-4	-
	Ceftriaxone	≤0.25	2	≤0.25-8	88.8
	Ceftazidime	2	32	≤0.12->32	-
	Cefepime	0.25	4	≤0.12->8	74.1
	Levofloxacin	1	2	≤0.5->4	95.7
	Gentamicin	4	8	≤1->8	-
	Penicillin	0.25	8	≤0.015->16	47.2
	Ampicillin	≤0.12	>16	≤0.12->16	64.0
	Piperacillin/Tazobactam	0.25	8	≤0.06-16	-
	Erythromycin	≤0.25	4	≤0.25->8	51.9
	Clindamycin	≤0.06	0.12	≤0.06->8	81.7
	Vancomycin	0.5	1	0.25-2	99.1
	Trimethoprim/Sulfamethoxazole	≤0.5	4	≤0.5	-
S. pneumoniae[d] penicillin-susc. (44)	Ertapenem	≤0.015	≤0.015	≤0.015-0.12	100.0
	Ceftriaxone	0.03	0.06	0.015-0.06	100.0
	Ceftazidime	≤0.25	0.5	≤0.25-1	-
	Cefepime	≤0.06	0.12	≤0.06-0.12	100.0
	Levofloxacin	1	1	0.12->4	90.9
	Penicillin	0.03	0.03	≤0.015-0.06	100.0
	Amoxicillin	≤0.06	≤0.06	≤0.06-0.12	100.0
	Piperacillin/Tazobactam	≤0.06	≤0.06	≤0.06-0.5	-
	Erythromycin	≤0.25	4	≤0.25->32	84.1
	Clindamycin	≤0.25	≤0.25	≤0.25->2	97.7
	Vancomycin	0.25	0.5	≤0.12-0.5	100.0
	Trimethoprim/Sulfamethoxazole	≤0.5	4	≤0.5->4	72.7
penicillin-intermediate (35)	Ertapenem	0.12	0.5	≤0.015-1	77.1
	Ceftriaxone	0.25	1	0.015-4	86.7
	Ceftazidime	4	8	≤0.25-32	-
	Cefepime	0.25	0.5	≤0.12-2	94.3
	Levofloxacin	1	>4	0.5->4	85.7
	Penicillin	0.5	1	0.12-1	0.0
	Amoxicillin	0.5	1	≤0.06-2	100.0
	Piperacillin/Tazobactam	1	2	≤0.06-4	-
	Erythromycin	≤0.25	>32	≤0.25->32	51.4
	Clindamycin	≤0.25	>2	≤0.25->2	80.0
	Vancomycin	0.5	0.5	0.25-1	100.0
	Trimethoprim/Sulfamethoxazole	1	>4	≤0.5->4	45.7
penicillin-resistant (35)	Ertapenem	0.5	2	0.25-2	5.7
	Ceftriaxone	1	1	0.5-4	13.3
	Ceftazidime	8	16	8-32	-
	Cefepime	1	1	0.5-2	11.4
	Levofloxacin	1	>4	0.06->4	82.9
	Penicillin	2	4	2->4	0.0
	Amoxicillin	2	8	1->8	71.4
	Piperacillin/Tazobactam	4	4	2-8	-
	Erythromycin	2	>32	≤0.25->32	11.4
	Clindamycin	≤0.25	>2	≤0.25->2	71.4
	Vancomycin	0.5	0.5	0.25-0.5	100.0
	Trimethoprim/Sulfamethoxazole	4	>4	≤0.5->4	2.9
CoNS (16)[e]	Ertapenem	0.12	0.25	0.06-0.5	100.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0
	Ceftriaxone	2	4	0.5-8	100.0
	Ceftazidime	4	8	1-16	93.8
	Cefepime	0.5	2	≤0.12-2	100.0
	Levofloxacin	0.25	0.5	0.12->4	93.8
	Gentamicin	≤1	≤1	≤1	100.0
	Penicillin	0.25	2	≤0.015-8	37.5
	Oxacillin	0.12	0.25	0.12-0.25	100.0
	Ampicillin	≤0.12	2	≤0.12-4	56.3
	Piperacillin/Tazobactam	0.12	0.5	≤0.06-1	100.0
	Erythromycin	0.25	>8	0.25->8	68.8
	Clindamycin	≤0.06	0.12	≤0.06-0.12	100.0
	Vancomycin	1	2	0.5-2	100.0
	Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->1	93.8
S. aureus (51)	Ertapenem	0.12	0.12	0.03-0.25	100.0
	Imipenem	≤0.06	≤0.06	≤0.06-0.5	100.0
	Ceftriaxone	2	4	1-4	100.0
	Ceftazidime	8	8	4-16	98.0
	Cefepime	2	4	0.25-4	100.0
	Levofloxacin	0.12	0.25	0.06->4	94.1
	Gentamicin	≤1	≤1	≤1-8	98.0
	Penicillin	2	32	≤0.015->32	23.5
	Oxacillin	0.25	1	0.12-2	100.0
	Ampicillin	2	>16	≤0.12->16	25.5
	Piperacillin/Tazobactam	0.5	1	0.12-2	100.0
	Erythromycin	0.5	>8	0.25->8	70.6
	Clindamycin	0.12	0.12	≤0.06->8	96.1
	Vancomycin	1	1	0.5-2	100.0
	Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0
Bacillus spp. (12)	Ertapenem	0.06	0.5	≤0.015-1	100.0
	Imipenem	≤0.06	0.5	≤0.06-2	100.0
	Ceftriaxone	16	>32	≤0.25->32	41.7
	Ceftazidime	>16	>16	0.25->16	25.0
	Cefepime	>16	>16	≤0.12->16	33.3
	Levofloxacin	0.12	0.25	0.12-0.25	100.0
	Gentamicin	≤1	2	≤1-2	100.0
	Oxacillin	8	>8	0.12->8	33.3
	Penicillin	4	16	≤0.015-32	33.3
	Piperacillin/Tazobactam	0.5	1	≤0.06-32	91.7
	Erythromycin	0.5	>8	0.12->8	50.0
	Clindamycin	1	>8	0.5->8	0.0
	Vancomycin	1	1	≤0.12->16	91.7
	Trimethoprim/Sulfamethoxazole	≤0.5	2	≤0.5->2	66.7
Corynebacterium jeikeium (8)	Ertapenem	>32	-	4->32	12.5
	Imipenem	>8	-	>8	0.0
	Ceftriaxone	>32	-	>32	0.0
	Ceftazidime	>16	-	>16	0.0
	Cefepime	>16	-	>16	0.0
	Ciprofloxacin	>2	-	>2	0.0
	Gentamicin	>8	-	≤1->8	12.5
	Oxacillin	>8	-	>8	0.0
	Ampicillin	>16	-	>16	0.0
	Piperacillin/Tazobactam	>128	-	16->128	12.5
	Erythromycin	8	-	4->8	0.0
	Clindamycin	>8	-	>8	0.0
	Vancomycin	0.5	-	0.5-1	100.0
	Trimethoprim/Sulfamethoxazole	>2	-	>2	0.0
Corynebacterium spp. (11)	Ertapenem	0.5	>32	0.06->32	81.8
	Imipenem	≤0.06	0.5	≤0.06->8	90.9
	Ceftriaxone	1	32	≤0.25->32	81.8
	Ceftazidime	16	>16	2-.16	27.3
	Cefepime	0.25	2	≤0.12->16	90.9
	Ciprofloxacin	>2	>2	≤0.25->2	36.4
	Gentamicin	≤1	8	≤1->8	81.8
	Oxacillin	4	>8	0.5->8	18.2
	Ampicillin	4	>16	≤0.12->16	27.3
	Piperacillin/Tazobactam	2	32	≤0.06->128	81.8
	Erythromycin	>8	>8	≤0.06->8	9.1
	Clindamycin	>8	>8	≤0.06->8	9.1
	Vancomycin	0.25	0.5	0.25-0.5	100.0
	Trimethoprim/Sulfamethoxazole	1	>2	≤0.5->2	27.3

a. Breakpoints for susceptibility as defined by the NCCLS [2001] or as follows: ertapenem-susceptible at ≤4 µg/mL for enterococci and staphylococci; ≤0.25 µg/mL for *S. pneumoniae*; and ≤0.5 µg/mL for other streptococci (same as used for meropenem).
b. Includes strains from serogroups A (41), B (32), C (10), F (6) and G (10).
c. Includes: *S. anginosus* (2), *S. constellatus* (2), *S. intermedius* (5), *S. mitis* (19), *S. mutans* (1), *S. oralis* (4), *S. parasanguis* (1), *S. sanguis* (7), *S. uberis* (1), and viridans group. streptococcus NOS (66). All strains were isolated from blood cultures.
d. All strains were isolated from blood stream infections.
e. CoNS = coagulase-negative staphylococci.

Table 4.

Bactericidal activity of ertapenem tested against eight organisms by the kill curve method.

Organism (no. tested)	Concentration Tested[a]	No. with ≥3 $\log_{10}$ killing at: 4 Hours	8 Hours	24 Hours	Interpretation[b]
Staphylococci (4)[c]	4x	0	3	4	Cidal
	8x	0	2	4	Cidal
E. coli (2)[d]	4x	2	2	2	Cidal
	8x	2	2	2	Cidal
K. pneumoniae (2)[d]	4x	2	2	0[e]	Cidal
	8x	2	2	2	Cidal

a. Concentrations listed as a multiple of the organisms MIC (µg/mL).
b. Interpretation of bactericidal (cidal) action was defined as ≥3 $\log_{10}$ reduction in viability of the initial inoculum, generally 5×10^5 CFU/ml.
c. Includes two strains each of *S. aureus* and coagulase-negative staphylococci. All strains were susceptible to oxacillin [NCCLS, 2000].
d. Includes one strain with an extended spectrum β-lactamase.
e. Regrowth to near control level was observed after eight hours.

Table 5.

Results of broth microdilution checkerboard synergy studies of ertapenem combined with ciprofloxacin (47 strains) or gentamicin (48 strains) tested against staphylococci, *E. coli* and *K. pneumoniae.*

Co-Drug	Organism (no. tested)	Interaction Category:[a] Synergy: Complete	Synergy: Partial	Additive	Indifferent	Antagonism	Indeterminate
Ciprofloxacin	*S. aureus* (10)	-	4	4	1	-	1
	CoNS (15)	-	4	2	9	-	-
	E. coli (11)	1	2	3	5	-	-
	K. pneumoniae (11)	-	9	1	-	-	1
Gentamicin	*S. aureus* (15)	-	2	3	10	-	-
	CoNS (15)	-	3	6	6	-	-
	E. coli (10)	-	2	3	4	-	1
	K. pneumoniae (8)	-	4	3	-	-	1

a. Definitions of various drug interaction categories are found in the Materials and Methods. Indeterminate results indicate that one or both drugs had resistant level results after combining drugs, therefore, of no clinical utility as a co-drug.

CONCLUSIONS

- In this study, ertapenem was highly potent against Gram-negative species, including *E. coli* and *K. pneumoniae*, with MIC_{90}s generally <0.5 µg/mL. The MICs for ertapenem versus some ESBL-producing isolates, although supporting efficacy, were higher than those observed by several investigators, but confirmed by Livermore et al.
- Ertapenem was comparable in potency to the "third-generation" cephalosporins against *H. influenzae* and 32-fold more potent than cefuroxime. *Enterobacter* spp. resistant to the "third-generation" cephalosporins were susceptible to ertapenem, but strains resistant to ceftazidime exhibited elevated MICs to the carbapenem compared to ceftazidime-susceptible isolates.
- As with other carbapenems, ertapenem was quite active against most Gram-positive species examined in this study. However, an MIC_{90} of >32 µg/mL was observed for ertapenem against *Corynebacterium* spp., penicillin-resistant streptococci, *P. aeruginosa* and most enterococci.
- Ertapenem displayed clear bactericidal activity against Gram-positive and -negative pathogens, including *S. aureus*, a common nosocomial pathogen. Synergy analysis revealed that at least additive antimicrobial effects can be achieved when ertapenem is combined with commonly-used parenteral antimicrobials.
- Of concern was the detectable, but limited hydrolysis of ertapenem exhibited by elevated MICs of ceftazidime-resistant strain subsets when compared to susceptible strains. This occurred for ESBL and Amp C enzyme-hyperproducing isolates of *E. coli, K. pneumoniae, Citrobacter freundii*, and *Enterobacter* spp; however, only 6 of 186 (3.2%) ceftazidime-resistant strains had an ertapenem MIC of >4 µg/ml (non-susceptible).

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