



In Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, Against Gram-Negative Bacilli Isolated by Clinical Laboratories in North America and Europe in 2015–2016: SIDERO-WT-2015

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ABSTRACT

Cefiderocol (S-649266) is a parenteral siderophore cephalosporin in phase III of clinical development. In this study, we determined the in vitro susceptibility to cefiderocol and comparators of a 2015–2016 collection of 8954 clinical isolates of Gram-negative bacilli (GNB), provided by 100 clinical laboratories in North America and Europe, using the Clinical and Laboratory Standards Institute broth microdilution method. Iron-depleted cation-adjusted Mueller-Hinton broth was used to test cefiderocol. The concentration of cefiderocol inhibiting 90% of isolates (MIC₉₀) was 0.5 mg/L (North America; n=2470) and 1 mg/L (Europe; n=3,543) for Enterobacteriaceae, 0.5 mg/L (North America; n=619) and 0.5 mg/L (Europe; n=921) for *Pseudomonas aeruginosa*, 1 mg/L (North America; n=308) and 2 mg/L (Europe; n=664) for *Acinetobacter* spp., 0.5 mg/L (North America; n=165) and 0.25 mg/L (Europe; n=175) for *Stenotrophomonas maltophilia*, and 0.12 mg/L (North America; n=40) and 0.5 mg/L (Europe; n=49) for *Burkholderia cepacia* complex spp. Cefiderocol MICs were ≤4 mg/L for 99.9% (6005/6013) of Enterobacteriaceae, 99.9% (1539/1540) of *P. aeruginosa*, 96.4% (937/972) of *Acinetobacter* spp., 99.4% (338/340) of *S. maltophilia*, and 94.4% (84/89) of *Burkholderia cepacia* complex spp. isolates tested. Against meropenem-non-susceptible isolates, MICs to cefiderocol were ≤4 mg/L for 99.6% (245/246) of Enterobacteriaceae, 99.7% (394/395) of *P. aeruginosa*, 96.1% (540/562) of *Acinetobacter* spp., and 87.1% (27/31) of *B. cepacia* complex spp. We conclude that cefiderocol demonstrated potent in vitro activity (MIC ≤4 mg/L) against the majority (99.4%, 8903/8954) of clinical isolates of GNB in a recent (2015–2016), multi-continent collection, including carbapenem-non-susceptible isolates.

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1. Introduction

The prevalence of pathogenic multidrug-resistant (MDR) and carbapenem-non-susceptible Gram-negative bacilli (GNB) is increasing worldwide [1–3]. Therapeutic options to treat patients with MDR and carbapenem-resistant GNB infections are limited [4,5]. New β-lactam/β-lactamase inhibitor combinations

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have recently been approved (ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam); however, none of these agents is active against isolates of GNB carrying Ambler class B metallo-β-lactamases, and their activity against Class D (OXA) β-lactamases may be limited [1,2,6–8]. Ceftolozane-tazobactam is also inactive against *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae [6,7,9]. Other antimicrobial agents with potential to treat patients infected with carbapenem-resistant GNB (e.g., amikacin, colistin, tigecycline) are associated with toxicities, increasing resistance and, in the case of colistin and tigecycline, intrinsic resistance to, or decreased activity against, several species of Enterobacteriaceae (*Proteus* spp., *Providencia* spp.,

Morganella morganii, *Serratia* spp.) and *P. aeruginosa* (tigecycline only). New agents with unique mechanisms of action and low propensities for resistance development are urgently needed [10].

Cefiderocol, formerly S-649266, is an investigational, parenteral siderophore cephalosporin in phase III of clinical development for the treatment of serious GNB infections, including infections caused by carbapenem-resistant GNB [11–13]. In vivo human pharmacokinetic data and animal infection model pharmacokinetic/pharmacodynamic data have been published for cefiderocol, including several animal infection studies demonstrating dose-dependent efficacy against ESBL-producing, KPC-producing, and MDR isolates of GNB [14–20]. Cefiderocol has demonstrated efficacy against GNB based on human pharmacokinetic properties (i.e., tissue distribution and potential for use in patients with renal impairment) superior to those of both colistin and tigecycline [9,14].

The chemical structure of cefiderocol includes a catechol moiety within its 3-position side chain that promotes formation of chelated complexes with ferric iron and facilitates cefiderocol transport across the outer membrane of GNB via existing iron transport systems [21–23]. Once cefiderocol has crossed the outer membrane and reached the periplasmic space, the iron atom dissociates and cefiderocol is released and binds to penicillin-binding proteins, primarily penicillin-binding protein 3, similar to other cephalosporins, and inhibits peptidoglycan synthesis [21–24]. The unique mechanism of cell entry of cefiderocol and its stability to hydrolysis by nearly all β -lactamases (including both serine and metallo- β -lactamases), porin deletions, and efflux-mediated resistance mechanisms accounts for its enhanced antimicrobial activity compared with carbapenems, β -lactam/ β -lactamase inhibitor combinations, and advanced-generation cephalosporins [22–25].

Cefiderocol has demonstrated potent in vitro activity (minimum inhibitory concentration [MIC] ≤ 4 mg/L) against carbapenem-resistant and MDR GNB, including Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* harboring Ambler class A (KPC), B (IMP, NDM, VIM), and D (OXA) carbapenemases, as well as those harboring ESBL- (CTX-type, SHV-type, TEM-type) and Ambler class C (AmpC) β -lactamases [7,9,23–31]. Recent studies reported cefiderocol MICs to be ≤ 4 mg/L for most NDM-1-producing isolates of *E. coli* (73.7%, 14/19), *K. pneumoniae* (100%, 24/24), and *S. marcescens*, *C. freundii*, and *E. cloacae* (100%, 6/6) [24]; and for 97.3% (733/753) of clinical isolates of GNB (Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*) with MDR phenotypes and carrying carbapenemases (KPC, NDM, IMP, VIM, OXA) [9]. Cefiderocol also inhibits clinical isolates of *Stenotrophomonas maltophilia* at in vitro concentrations ≤ 4 mg/L, with MIC₉₀ concentrations in previous surveillance studies ranging from 0.25 to 0.5 mg/L [28,29]. The activity of cefiderocol against *S. maltophilia* is significant given that this pathogen is intrinsically resistant to many broad-spectrum antimicrobial agents, including carbapenems, due to the production of two inducible chromosomal metallo- and serine- β -lactamases (L1, L2).

The current surveillance study, SIDERO-WT-2015, tested a 2015–2016 collection of 8954 clinical isolates of GNB from patients in North America and Europe against cefiderocol and comparators using standardized Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology [32,33]. This report summarizes the second year of data generated by an ongoing in vitro global surveillance initiative for cefiderocol as it progresses through the stages of clinical development [28].

2. Materials and Methods

2.1. Bacterial isolates

From November 1, 2015 to October 31, 2016, 100 clinical laboratories in 13 countries in North America (United States [37

clinical laboratories] and Canada [eight]) and Europe (Italy [nine clinical laboratories], France [eight], Spain [seven], Germany [six], Turkey [five], United Kingdom [five], Greece [four], Hungary [four], Czech Republic [three], Sweden [three] and Russia [one]) were each requested to sequentially collect 100 clinical isolates with a specific species distribution (15 *E. coli*, 15 *K. pneumoniae*, five *Klebsiella* spp. other than *K. pneumoniae*, 10 *Enterobacter* spp., 10 *Serratia* spp., five *Citrobacter* spp., 15 *P. aeruginosa*, 15 *A. baumannii*, five *Burkholderia cepacia*, and five *Stenotrophomonas maltophilia*) from patients with documented lower respiratory tract (33.5% of total isolates), urinary tract (22.4%), skin and soft tissue (16.5%), bloodstream (14.7%), or intra-abdominal (12.7%) infections. Nineteen isolates (0.2%) were from an unknown infection source. Only one isolate per patient per bacterial species was accepted into the study. Isolates were collected independently of their antimicrobial susceptibility phenotype. All isolates were shipped to International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA) where their identities were confirmed using MALDI-TOF mass spectrometry (Bruker Daltonics, Billerica, MA, USA). A total of 8954 isolates of GNB submitted by the 45 clinical laboratories in North America ($n=3602$) and the 55 clinical laboratories in Europe ($n=5352$) met study inclusion criteria and proceeded to antimicrobial susceptibility testing.

2.2. Antimicrobial susceptibility testing

Broth microdilution panels were produced in-house at IHMA and broth microdilution antimicrobial susceptibility testing performed according to current CLSI standard methods [32,33]. All antimicrobial agent powders were obtained from the U.S. Pharmacopeia (Rockville, MD) apart from cefiderocol and ceftolozane (Shionogi & Co., Ltd., Osaka, Japan), and avibactam (Biochempartner, Wuhan, China). Iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB) was used to determine susceptibilities to cefiderocol; it was prepared as previously described [28,29,34,35] using Chelex® 100 resin 200–400 mesh, sodium form (Bio-Rad Laboratories, Hercules, CA) and CAMHB from Becton-Dickinson BBL™ (Sparks, MD) [33]. The method of ID-CAMHB preparation used was approved by the CLSI Subcommittee on Antimicrobial Susceptibility Testing in January 2016 [34]. The final concentration of iron in ID-CAMHB prepared using the previously described method [28,29,34,35] is ≤ 0.03 mg/L. Accurate in vitro susceptibility testing of cefiderocol requires the use of iron-depleted conditions to ensure induction of ferric iron transporters and mimic the environment encountered by bacteria infecting human tissues and fluids [24,36]. Broth microdilution panels were frozen at -80°C and thawed to room temperature prior to use. The quality control strains recommended by CLSI (i.e., *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853) were tested each day clinical isolates were tested and all quality control results were within specified CLSI ranges [33]. The broth microdilution panels included growth control wells for CAMHB and ID-CAMHB. The panels were incubated at 35°C for 20 h in ambient air before MIC endpoints were read. ID-CAMHB did not significantly affect the growth of any quality control or test organism. Reading the MIC of cefiderocol was contingent on the presence of strong growth in the ID-CAMHB growth control (i.e., a button of approximately 2 mm or greater). The cefiderocol MIC was read as the first panel well in which isolate growth was significantly reduced (i.e., a button of <1 mm or light/faint turbidity) relative to the growth observed in the ID-CAMHB growth control well [28,29,34].

CLSI MIC interpretive criteria were used when available, including to interpret colistin MICs for *P. aeruginosa* and *Acinetobacter* spp. [33]. European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints for colistin tested against Enterobacteriaceae (susceptible, ≤ 2 mg/L; resistant, ≥ 4 mg/L) were

employed because neither the CLSI nor FDA publishes breakpoints [37]. Currently, ceftiderocol does not have approved MIC interpretative breakpoints. An MIC of ≤ 4 mg/L was used as the working MIC breakpoint for ceftiderocol activity because it is supported by in vivo pharmacokinetic/pharmacodynamic data [14–18].

3. Results

The in vitro activities of ceftiderocol and six comparators are summarized in Table 1 for the 3602 GNB isolates collected from North American clinical laboratories and in Table 2 for the 5352 isolates from European clinical laboratories. The concentration of antimicrobial agent inhibiting 50% (MIC₅₀) and 90% (MIC₉₀) of isolates of Enterobacteriaceae tested against ceftiderocol were 0.12 and 0.5 mg/L for North American isolates (MIC range ≤ 0.002 –128 mg/L) and 0.25 and 1 mg/L for European isolates (MIC range ≤ 0.002 –8 mg/L). Ceftiderocol inhibited 99.9% (6005/6013) of all isolates of Enterobacteriaceae tested, at both North American and European clinical laboratories, at a concentration (MIC) of ≤ 4 mg/L. Of the eight isolates of Enterobacteriaceae with ceftiderocol MICs of ≥ 8 mg/L, three were European isolates (two isolates of *E. coli* and one isolate of *Citrobacter freundii*, all with ceftiderocol MICs of 8 mg/L) and five were North American isolates (two isolates of *Enterobacter cloacae* [MICs 8 and 128 mg/L] two isolates of *Serratia marcescens* [MICs 16 and 32 mg/L], and one isolate of *Citrobacter koseri* [MIC 8 mg/L]). Each isolate of Enterobacteriaceae with a ceftiderocol MIC ≥ 8 mg/L was from a unique clinical laboratory location. Seven of the eight isolates with ceftiderocol MICs of 8 mg/L were susceptible to both meropenem and ceftazidime-avibactam compared with six isolates susceptible to colistin, four isolates susceptible to ciprofloxacin, and only one isolate susceptible to ceftolozane-tazobactam.

Against meropenem-non-susceptible (MIC ≥ 2 mg/L) isolates of Enterobacteriaceae from North America ($n=50$) and Europe ($n=196$), ceftiderocol MIC₉₀ values were 2 and 4 mg/L, respectively; 99.6% (245/246) of all meropenem-non-susceptible Enterobacteriaceae had MICs to ceftiderocol of ≤ 4 mg/L (Table 3, Supplementary Figure 1). Supplementary Figure 1 compares ceftiderocol MIC distributions for meropenem-susceptible (MIC ≤ 1 mg/L; $n=5767$) and meropenem-non-susceptible (MIC ≥ 2 mg/L; $n=246$) isolates of Enterobacteriaceae; the MIC₉₀ value for ceftiderocol was 1 mg/L for meropenem-susceptible isolates and 99.9% (5760/5767) of meropenem-susceptible Enterobacteriaceae had MICs to ceftiderocol of ≤ 4 mg/L. Both ceftazidime-avibactam and ceftolozane-tazobactam had MIC₉₀ values of >64 mg/L for isolates of meropenem-non-susceptible Enterobacteriaceae (compared with MIC₉₀s of ≤ 1 mg/L for both agents tested against meropenem-susceptible isolates of Enterobacteriaceae) and percent susceptibilities for isolates of meropenem-non-susceptible Enterobacteriaceae of $<80\%$ for ceftazidime-avibactam and colistin, and $<10\%$ for ceftolozane-tazobactam and ceftipime (Table 3).

Ceftiderocol, at a concentration of ≤ 4 mg/L, inhibited 98.2% (56/57) of isolates of ceftazidime-avibactam-non-susceptible Enterobacteriaceae and 98.8% (590/597) of isolates of ceftolozane-tazobactam-non-susceptible Enterobacteriaceae (Table 4) as well as 99.5% (997/1002) of isolates of ceftipime-non-susceptible Enterobacteriaceae, 99.7% (1295/1299) of isolates of ciprofloxacin-non-susceptible Enterobacteriaceae, and 99.8% (928/930) of isolates of colistin-non-susceptible Enterobacteriaceae (Supplementary Table 1). Ceftiderocol activity against colistin-susceptible isolates ($n=5083$; MIC₅₀, 0.12 mg/L; MIC₉₀, 1 mg/L; 99.9% [5077/5083] of isolates with a ceftiderocol MIC ≤ 4 mg/L) was indistinguishable from its activity against colistin-non-susceptible isolates of Enterobacteriaceae. Supplementary Figure 2 depicts the MIC distributions for ceftiderocol tested against ceftazidime-avibactam and ceftolozane-tazobactam-susceptible and non-susceptible subsets

of isolates. For each non-susceptible isolate subset there is a rightward shift in the ceftiderocol MIC distribution compared with the MIC distribution of the susceptible isolate subset, but in every instance $>98\%$ of ceftiderocol MICs remained ≤ 4 mg/L. Against isolates of Enterobacteriaceae non-susceptible to both ceftazidime-avibactam and ceftolozane-tazobactam ($n=55$), the ceftiderocol MIC₅₀ and MIC₉₀ were 1 and 4 mg/L; 98.2% (54/55) of isolates non-susceptible to both ceftazidime-avibactam and ceftolozane-tazobactam had ceftiderocol MICs ≤ 4 mg/L (Supplementary Figures 4 and 5).

The MIC₅₀ and MIC₉₀ values for ceftiderocol against *P. aeruginosa* were 0.12 and 0.5 mg/L for both North American (MIC range ≤ 0.002 –4 mg/L) and European (MIC range ≤ 0.002 –8 mg/L) isolates; 99.9% (1539/1540) of all isolates of *P. aeruginosa* had ceftiderocol MICs ≤ 4 mg/L. The one isolate of *P. aeruginosa* with an MIC to ceftiderocol of 8 mg/L was from a European clinical laboratory. Meropenem-non-susceptible isolates accounted for 20.8% (North America) and 28.9% (Europe) of isolates of *P. aeruginosa* (Tables 1 and 2). Against meropenem-non-susceptible (MIC ≥ 4 mg/L) isolates of *P. aeruginosa*, the MIC₉₀ value for ceftiderocol was 1 mg/L and 99.7% (394/395) of isolates had ceftiderocol MICs ≤ 4 mg/L (Supplementary Figure 1). In comparison, the MIC₉₀ values for ceftazidime-avibactam and ceftolozane-tazobactam against isolates of meropenem-non-susceptible *P. aeruginosa* were 64 mg/L and ≥ 64 mg/L, respectively, with percent susceptibilities of 72.9% (ceftazidime-avibactam) and 73.9% (ceftolozane-tazobactam) (Table 3) markedly lower than the 99.5% (1139/1145) susceptibility to ceftazidime-avibactam and 99.3% (1137/1145) susceptibility to ceftolozane-tazobactam for meropenem-susceptible isolates of *P. aeruginosa*. Against meropenem-susceptible isolates (MIC ≤ 2 mg/L) from both North America and Europe, the MIC₉₀ value for ceftiderocol was 0.5 mg/L ($n=1145$) and all meropenem-susceptible isolates of *P. aeruginosa* had MICs to ceftiderocol of ≤ 4 mg/L. All ceftazidime-avibactam-non-susceptible and ceftolozane-tazobactam-non-susceptible isolates of *P. aeruginosa* had ceftiderocol MICs ≤ 4 mg/L (Table 4). Ceftiderocol, at a concentration of ≤ 4 mg/L, inhibited 99.7% (299/300) of isolates of ceftipime-non-susceptible *P. aeruginosa* and 99.8% (423/424) of isolates of ciprofloxacin-non-susceptible *P. aeruginosa* (Supplementary Table 1). Figure 3 depicts the MIC distributions for ceftiderocol against ceftazidime-avibactam- and ceftolozane-tazobactam-susceptible and -non-susceptible isolates of *P. aeruginosa*. For each non-susceptible isolate subset there was approximately a one doubling-dilution rightward shift in the ceftiderocol MIC distribution compared with the MIC distribution of the susceptible isolate subset, but in almost every instance ($\geq 99.7\%$), ceftiderocol MICs remained ≤ 4 mg/L. Against isolates of *P. aeruginosa* non-susceptible to both ceftazidime-avibactam and ceftolozane-tazobactam ($n=89$), the ceftiderocol MIC₅₀ and MIC₉₀ were 0.25 and 1 mg/L; 100% (89/89) of isolates non-susceptible to both ceftazidime-avibactam and ceftolozane-tazobactam had ceftiderocol MICs ≤ 4 mg/L (Supplementary Figures 6 and 7).

The MIC₅₀ and MIC₉₀ values for ceftiderocol tested against *Acinetobacter* spp. were 0.25 and 1 mg/L for North American isolates and 0.25 and 2 mg/L for European isolates, respectively; 96.4% (937/972) of all *Acinetobacter* spp. had MICs to ceftiderocol of ≤ 4 mg/L. Of the 35 isolates with ceftiderocol MIC values ≥ 8 mg/L, 29 were from European clinical laboratories (19 isolates from four laboratories in Russia; five isolates from three laboratories in Italy, three isolates from two laboratories in Turkey; and one isolate from laboratories in each of France and Germany) and six were from three laboratories in the United States. Twenty-two of the 35 isolates (62.9%) with MICs to ceftiderocol of ≥ 8 mg/L were also non-susceptible to meropenem (MIC ≥ 4 mg/L). Against meropenem-non-susceptible isolates of *Acinetobacter* spp., the MIC₉₀ value for ceftiderocol was 2 mg/L; 96.1% (540/562)

Table 1
In vitro activity of cefiderocol and comparators against Gram-negative bacilli isolated by 45 clinical laboratories in North America in 2015 (n=3602)

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (mg/L) ^a			MIC interpretation ^b		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
Enterobacteriaceae (2470)	Cefiderocol	≤0.002-128	0.12	0.5			
	Cefepime	≤0.06->64	≤0.06	4	89.9	2.6	7.5
	Ceftazidime-avibactam	≤0.06-32	0.12	0.5	99.9	0	0.1
	Ceftolozane-tazobactam	≤0.06->64	0.25	1	93.9	1.4	4.7
	Ciprofloxacin	≤0.12->8	≤0.12	>8	83.9	1.3	14.7
	Colistin	≤0.25->8	0.5	>8	83.5		16.5
	Meropenem	≤0.06->64	≤0.06	≤0.06	98.0	0.1	1.9
<i>Klebsiella</i> spp. ^c (798)	Cefiderocol	≤0.002-4	0.06	0.5			
	Cefepime	≤0.06->64	≤0.06	2	90.7	1.6	7.6
	Ceftazidime-avibactam	≤0.06-32	0.12	0.5	99.9	0	0.1
	Ceftolozane-tazobactam	≤0.06->64	0.25	1	95.6	0.5	3.9
	Ciprofloxacin	≤0.12->8	≤0.12	2	89.5	1.3	9.3
	Colistin	≤0.25->8	0.5	1	98.6		1.4
	Meropenem	≤0.06->64	≤0.06	≤0.06	97.2	0	2.8
<i>Klebsiella pneumoniae</i> (614)	Cefiderocol	≤0.002-4	0.12	0.5			
	Cefepime	≤0.06->64	≤0.06	8	88.9	1.8	9.3
	Ceftazidime-avibactam	≤0.06-8	0.12	0.5	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.25	1	94.8	0.5	4.7
	Ciprofloxacin	≤0.12->8	≤0.12	4	87.5	1.6	10.9
	Colistin	≤0.25->8	0.5	1	98.2		1.8
	Meropenem	≤0.06->64	≤0.06	≤0.06	96.9	0	3.1
<i>Klebsiella oxytoca</i> (149)	Cefiderocol	≤0.002-2	0.06	0.5			
	Cefepime	≤0.06-64	≤0.06	0.5	96.0	1.3	2.7
	Ceftazidime-avibactam	≤0.06-32	0.12	0.5	99.3	0	0.7
	Ceftolozane-tazobactam	≤0.06->64	0.25	0.5	98.0	0.7	1.3
	Ciprofloxacin	≤0.12->8	≤0.12	0.25	95.3	0	4.7
	Colistin	≤0.25-2	0.5	1	100		0
	Meropenem	≤0.06->64	≤0.06	≤0.06	98.7	0	1.3
<i>Klebsiella variicola</i> (35)	Cefiderocol	≤0.002-2	0.03	0.25			
	Cefepime	≤0.06-0.5	≤0.06	0.25	100	0	0
	Ceftazidime-avibactam	≤0.06-0.5	0.12	0.5	100	0	0
	Ceftolozane-tazobactam	≤0.06-2	0.25	0.5	100	0	0
	Ciprofloxacin	≤0.12-1	≤0.12	0.25	100	0	0
	Colistin	≤0.25-2	0.5	1	100		0
	Meropenem	≤0.06-4	≤0.06	≤0.06	97.1	0	2.9
<i>Escherichia coli</i> (748)	Cefiderocol	≤0.002-4	0.12	0.5			
	Cefepime	≤0.06->64	≤0.06	64	84.4	2.5	13.1
	Ceftazidime-avibactam	≤0.06-8	0.12	0.25	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.25	0.5	98.1	0.3	1.6
	Ciprofloxacin	≤0.12->8	≤0.12	> 8	65.9	0.3	33.8
	Colistin	≤0.25-8	0.5	1	99.6		0.4
	Meropenem	≤0.06-16	≤0.06	≤0.06	99.2	0	0.8
<i>Serratia</i> spp. ^d (377)	Cefiderocol	0.015-32	0.12	0.5			
	Cefepime	≤0.06->64	0.12	0.5	95.2	1.6	3.2
	Ceftazidime-avibactam	≤0.06-16	0.25	0.5	99.7	0	0.3
	Ceftolozane-tazobactam	0.12->64	0.5	1	99.4	1.9	3.7
	Ciprofloxacin	≤0.12->8	≤0.12	1	91.3	2.9	5.8
	Colistin	0.5->8	> 8	> 8	5.3		94.7
	Meropenem	≤0.06-64	≤0.06	0.12	96.6	0.3	3.2
<i>Serratia marcescens</i> (368)	Cefiderocol	0.015-32	0.12	0.5			
	Cefepime	≤0.06->64	0.12	0.5	95.1	1.6	3.3
	Ceftazidime-avibactam	≤0.06-16	0.25	0.5	99.7	0	0.3
	Ceftolozane-tazobactam	0.12->64	0.5	1	94.3	1.9	3.8
	Ciprofloxacin	≤0.12->8	≤0.12	1	91.0	3.0	6.0
	Colistin	0.5->8	>8	>8	5.4		94.6
	Meropenem	≤0.06->64	≤0.06	0.12	96.5	0.3	3.3
<i>Enterobacter</i> spp. ^e (372)	Cefiderocol	0.004-128	0.25	1			
	Cefepime	≤0.06->64	≤0.06	2	91.1	5.9	3.0
	Ceftazidime-avibactam	≤0.06-8	0.25	1	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.25	8	83.6	4.6	11.8
	Ciprofloxacin	≤0.12->8	≤0.12	0.25	94.9	1.3	3.8
	Colistin	≤0.25->8	0.5	2	90.1		10.0
	Meropenem	≤0.06-32	≤0.06	0.12	98.9	0.3	0.8
<i>Enterobacter cloacae</i> (214)	Cefiderocol	0.008-128	0.25	1			
	Cefepime	≤0.06->64	≤0.06	4	85.1	10.3	4.7
	Ceftazidime-avibactam	≤0.06-8	0.25	1	100	0	0
	Ceftolozane-tazobactam	0.12->64	0.25	16	79.0	4.2	16.8
	Ciprofloxacin	≤0.12->8	≤0.12	0.5	93.9	0.9	5.1
	Colistin	≤0.25->8	0.5	1	94.9		5.1
	Meropenem	≤0.06-32	≤0.06	0.12	98.6	0.5	0.9

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Table 1 (continued)

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (mg/L) ^a			MIC interpretation ^b		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
<i>Enterobacter aerogenes</i> (114)	Cefiderocol	0.004-2	0.12	0.5			
	Cefepime	≤0.06-16	≤0.06	0.5	99.1	0	0.9
	Ceftazidime-avibactam	≤0.06-8	0.25	0.5	100	0	0
	Ceftolozane-tazobactam	≤0.06-32	0.25	4	88.6	6.1	5.3
	Ciprofloxacin	≤0.12->8	≤0.12	0.25	95.6	2.6	1.8
	Colistin	≤0.25-2	0.5	1	100		0
	Meropenem	≤0.06-16	≤0.06	0.12	99.1	0	0.9
<i>Citrobacter</i> spp. ^f (175)	Cefiderocol	≤0.002-8	0.25	1			
	Cefepime	≤0.06->64	≤0.06	1	95.4	2.3	2.3
	Ceftazidime-avibactam	≤0.06-8	0.12	0.5	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.25	4	88.0	2.9	9.1
	Ciprofloxacin	≤0.12->8	≤0.12	0.5	95.4	1.7	2.9
	Colistin	≤0.25-2	0.5	1	100		0
	Meropenem	≤0.06-16	≤0.06	≤0.06	97.1	0.6	2.3
<i>Citrobacter freundii</i> (100)	Cefiderocol	0.004-4	0.12	1			
	Cefepime	≤0.06->64	≤0.06	2	94.0	2.0	4.0
	Ceftazidime-avibactam	≤0.06-8	0.12	0.5	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.25	8	80.0	5.0	15.0
	Ciprofloxacin	≤0.12->8	≤0.12	1	93.0	3.0	4.0
	Colistin	≤0.25-2	0.5	1	100		0
	Meropenem	≤0.06-16	≤0.06	≤0.06	95.0	1.0	4.0
<i>Citrobacter koseri</i> (56)	Cefiderocol	0.015-8	0.5	1			
	Cefepime	≤0.06-4	≤0.06	0.12	96.4	3.6	0
	Ceftazidime-avibactam	≤0.06-0.5	0.12	0.25	100	0	0
	Ceftolozane-tazobactam	≤0.06-1	0.25	0.5	100	0	0
	Ciprofloxacin	≤0.12-8	≤0.12	≤0.12	98.2	0	1.8
	Colistin	≤0.25-2	≤0.25	1	100		0
	Meropenem	≤0.06	≤0.06	≤0.06	100	0	0
<i>Pseudomonas aeruginosa</i> (619)	Cefiderocol	≤0.002-4	0.12	0.5			
	Cefepime	≤0.06->64	4	16	83.4	11.2	5.5
	Ceftazidime-avibactam	0.12->64	2	8	96.9	0	3.1
	Ceftolozane-tazobactam	≤0.06->64	0.5	2	97.6	1.1	1.3
	Ciprofloxacin	≤0.12->8	0.25	>8	74.6	4.2	21.2
	Colistin	≤0.25-4	1	2	99.8		0.2
	Meropenem	≤0.06->64	0.5	8	79.2	7.1	13.7
<i>Acinetobacter</i> spp. ^g (308)	Cefiderocol	≤0.002->256	0.25	1			
	Cefepime	0.12->64	4	64	59.4	11.4	29.2
	Ceftazidime-avibactam	0.25->64	8	>64			
	Ceftolozane-tazobactam	≤0.06->64	1	>64			
	Ciprofloxacin	≤0.12->8	0.5	>8	57.5	1.6	40.9
	Colistin	≤0.25->8	0.5	1	96.1		3.9
	Meropenem	≤0.06->64	0.5	>64	62.3	0.6	37.0
<i>Acinetobacter baumannii</i> (223)	Cefiderocol	0.008->256	0.25	2			
	Cefepime	0.12->64	16	>64	44.8	14.8	40.4
	Ceftazidime-avibactam	0.5->64	8	>64			
	Ceftolozane-tazobactam	≤0.06->64	4	>64			
	Ciprofloxacin	≤0.12->8	>8	>8	41.7	1.8	56.5
	Colistin	≤0.25->8	0.5	1	94.6		5.4
	Meropenem	≤0.06->64	8	>64	48.4	0.9	50.7
<i>Acinetobacter pittii</i> (66)	Cefiderocol	≤0.002-1	0.12	0.5			
	Cefepime	0.12-16	4	8	97.0	3.0	0
	Ceftazidime-avibactam	0.25-16	8	16			
	Ceftolozane-tazobactam	≤0.06-4	0.5	2			
	Ciprofloxacin	≤0.12-2	0.25	0.5	98.5	1.5	0
	Colistin	≤0.25-2	0.5	1	100		0
	Meropenem	≤0.06-16	0.25	0.5	98.5	0	1.5
<i>Stenotrophomonas maltophilia</i> (165)	Cefiderocol	0.004-64	0.12	0.5			
	Cefepime	1->64	32	>64			
	Ceftazidime-avibactam	0.5->64	16	64			
	Ceftolozane-tazobactam	0.25->64	16	>64			
	Ciprofloxacin	0.5->8	2	>8			
	Colistin	≤0.25->8	1	8			
	Meropenem	0.25->64	>64	>64			
<i>Burkholderia cepacia</i> complex ^h (40)	Cefiderocol	≤0.002-32	0.015	0.12			
	Cefepime	0.5->64	32	>64			
	Ceftazidime-avibactam	0.5-32	4	8			
	Ceftolozane-tazobactam	0.25->64	4	32			
	Ciprofloxacin	≤0.12->8	1	>8			

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Table 1 (continued)

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (mg/L) ^a			MIC interpretation ^b		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
	Colistin	1->8	>8	>8			
	Meropenem	0.12-32	4	8	62.5	35.0	2.5

^a MIC₅₀ and MIC₉₀ calculated only for genus or species where >30 isolates were tested. Species of Enterobacteriaceae with <30 isolates were grouped with the overall genus data.

^b Blank spaces mean that there are no CLSI, EUCAST, or FDA MIC breakpoints available for this agent.

^c The 798 isolates of *Klebsiella* spp. were composed of 614 *Klebsiella pneumoniae*, 149 *Klebsiella oxytoca*, and 35 *Klebsiella variicola*.

^d The 377 isolates of *Serratia* spp. were composed of 368 *Serratia marcescens*, 8 *Serratia liquefaciens*, and 1 *Serratia odorifera*.

^e The 372 isolates of *Enterobacter* spp. were composed of 214 *Enterobacter cloacae*, 114 *Enterobacter aerogenes*, 29 *Enterobacter asburiae*, 10 *Enterobacter kobei*, and 5 *Enterobacter ludwigii*.

^f The 175 isolates of *Citrobacter* spp. were composed of 100 *Citrobacter freundii*, 56 *Citrobacter koseri*, 11 *Citrobacter braakii*, 3 *Citrobacter amalonicus*, 3 *Citrobacter farmeri*, 1 *Citrobacter sedlakii*, and 1 *Citrobacter youngae*.

^g The 308 isolates of *Acinetobacter* spp. were composed of 223 *Acinetobacter baumannii*, 66 *Acinetobacter pittii*, and 19 *Acinetobacter nosocomialis*.

^h The 40 isolates of *Burkholderia cepacia* complex were composed of 17 *Burkholderia cepacia*, 13 *Burkholderia cenocepacia*, 7 *Burkholderia multivorans*, 2 *Burkholderia vietnamensis*, and 1 *Burkholderia dolosa*.

of meropenem-non-susceptible *Acinetobacter* spp. had ceftiderocol MICs of ≤ 4 mg/L (Supplementary Figure 8). Against meropenem-susceptible isolates from North America and Europe combined, the MIC₉₀ value for ceftiderocol was 0.5 mg/L ($n=410$); 96.8% (397/410) of meropenem-susceptible *Acinetobacter* spp. had ceftiderocol MICs ≤ 4 mg/L (Supplementary Figure 1). Of the other agents tested against isolates of *Acinetobacter* spp., only colistin demonstrated significant in vitro activity; MIC₉₀ values for both ceftazidime-avibactam and ceftolozane-tazobactam were >64 mg/L for *Acinetobacter* spp. (Tables 1 and 2). Ceftiderocol inhibited 94.2% (567/602) of isolates of cefepime-non-susceptible *Acinetobacter* spp., 94.5% (598/633) of isolates of ciprofloxacin-non-susceptible *Acinetobacter* spp., and 99.1% (113/114) of isolates of colistin-non-susceptible *Acinetobacter* spp. at ≤ 4 mg/L (Supplementary Table 1).

The ceftiderocol MIC₅₀ and MIC₉₀ values for *S. maltophilia* were 0.12 and 0.5 mg/L for North American isolates and 0.12 and 0.25 mg/L for European isolates, respectively; 99.4% (338/340) of all isolates of *S. maltophilia* had ceftiderocol MICs of ≤ 4 mg/L (Tables 1 and 2). In contrast to ceftiderocol, the MIC₉₀ values for cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem were ≥ 64 mg/L and for colistin and ciprofloxacin were ≥ 8 mg/L. CLSI breakpoints have not been established for any of the agents tested in this study against *S. maltophilia*.

The MIC₅₀ and MIC₉₀ values for ceftiderocol against *B. cepacia* complex were 0.015 and 0.12 mg/L for North American isolates and 0.015 and 0.5 mg/L for European isolates, respectively; 94.4% (84/89) of all isolates of *B. cepacia* complex demonstrated ceftiderocol MICs of ≤ 4 mg/L. The five isolates of *B. cepacia* complex with a ceftiderocol MIC ≥ 8 mg/L, all of which were *B. multivorans*, included three isolates from one site in the United Kingdom and one isolate from each of two sites in the United States. Thirty-one of the 89 (34.8%) isolates of *B. cepacia* complex tested were meropenem-non-susceptible (MIC ≥ 8 mg/L); 87.1% (27/31) of meropenem-non-susceptible isolates were inhibited by ceftiderocol at a concentration of ≤ 1 mg/L, the remaining four isolates had ceftiderocol MICs of ≥ 8 mg/L. The ceftiderocol MIC₉₀ for isolates of *B. cepacia* complex was ≥ 16 -fold lower than the MIC₉₀s of cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin, and meropenem. The MIC₉₀ value for ceftiderocol for meropenem-susceptible isolates ($n=58$) was 0.06 mg/L and 98.3% (57/58) of meropenem-susceptible *B. cepacia* complex had ceftiderocol MICs of ≤ 4 mg/L.

4. Discussion

In the current study, 99.4% of isolates of GNB had ceftiderocol MICs ≤ 4 mg/L. The 51 isolates with ceftiderocol MICs ≥ 8 mg/L com-

prised 35 *Acinetobacter* spp., eight Enterobacteriaceae (two isolates each of *E. cloacae*, *E. coli*, and *S. marcescens*, and one isolate each of *C. freundii* and *C. koseri*), five *B. cepacia* complex, two *S. maltophilia*, and one *P. aeruginosa*. The SIDERO-WT-2014 surveillance study previously reported 99.6% (9166/9205) of all isolates of GNB tested had ceftiderocol MICs ≤ 4 mg/L [28]. An earlier study reported that $>98\%$ of 617 clinical isolates of Enterobacteriaceae tested with ceftiderocol MICs ≤ 4 mg/L [24].

Carbapenems may provide effective therapy for patients infected with ESBL-producing Enterobacteriaceae and are considered agents of last resort for many GNB infections. Therefore, determining whether investigational and recently approved agents are active against carbapenem-non-susceptible isolates is important considering the increasing prevalence of these isolates [1–5]. In the current study, ceftiderocol (MIC₉₀, 4 mg/L) demonstrated in vitro potency superior to that of ceftazidime-avibactam (MIC₉₀, ≥ 64 mg/L), ceftolozane-tazobactam (MIC₉₀, >64 mg/L), and cefepime (MIC₉₀, >64 mg/L) against clinical isolates of meropenem-non-susceptible Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* (Table 3), confirming earlier reports [7,24,28,29,31]. Ceftiderocol at a concentration of ≤ 4 mg/L in this study also inhibited 99.6% of isolates of meropenem-non-susceptible Enterobacteriaceae, 99.7% of isolates of meropenem-non-susceptible *P. aeruginosa*, and 96.1% of isolates of meropenem-non-susceptible *Acinetobacter* spp. (Table 3). In vitro susceptibility to ceftazidime-avibactam and ceftolozane-tazobactam was 78.5% and 7.7%, and 72.9% and 73.9%, respectively, for meropenem-non-susceptible isolates of Enterobacteriaceae and *P. aeruginosa* (Table 3). In the SIDERO-WT-2014 surveillance study, most isolates of meropenem-non-susceptible Enterobacteriaceae (97.0%; 164/169), *P. aeruginosa* (100%; 353/353), and *A. baumannii* (96.9%; 744/768) also had ceftiderocol MICs ≤ 4 mg/L [28]. Another study of worldwide clinical isolates of carbapenem-non-susceptible Enterobacteriaceae ($n=1022$) collected from 2014 to 2016 reported a ceftiderocol MIC₉₀ of 4 mg/L with MICs ranging from 0.004 to 32 mg/L and that 97.0% (991/1022) of isolates of carbapenem-non-susceptible Enterobacteriaceae tested with a ceftiderocol MIC of ≤ 4 mg/L [29]. Falagas et al. studied clinical isolates of Enterobacteriaceae ($n=282$), *P. aeruginosa* ($n=82$), and *A. baumannii* ($n=107$) that were carbapenem-resistant and reported all isolates had ceftiderocol MICs ≤ 2 mg/L, and MIC₉₀s were 1, 0.5, and 0.5 mg/L, respectively, for isolates of Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* compared with MIC₉₀s of >64 mg/L for both ceftazidime-avibactam and ceftolozane-tazobactam tested against the same set of isolates [31]. In the current study, colistin was also $>10\%$ less active against meropenem-non-susceptible Enterobacteriaceae (69.5% susceptible) and meropenem-non-susceptible *Acinetobacter* spp. (80.1% susceptible) than against all other isolates (Tables 1 and 3).

Table 2
In vitro activity of cefiderocol and comparators against Gram-negative bacilli isolated by 55 clinical laboratories in Europe in 2015 (n=5352)

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (mg/L) ^a			MIC interpretation ^b		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
Enterobacteriaceae (3543)	Cefiderocol	≤0.002-8	0.25	1			
	Cefepime	≤0.06->64	≤0.06	64	78.8	3.8	17.4
	Ceftazidime-avibactam	≤0.06->64	0.25	0.5	98.5	0	1.6
	Ceftolozane-tazobactam	≤0.06->64	0.25	8	87.4	2.1	10.5
	Ciprofloxacin	≤0.12->8	≤0.12	>8	74.6	1.8	23.6
	Colistin	≤0.25->8	0.5	>8	85.3		14.7
	Meropenem	≤0.06->64	≤0.06	0.12	94.5	0.6	4.9
<i>Klebsiella</i> spp. ^c (1183)	Cefiderocol	≤0.002-4	0.25	1			
	Cefepime	≤0.06->64	≤0.06	>64	67.4	4.3	28.3
	Ceftazidime-avibactam	≤0.06->64	0.25	1	97.6	0	2.5
	Ceftolozane-tazobactam	≤0.06->64	0.25	>64	80.2	2.4	17.4
	Ciprofloxacin	≤0.12->8	≤0.12	>8	66.8	2.0	31.2
	Colistin	≤0.25->8	0.5	1	95.1		4.9
	Meropenem	≤0.06->64	≤0.06	4	87.5	0.9	11.6
<i>Klebsiella pneumoniae</i> (914)	Cefiderocol	≤0.002-4	0.25	2			
	Cefepime	≤0.06->64	0.12	>64	59.6	4.4	36.0
	Ceftazidime-avibactam	≤0.06->64	0.25	1	96.8	0	3.2
	Ceftolozane-tazobactam	≤0.06->64	0.5	>64	75.6	2.7	21.7
	Ciprofloxacin	≤0.12->8	0.25	>8	58.6	2.3	39.1
	Colistin	≤0.25->8	0.5	1	93.7		6.4
	Meropenem	≤0.06->64	≤0.06	16	84.0	1.2	14.8
<i>Klebsiella oxytoca</i> (240)	Cefiderocol	≤0.002-2	0.06	0.5			
	Cefepime	≤0.06-16	≤0.06	1	93.8	4.2	2.1
	Ceftazidime-avibactam	≤0.06-2	0.12	0.5	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.25	1	95.4	1.3	3.3
	Ciprofloxacin	≤0.12->8	≤0.12	0.5	94.6	1.3	4.2
	Colistin	≤0.25-1	0.5	1	100		0
	Meropenem	≤0.06-8	≤0.06	≤0.06	99.2	0	0.8
<i>Escherichia coli</i> (1082)	Cefiderocol	≤0.002-8	0.12	1			
	Cefepime	≤0.06->64	≤0.06	64	79.1	3.6	17.3
	Ceftazidime-avibactam	≤0.06->64	0.12	0.25	99.5	0	0.6
	Ceftolozane-tazobactam	≤0.06->64	0.25	0.5	97.3	0.7	1.9
	Ciprofloxacin	≤0.12->8	≤0.12	>8	64.4	0.7	34.8
	Colistin	≤0.25->8	0.5	1	99.7		0.3
	Meropenem	≤0.06->64	≤0.06	≤0.06	99.4	0.2	0.5
<i>Serratia</i> spp. ^d (417)	Cefiderocol	0.015-2	0.12	0.5			
	Cefepime	≤0.06->64	≤0.06	1	91.6	1.7	6.7
	Ceftazidime-avibactam	≤0.06->64	0.25	0.5	98.8	0	1.2
	Ceftolozane-tazobactam	0.12->64	0.5	1	94.7	1.4	3.8
	Ciprofloxacin	≤0.12->8	≤0.12	1	91.6	2.9	5.5
	Colistin	≤0.25->8	>8	>8	4.3		95.7
	Meropenem	≤0.06->64	≤0.06	0.12	95.9	1.0	3.1
<i>Serratia marcescens</i> (408)	Cefiderocol	0.015-2	0.12	0.5			
	Cefepime	≤0.06->64	≤0.06	1	91.7	1.7	6.6
	Ceftazidime-avibactam	≤0.06->64	0.25	0.5	98.8	0	1.2
	Ceftolozane-tazobactam	0.12->64	0.5	1	94.6	1.5	3.9
	Ciprofloxacin	≤0.12->8	≤0.12	1	91.7	2.9	5.4
	Colistin	≤0.25->8	>8	>8	4.4		95.6
	Meropenem	≤0.06->64	≤0.06	0.12	95.8	1.0	3.2
<i>Enterobacter</i> spp. ^e (561)	Cefiderocol	≤0.002-4	0.25	1			
	Cefepime	≤0.06->64	0.12	16	84.0	5.5	10.5
	Ceftazidime-avibactam	≤0.06->64	0.25	1	97.9	0	2.1
	Ceftolozane-tazobactam	≤0.06-64	0.5	8	77.9	4.6	17.5
	Ciprofloxacin	≤0.12->8	≤0.12	2	88.2	2.1	9.6
	Colistin	≤0.25->8	0.5	8	89.0		11.1
	Meropenem	≤0.06-64	≤0.06	0.12	96.1	0.9	3.0
<i>Enterobacter cloacae</i> (380)	Cefiderocol	≤0.002-4	0.5	1			
	Cefepime	≤0.06->64	0.12	32	78.2	8.2	13.7
	Ceftazidime-avibactam	≤0.06->64	0.25	1	96.8	0	3.2
	Ceftolozane-tazobactam	≤0.06->64	0.5	16	76.3	3.4	20.3
	Ciprofloxacin	≤0.12->8	≤0.12	8	85.5	2.4	12.1
	Colistin	≤0.25->8	0.5	1	94.0		6.1
	Meropenem	≤0.06-64	≤0.06	0.12	95.3	0.8	4.0
<i>Enterobacter aerogenes</i> (130)	Cefiderocol	≤0.002-4	0.12	0.5			
	Cefepime	≤0.06->64	≤0.06	1	95.4	0	4.6
	Ceftazidime-avibactam	≤0.06-8	0.25	1	100	0	0
	Ceftolozane-tazobactam	≤0.06->64	0.5	8	77.7	9.2	13.1
	Ciprofloxacin	≤0.12->8	≤0.12	0.25	93.9	1.5	4.6
	Colistin	≤0.25->8	0.5	0.5	97.7		2.3
	Meropenem	≤0.06-4	≤0.06	0.12	96.9	1.5	1.5
<i>Enterobacter asburiae</i> (40)	Cefiderocol	≤0.002-4	0.5	1			
	Cefepime	≤0.06->64	≤0.06	0.25	97.5	0	2.5
	Ceftazidime-avibactam	≤0.06-1	0.12	0.5	100	0	0
	Ceftolozane-tazobactam	0.12-16	0.25	2	90.0	2.5	7.5
	Ciprofloxacin	≤0.12->8	≤0.12	0.5	92.5	2.5	5.0
	Colistin	≤0.25->8	>8	>8	15.0		85.0
	Meropenem	≤0.06-0.25	≤0.06	0.12	100	0	0

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Table 2 (continued)

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (mg/L) ^a			MIC interpretation ^b		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
<i>Citrobacter</i> spp. ^f (300)	Cefiderocol	≤0.002-8	0.25	0.5			
	Cefepime	≤0.06->64	≤0.06	1	95.0	2.0	3.0
	Ceftazidime-avibactam	≤0.06->64	0.12	0.5	99.0	0	1.0
	Ceftolozane-tazobactam	≤0.06->64	0.25	4	88.0	2.0	10.0
	Ciprofloxacin	≤0.12->8	≤0.12	0.5	93.0	2.3	4.7
	Colistin	≤0.25-2	0.5	1	100	0	0
	Meropenem	≤0.06-16	≤0.06	≤0.06	99.3	0	0.7
<i>Citrobacter freundii</i> (152)	Cefiderocol	≤0.002-8	0.12	1			
	Cefepime	≤0.06->64	≤0.06	2	92.8	3.3	4.0
	Ceftazidime-avibactam	≤0.06->64	0.25	1	98.0	0	2.0
	Ceftolozane-tazobactam	0.12->64	0.25	16	78.3	2.6	19.1
	Ciprofloxacin	≤0.12->8	≤0.12	2	86.8	4.6	8.6
	Colistin	≤0.25-2	0.5	1	100	0	0
	Meropenem	≤0.06-16	≤0.06	≤0.06	98.7	0	1.3
<i>Citrobacter koseri</i> (113)	Cefiderocol	0.12-1	0.5	0.5			
	Cefepime	≤0.06-1	≤0.06	0.12	100	0	0
	Ceftazidime-avibactam	≤0.06-4	0.12	0.25	100	0	0
	Ceftolozane-tazobactam	≤0.06-16	0.25	0.5	99.1	0	0.9
	Ciprofloxacin	≤0.12-0.5	≤0.12	≤0.12	100	0	0
	Colistin	≤0.25-2	≤0.25	0.5	100	0	0
	Meropenem	≤0.06-0.5	≤0.06	≤0.06	100	0	0
<i>Pseudomonas aeruginosa</i> (921)	Cefiderocol	≤0.002-8	0.12	0.5			
	Cefepime	≤0.06->64	4	16	78.6	11.6	9.8
	Ceftazidime-avibactam	≤0.06->64	2	16	89.8	0	10.2
	Ceftolozane-tazobactam	≤0.06->64	0.5	8	89.6	0.9	9.6
	Ciprofloxacin	≤0.12->8	0.25	>8	71.0	4.0	25.0
	Colistin	≤0.25->8	1	1	99.4	0	0.6
	Meropenem	≤0.06->64	0.5	16	71.1	6.3	22.6
<i>Acinetobacter</i> spp. (664)	Cefiderocol	≤0.002->256	0.25	2			
	Cefepime	≤0.06->64	32	>64	28.2	13.0	58.9
	Ceftazidime-avibactam	≤0.06->64	32	>64			
	Ceftolozane-tazobactam	≤0.06->64	16	>64			
	Ciprofloxacin	≤0.12->8	>8	>8	24.4		75.6
	Colistin	≤0.25->8	0.5	>8	84.6		15.4
	Meropenem	≤0.06->64	32	>64	32.8	0.9	66.3
<i>Acinetobacter baumannii</i> (614)	Cefiderocol	≤0.002->256	0.25	2			
	Cefepime	≤0.06->64	32	>64	22.8	13.8	63.4
	Ceftazidime-avibactam	≤0.06->64	32	>64			
	Ceftolozane-tazobactam	≤0.06->64	16	>64			
	Ciprofloxacin	≤0.12->8	>8	>8	19.5	0	80.5
	Colistin	≤0.25->8	0.5	>8	83.4		16.6
	Meropenem	≤0.06->64	64	>64	27.9	1.0	71.2
<i>Acinetobacter pittii</i> (45)	Cefiderocol	0.008-1	0.12	0.5			
	Cefepime	0.5-16	4	8	97.8	2.2	0
	Ceftazidime-avibactam	1-16	8	16			
	Ceftolozane-tazobactam	≤0.06-4	0.5	2			
	Ciprofloxacin	≤0.12->8	0.25	8	86.7	0	13.3
	Colistin	≤0.25-1	0.5	1	100	0	0
	Meropenem	0.12-32	0.25	0.5	97.8	0	2.2
<i>Stenotrophomonas maltophilia</i> (175)	Cefiderocol	≤0.002-64	0.12	0.25			
	Cefepime	0.5->64	32	64			
	Ceftazidime-avibactam	0.5->64	16	64			
	Ceftolozane-tazobactam	0.25->64	16	>64			
	Ciprofloxacin	0.25->8	2	8			
	Colistin	≤0.25->8	1	>8			
	Meropenem	0.5->64	>64	>64			
<i>Burkholderia cepacia</i> complex ^h (49)	Cefiderocol	≤0.002-32	0.015	0.5			
	Cefepime	≤0.06->64	16	>64			
	Ceftazidime-avibactam	0.25-32	4	8			
	Ceftolozane-tazobactam	0.25->64	2	32			
	Ciprofloxacin	≤0.12->8	2	>8			
	Colistin	≤0.25->8	>8	>8			
	Meropenem	1-64	4	16	67.4	20.4	12.2

^a MIC₅₀ and MIC₉₀ calculated only for genus or species where >30 isolates were tested. Species of Enterobacteriaceae with <30 isolates were grouped with the overall genus data.

^b Blank spaces mean that there are no CLSI, EUCAST, or FDA MIC breakpoints available for this agent.

^c The 1183 isolates of *Klebsiella* spp. were composed of 914 *Klebsiella pneumoniae*, 240 *Klebsiella oxytoca*, and 29 *Klebsiella varicola*.

^d The 417 isolates of *Serratia* spp. were composed of 408 *Serratia marcescens*, 7 *Serratia liquefaciens*, 1 *Serratia rubidaea*, and 1 *Serratia*, non-specified.

^e The 561 isolates of *Enterobacter* spp. were composed of 380 *Enterobacter cloacae*, 130 *Enterobacter aerogenes*, 40 *Enterobacter asburiae*, 6 *Enterobacter kobei*, 4 *Enterobacter ludwigii*, and 1 *Enterobacter*, non-specified.

^f The 300 isolates of *Citrobacter* spp. were composed of 152 *Citrobacter freundii*, 113 *Citrobacter koseri*, 25 *Citrobacter braakii*, 6 *Citrobacter amalonaticus*, 2 *Citrobacter farmeri*, 1 *Citrobacter murlinae*, and 1 *Citrobacter sedlakii*.

^g The 664 isolates of *Acinetobacter* spp. were composed of 614 *Acinetobacter baumannii*, 45 *Acinetobacter pittii*, and 5 *Acinetobacter nosocomialis*.

^h The 49 *Burkholderia cepacia* complex were composed of 28 *Burkholderia cepacia*, 13 *Burkholderia multivorans*, and 8 *Burkholderia cenocepacia*.

Table 3

In vitro activities of ceftiderocol and comparative agents against clinical isolates of meropenem-nonsusceptible Gram-negative bacilli from North America and Europe, combined data

Family/genus/species (no. of isolates)	Antimicrobial agent	MIC (mg/L) ^a			MIC interpretation ^b		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
Enterobacteriaceae ^c (246)	Ceftiderocol	0.008-8	1	4			
	Cefepime	≤0.06->64	>64	>64	8.5	8.9	82.5
	Ceftazidime-avibactam	0.12->64	1	>64	78.5	0	21.5
	Ceftolozane-tazobactam	0.25->64	>64	>64	7.7	3.3	89.0
	Ciprofloxacin	≤0.12->8	>8	>8	12.6	3.3	84.2
	Colistin	≤0.25->8	0.5	>8	69.5	0	30.5
	Meropenem	2->64	16	>64	0	10.2	89.8
<i>K. pneumoniae</i> (165)	Ceftiderocol	0.015-4	1	4			
	Cefepime	0.25->64	>64	>64	1.8	5.5	92.7
	Ceftazidime-avibactam	0.25->64	1	>64	82.4		17.6
	Ceftolozane-tazobactam	1->64	>64	>64	0.6	1.2	98.2
	Ciprofloxacin	≤0.12->8	>8	>8	1.2	1.8	97.0
	Colistin	≤0.25->8	0.5	>8	72.7		27.3
	Meropenem	2->64	16	>64	0	6.7	93.3
<i>S. marcescens</i> (30)	Ceftiderocol	0.03-2	0.25	1			
	Cefepime	≤0.06->64	8	>64	30.0	23.3	46.7
	Ceftazidime-avibactam	0.12->64	0.5	>64	80.0		20.0
	Ceftolozane-tazobactam	0.5->64	8	>64	36.7	6.7	56.7
	Ciprofloxacin	≤0.12->8	2	>8	46.7	3.3	50.0
	Colistin	0.5->8	>8	>8	3.3		96.7
	Meropenem	2->64	32	>64	0	16.7	83.3
<i>P. aeruginosa</i> (395)	Ceftiderocol	≤0.002-8	0.25	1			
	Cefepime	≤0.06->64	16	64	47.1	26.6	26.3
	Ceftazidime-avibactam	0.25->64	4	64	72.9	0	27.1
	Ceftolozane-tazobactam	0.25->64	1	>64	73.9	3.0	23.0
	Ciprofloxacin	≤0.12->8	8	>8	36.7	5.8	57.5
	Colistin	≤0.25->8	1	1	98.7	0.5	0.8
	Meropenem	4->64	8	>64	0	25.8	74.2
<i>Acinetobacter</i> spp. ^d (562)	Ceftiderocol	≤0.002->256	0.5	2			
	Cefepime	0.12->64	64	>64	4.8	15.5	79.7
	Ceftazidime-avibactam	1->64	64	>64			
	Ceftolozane-tazobactam	1->64	32	>64			
	Ciprofloxacin	4->8	>8	>8	0.2	0	99.8
	Colistin	≤0.25->8	0.5	>8	80.3		19.8
	Meropenem	4->64	64	>64	0	1.4	98.6
<i>Burkholderia cepacia</i> complex ^e (31)	Ceftiderocol	≤0.002-32	0.06	8			
	Cefepime	≤0.06->64	64	>64			
	Ceftazidime-avibactam	0.25-32	4	8			
	Ceftolozane-tazobactam	0.5->64	4	32			
	Ciprofloxacin	0.25->8	4	>8			
	Colistin	8->8	>8	>8			
	Meropenem	8-64	8	162	0	77.4	22.6

^a MIC₅₀ and MIC₉₀ values for individual genus or species were calculated when >30 isolates were tested. Species of Enterobacteriaceae with <30 isolates were grouped together as genus data.

^b Blank spaces indicate that CLSI, EUCAST, and FDA MIC breakpoints were not available for this agent.

^c The 246 isolates of Enterobacteriaceae were composed of 165 *Klebsiella pneumoniae*, 30 *Serratia marcescens*, 21 *Enterobacter cloacae*, 13 *Escherichia coli*, 7 *Citrobacter freundii*, 5 *Enterobacter aerogenes*, 4 *Klebsiella oxytoca*, and 1 *Klebsiella varicola*.

^d *Acinetobacter* spp. were composed of 558 isolates of *Acinetobacter baumannii*, 2 isolates of *Acinetobacter nosocomialis*, and 2 isolates of *Acinetobacter pittii*.

^e The 31 isolates of *Burkholderia cepacia* complex were composed of 16 *Burkholderia cepacia*, 9 *Burkholderia cenocepacia*, 5 *Burkholderia multivorans*, and 1 *Burkholderia dolosa*.

We observed that ceftiderocol at ≤4 mg/L inhibited 98.2% of isolates of ceftazidime-avibactam-nonsusceptible Enterobacteriaceae and 98.8% of isolates of ceftolozane-tazobactam-nonsusceptible Enterobacteriaceae (Table 4), similar to a previous report [29], as well as 99.5% of isolates of cefepime-nonsusceptible Enterobacteriaceae and 99.7% of isolates of ciprofloxacin-nonsusceptible Enterobacteriaceae at ≤4 mg/L (Supplementary Table 1). All ceftazidime-avibactam-nonsusceptible *P. aeruginosa* and all ceftolozane-tazobactam-nonsusceptible isolates of *P. aeruginosa* had ceftiderocol MICs ≤4 mg/L (Table 4), confirming results from an earlier study [29]. Ceftiderocol at ≤4 mg/L also inhibited 99.7% of isolates of cefepime-nonsusceptible *P. aeruginosa* and 99.8% of isolates of ciprofloxacin-nonsusceptible *P. aeruginosa* (Supplementary Table 1).

In the current study, rates of colistin-nonsusceptibility were 15.5%, 11.7%, and 0.5% for Enterobacteriaceae, *Acinetobacter* spp., and *P. aeruginosa*, respectively, and 24.1% and 95.5% of isolates of *S. maltophilia* and *B. cepacia* complex had colistin MICs ≥4 mg/L. Ceftiderocol MICs were ≤4 mg/L for 99.8%, 99.1%, and 100% of isolates of colistin-nonsusceptible Enterobacteriaceae, *Acinetobacter* spp. (Supplementary Table 1), and *P. aeruginosa*, respectively, as well as for 99.4% and 94.4% of all isolates of *S. maltophilia* and *B. cepacia* complex, respectively, indicating that cross resistance does not occur between colistin and ceftiderocol in any of the genera/species of GNB studied.

The current study showed that ceftiderocol was the most potent agent tested against *S. maltophilia* (MIC₉₀, 0.5 mg/L) whereas the six comparator agents, including ceftazidime-avibactam,

Table 4

In vitro activities of ceftiderocol and comparative agents against clinical isolates of Enterobacteriaceae and *P. aeruginosa* that demonstrated non-susceptibility to ceftazidime-avibactam or ceftolozane-tazobactam, North America and Europe, combined data

Antimicrobial susceptibility phenotype (no. of isolates)	Antimicrobial agent	MIC (mg/L)			MIC interpretation ^a		
		Range	MIC ₅₀	MIC ₉₀	% Susceptible	% Intermediate	% Resistant
Enterobacteriaceae							
Non-susceptible to ceftazidime-avibactam (57)							
	Ceftiderocol	0.12-8	1	4			
	Cefepime	0.12->64	>64	>64	3.5	1.8	94.7
	Ceftazidime-avibactam	16->64	>64	>64	0		100
	Ceftolozane-tazobactam	0.12->64	>64	>64	3.5	1.8	94.7
	Ciprofloxacin	≤0.12->8	>8	>8	17.5	3.5	78.9
	Colistin	≤0.25->8	0.5	8	84.7		15.3
	Meropenem	≤0.06->64	32	>64	7.0	3.5	89.5
Non-susceptible to ceftolozane-tazobactam (597)							
	Ceftiderocol	0.008-128	1	2			
	Cefepime	≤0.06->64	32	>64	25.6	15.6	58.8
	Ceftazidime-avibactam	≤0.06->64	1	8	90.8		9.2
	Ceftolozane-tazobactam	4->64	32	>64	0	18.3	81.7
	Ciprofloxacin	≤0.12->8	>8	>8	38.4	2.0	59.6
	Colistin	≤0.25->8	0.5	>8	83.1		16.9
	Meropenem	≤0.06->64	0.12	64	62.0	3.4	34.7
<i>P. aeruginosa</i>							
Non-susceptible to ceftazidime-avibactam (113)							
	Ceftiderocol	0.008-4	0.25	1			
	Cefepime	4->64	32	>64	5.3	24.8	69.9
	Ceftazidime-avibactam	16->64	32	>64	0		100
	Ceftolozane-tazobactam	0.5->64	>64	>64	21.2	6.2	72.6
	Ciprofloxacin	≤0.12->8	>8	>8	12.4	4.4	83.2
	Colistin	≤0.25-4	1	1	99.1		0.9
	Meropenem	0.12->64	64	>64	5.3	4.4	90.3
Non-susceptible to ceftolozane-tazobactam (111)							
	Ceftiderocol	0.004-4	0.25	1			
	Cefepime	1->64	32	>64	6.3	20.7	73.0
	Ceftazidime-avibactam	1->64	32	>64	19.8		80.2
	Ceftolozane-tazobactam	8->64	>64	>64	0	13.5	86.5
	Ciprofloxacin	≤0.12->8	>8	>8	12.6	3.6	83.8
	Colistin	≤0.25-4	1	1	99.1		0.9
	Meropenem	0.12->64	64	>64	7.2	5.4	87.4

^a Blank spaces indicate that CLSI, EUCAST, and FDA MIC breakpoints were not available for this agent.

ceftolozane-tazobactam, and colistin, were inactive (Tables 1 and 2), which confirms earlier observations of MIC₉₀s of 0.25-0.5 mg/L and 100% of isolates inhibited by ceftiderocol at ≤4 mg/L [28,29]. Our observations that 94.4% of all isolates of *B. cepacia* complex and 87.1% of meropenem-non-susceptible isolates of *B. cepacia* complex had ceftiderocol MICs ≤4 mg/L (Tables 1-3) also agree with data presented in previous studies where ceftiderocol MICs ranged from 0.004 to 16 mg/L for isolates of *B. cepacia* [28,29].

Data have been published describing the in vitro activity of ceftiderocol against MDR Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* [9,29]. Dobias et al. tested ceftiderocol against a collection of 753 MDR GNB clinical isolates (621 Enterobacteriaceae, 87 *A. baumannii*, 45 *P. aeruginosa*) from hospitals worldwide and reported the MIC₅₀ and MIC₉₀ of ceftiderocol to be 0.5 and 2 mg/L compared with 1 and >64 mg/L, 64 and >64 mg/L, 8 and >64 mg/L, >16 and >16 mg/L, and <0.5 and 8 mg/L, respectively, for ceftazidime-avibactam, ceftolozane-tazobactam, meropenem, cefepime, and colistin; and that 20 of the 753 isolates (2.7%) had MICs to ceftiderocol of ≥8 mg/L [9]. A second study of MDR GNB reported the MIC₉₀s for ceftiderocol for MDR *A. baumannii* and MDR *P. aeruginosa* as 8 and 1 mg/L, respectively, with 89.7% (330/368) and 99.2% (260/262) of isolates demonstrating ceftiderocol MICs ≤4 mg/L [29].

5. Conclusions

Ceftiderocol demonstrated potent in vitro activity (MIC ≤4 mg/L) against frequently encountered clinical isolates of GNB, including carbapenem-resistant isolates. At a concentration of ≤4 mg/L, ceftiderocol inhibited 99.4% of all isolates of GNB tested, including 99.9% of Enterobacteriaceae and *P. aeruginosa*, 99.4% of

S. maltophilia, 97.6% of *Acinetobacter* spp., and 94.4% of *B. cepacia* complex. Importantly, there was no cross resistance between ceftiderocol and colistin. The demonstrated activity of ceftiderocol against GNB with carbapenem-non-susceptible and MDR phenotypes, its stability to hydrolysis against isolates known to harbor ESBLs, Ambler class A, B, C, and D carbapenemases, and its activity against isolates resistant to carbapenems by alternate mechanisms [7,9,24-31] clearly warrants further clinical development of ceftiderocol as a potentially significant treatment option for patients infected with antimicrobial-resistant GNB.

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Competing Interests

JAK is a consultant to IHMA. MAH and DFS are employees of IHMA. MT and YY, and RE are employees of Shionogi & Co., Ltd. and Shionogi Inc., respectively. The IHMA authors do not have personal financial interests in Shionogi & Co., Ltd.

Ethical Approval

Not required

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.11.007.

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