



Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli

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Abstract

Cefiderocol is an injectable siderophore cephalosporin discovered and being developed by Shionogi & Co., Ltd., Japan. As with other β -lactam antibiotics, the principal antibacterial/bactericidal activity of cefiderocol occurs by inhibition of Gram-negative bacterial cell wall synthesis by binding to penicillin binding proteins; however, it is unique in that it enters the bacterial periplasmic space as a result of its siderophore-like property and has enhanced stability to β -lactamases. The chemical structure of cefiderocol is similar to both ceftazidime and cefepime, which are third- and fourth-generation cephalosporins, respectively, but with high stability to a variety of β -lactamases, including AmpC and extended-spectrum β -lactamases (ESBLs). Cefiderocol has a pyrrolidinium group in the side chain at position 3 like cefepime and a carboxypropanoxyimino group in the side chain at position 7 of the cephem nucleus like ceftazidime. The major difference in the chemical structures of cefiderocol, ceftazidime and cefepime is the presence of a catechol group on the side chain at position 3. Together with the high stability to β -lactamases, including ESBLs, AmpC and carbapenemases, the microbiological activity of cefiderocol against aerobic Gram-negative bacilli is equal to or superior to that of ceftazidime-avibactam and meropenem, and it is active against a variety of Ambler class A, B, C and D β -lactamases. Cefiderocol is also more potent than both ceftazidime-avibactam and meropenem versus *Acinetobacter baumannii*, including meropenem non-susceptible and multidrug-resistant (MDR) isolates. Cefiderocol's activity against meropenem-non-susceptible and *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriales is comparable or superior to ceftazidime-avibactam. Cefiderocol is also more potent than both ceftazidime-avibactam and meropenem against all resistance phenotypes of *Pseudomonas aeruginosa* and against *Stenotrophomonas maltophilia*. The current dosing regimen being used in phase III studies is 2 g administered intravenously every 8 h (q8 h) using a 3-h infusion. The pharmacokinetics of cefiderocol are best described by a three-compartment linear model. The mean plasma half-life ($t_{1/2}$) was ~ 2.3 h, protein binding is 58%, and total drug clearance ranged from 4.6–6.0 L/h for both single- and multi-dose infusions and was primarily renally excreted unchanged (61–71%). Cefiderocol is primarily renally excreted unchanged and clearance correlates with creatinine clearance. Dosage adjustment is thus required for both augmented renal clearance and in patients with moderate to severe renal impairment. In vitro and in vivo pharmacodynamic studies have reported that as with other cephalosporins the pharmacodynamic index that best predicts clinical outcome is the percentage of time that free drug concentrations exceed the minimum inhibitory concentration (%fT > MIC). In vivo efficacy of cefiderocol has been studied in a variety of humanized drug exposure murine and rat models of infection utilizing a variety of MDR and extremely drug resistant strains. Cefiderocol has performed similarly to or has been superior to comparator agents, including ceftazidime and cefepime. A phase II prospective, multicenter, double-blind, randomized clinical trial assessed the safety and efficacy of cefiderocol 2000 mg q8 h versus imipenem/cilastatin 1000 mg q8 h, both administered intravenously for 7–14 days over 1 h, in the treatment of complicated urinary tract infection (cUTI, including pyelonephritis) or acute uncomplicated pyelonephritis in hospitalized adults. A total of 452 patients were initially enrolled in the study, with 303 in the cefiderocol arm and 149 in the imipenem/cilastatin arm. The primary outcome measure was a composite of clinical cure and microbiological eradication at the test-of-cure (TOC) visit, that is, 7 days after the end of treatment in the microbiological intent-to-treat (MITT) population. Secondary outcome measures included microbiological response per pathogen and per patient at early assessment (EA), end of treatment (EOT), TOC, and follow-up (FUP); clinical

response per pathogen and per patient at EA, EOT, TOC, and FUP; plasma, urine and concentrations of cefiderocol; and the number of participants with adverse events. The composite of clinical and microbiological response rates was 72.6% (183/252) for cefiderocol and 54.6% (65/119) for imipenem/cilastatin in the MITT population. Clinical response rates per patient at the TOC visit were 89.7% (226/252) for cefiderocol and 87.4% (104/119) for imipenem/cilastatin in the MITT population. Microbiological eradication rates were 73.0% (184/252) for cefiderocol and 56.3% (67/119) for imipenem/cilastatin in the MITT population. Additionally, two phase III clinical trials are currently being conducted by Shionogi & Co., Ltd., Japan. The two trials are evaluating the efficacy of cefiderocol in the treatment of serious infections in adult patients caused by carbapenem-resistant Gram-negative pathogens and evaluating the efficacy of cefiderocol in the treatment of adults with hospital-acquired bacterial pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia caused by Gram-negative pathogens. Cefiderocol appears to be well tolerated (minor reported adverse effects were gastrointestinal and phlebitis related), with a side effect profile that is comparable to other cephalosporin antimicrobials. Cefiderocol appears to be well positioned to help address the increasing number of infections caused by carbapenem-resistant and MDR Gram-negative bacilli, including ESBL- and carbapenemase-producing strains (including metallo- β -lactamase producers). A distinguishing feature of cefiderocol is its activity against resistant *P. aeruginosa*, *A. baumannii*, *S. maltophilia* and *Burkholderia cepacia*.

Key Points

Cefiderocol is an injectable siderophore cephalosporin discovered by and being developed by Shionogi & Co., Ltd., Japan.

Cefiderocol has intrinsic structural stability against a variety of Ambler class A, C, and D β -lactamases, and it is the first agent with activity versus class B β -lactamases. This confers upon it activity against multidrug-resistant (MDR) Gram-negative bacilli, including MDR Enterobacteriales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, all while possessing a safety and tolerability profile similar to other cephalosporins.

Cefiderocol is well positioned to help address the increasing number of infections caused by carbapenem-resistant and MDR Gram-negative bacilli, including extended-spectrum β -lactamase- and carbapenemase-producing strains (including metallo- β -lactamase producers).

inhibitor combinations (ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam) or older agents such as aminoglycosides are active against isolates of Gram-negative bacilli harboring Ambler class B metallo- β -lactamases, and these treatments may have limited activity against class D (OXA) β -lactamases [6–9]. Ceftolozane-tazobactam is also inactive against *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriales [6]. Other agents used to treat patients infected with carbapenem-resistant Gram-negative bacilli, such as amikacin, colistin, and 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 Enterobacteriales, including *Morganella morganii*, *Proteus* spp., *Providencia* spp., and *Serratia* spp. The list of pathogens with intrinsic resistance to tigecycline also includes *P. aeruginosa*. New agents, ideally with unique mechanisms of action and low propensities for resistance development, are required to address evolving resistance in Gram-negative bacilli [10].

Cefiderocol (formerly S-649266) is an investigational, parenteral catechol substituted siderophore cephalosporin that possesses potent activity against carbapenem-resistant and MDR Enterobacteriales, and non-fermentative Gram-negative bacilli, and is currently in phase III of clinical development for the treatment of serious Gram-negative infections, including infections caused by carbapenem-resistant and MDR Gram-negative bacteria [11]. Shionogi & Co., Ltd., Japan, the developer of cefiderocol, has completed a phase II clinical trial demonstrating clinical efficacy and safety of intravenous (IV) cefiderocol compared to imipenem/cilastatin in patients with complicated urinary tract infections (cUTIs) [12]. Clinical trials are also underway to evaluate the efficacy of cefiderocol in the treatment of healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and

1 Introduction

Carbapenems are broad-spectrum β -lactam antimicrobial agents that serve an integral role as agents frequently used as a last resort to treat infections caused by extended-spectrum β -lactamase (ESBL)-producing Enterobacteriales and multidrug-resistant (MDR) Gram-negative bacilli [1]. The emergence and dissemination of carbapenem-resistant Enterobacteriales and non-fermentative Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* is an increasingly important global public health concern [2–5]. No new β -lactam/ β -lactamase

ventilator-associated pneumonia (VAP) caused by Gram-negative bacteria, and to provide clinical evidence of efficacy of cefiderocol in the treatment of serious infections caused by carbapenem-resistant Gram-negative pathogens in adult patients (<http://clinicaltrials.gov>, identifiers NCT02321800, NCT02714595 and NCT03032380).

This article will review the existing published data for cefiderocol, including information on its chemistry, mechanism of action, mechanisms of resistance, microbiology, pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety data from animal models and human clinical trials, adverse effects, and place in therapy. Literature for this review was obtained through a comprehensive search of SCOPUS, MEDLINE and databases from scientific meetings from 2014 to 2018, for all materials containing the name “cefiderocol” or “S-649266.” These results were supplemented by bibliographies obtained from Shionogi & Co., Ltd., Japan.

2 Chemistry

The chemical structure of cefiderocol is shown in Fig. 1 in comparison to ceftazidime. The structural components responsible for the antibacterial activity of cefiderocol are highlighted in Fig. 2. As can be seen, cefiderocol's structure is related to both ceftazidime and cefepime. Similar to ceftazidime, cefiderocol's 7-position side chain is an amino-acyl group with an aminothiazole ring and a carboxypropyl-oxyimino chain attached to the alpha carbon. The aminothiazole ring, common to many extended-spectrum cephalosporins, provides enhanced activity against Gram-negative bacilli [13]. The carboxypropyl-oxyimino group confers stability against hydrolysis by β -lactamases and is responsible for increased activity versus Gram-negative bacilli, including *P. aeruginosa* [13, 14]. The principle distinction between cefiderocol and ceftazidime and cefepime lies in the 3-position side chain. Cefiderocol contains a catechol 2-chloro-3,4-dihydroxybenzoic acid moiety that is covalently bound to the pyrrolidine ring to form a quaternary ammonium at the 3-position via a non-cleavable linker. The catechol side

chain confers increased periplasmic concentrations of cefiderocol compared to ceftazidime and cefepime due to the ability of the two adjacent hydroxy groups at positions 3 and 4 of the aromatic ring to chelate ferric iron [15] and to take advantage of the utilization of iron transportation systems present in the outer membrane of Gram-negative bacilli. The pyrrolidine present on the 3-position side confers zwitterionic properties to cefiderocol that enhance its water solubility [13].

3 Mechanism of Action

The side chain at position 3 of cefiderocol (Figs. 1, 2) promotes formation of chelated complexes with ferric iron and thereby facilitates siderophore-like transport across the outer membrane of Gram-negative bacilli using iron transport systems [15–17]. Active iron transport systems, such as PiuA in *P. aeruginosa* [16], deliver cefiderocol across the outer membrane and to the periplasmic space, where the iron atom dissociates and enters the cytoplasm by crossing the cytoplasmic membrane (Fig. 3). Cefiderocol is released in the periplasmic space and binds to penicillin binding proteins (PBPs), primarily to PBP3, similar to other oxyimino-cephalosporins, and inhibits peptidoglycan synthesis, causing cell death [11, 15–17]. Most other β -lactams cross the outer membrane of Gram-negative bacilli by passive diffusion through porin-mediated channels [17]. Cefiderocol's unique mechanism of action is the result of different properties; (1) siderophore-like cell entry (sometimes referred to as a “Trojan horse strategy”), creating a high concentration of drug at the site of action, and (2) stability to hydrolysis by nearly all β -lactamases, including both serine- and metallo- β -lactamases, account for its enhanced antimicrobial activity compared to carbapenems, β -lactam/ β -lactamase inhibitor combinations, and advanced-generation cephalosporins [11, 17–19].

Studies evaluating the PBP inhibition profile of cefiderocol in Gram-negative bacilli demonstrated that in *P. aeruginosa* and *Escherichia coli*, cefiderocol inhibits PBP3

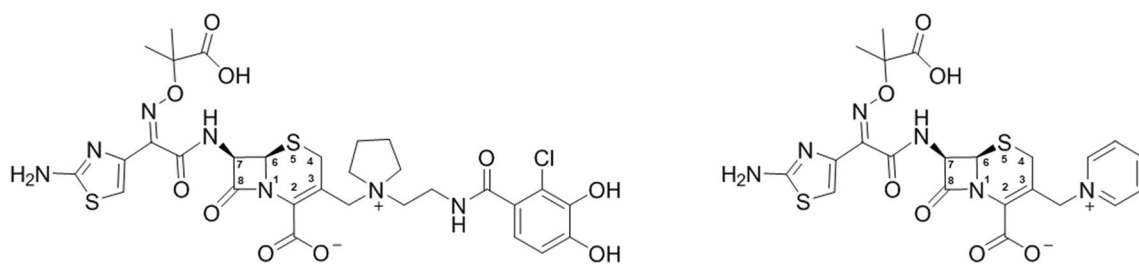


Fig. 1 Chemical structures of cefiderocol (left) and ceftazidime (right)

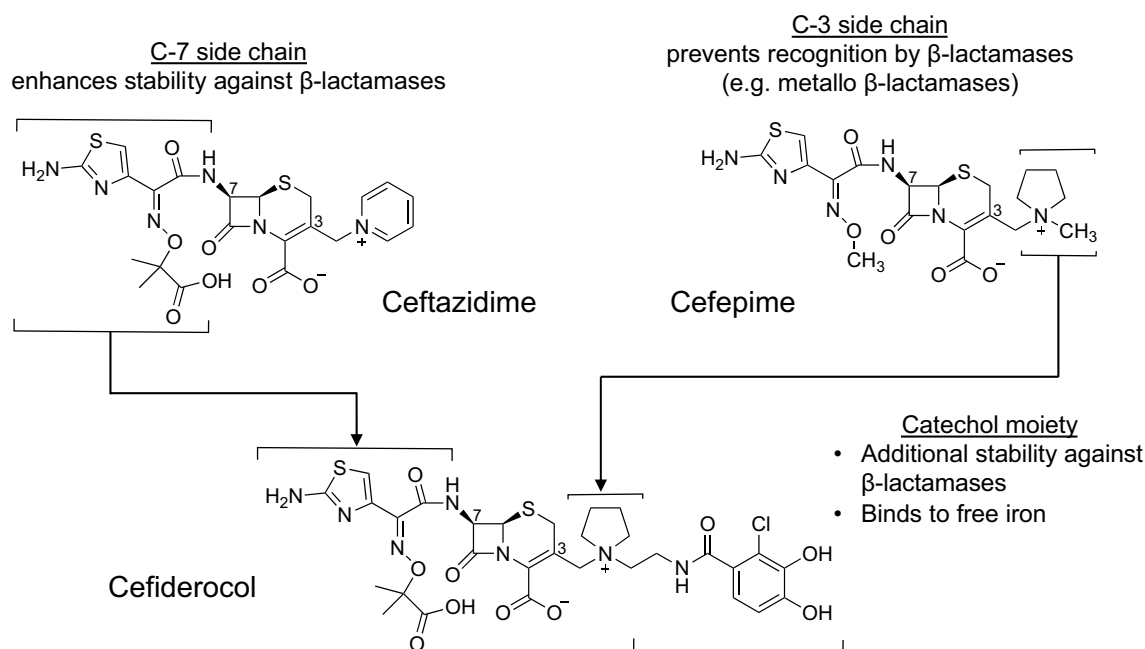


Fig. 2 Cefiderocol structure activity relationships

as well as PBP1a, PBP1b, and PBP2 [16]. Cefiderocol's potent inhibition of PBP3 was demonstrated by comparing its 50% inhibitory concentrations (IC_{50} s) (mean PBP3 IC_{50} of *E. coli* = 0.04 mg/L; mean PBP3 IC_{50} of *P. aeruginosa* = 0.06 mg/L) to the IC_{50} s of ceftazidime (mean PBP3 IC_{50} of *E. coli* = 0.45 mg/L; mean PBP3 IC_{50} of *P. aeruginosa* = 0.09 mg/L) [16].

4 Mechanisms of Resistance

β -Lactam and specifically carbapenem resistance in Gram-negative bacilli can arise due to a variety of mechanisms, including β -lactamases, PBP mutations, efflux, and reduced permeability due to outer membrane porin loss or mutation [20].

β -Lactamases are the most important contributors to β -lactam resistance in Enterobacteriales [21]. β -Lactamases are frequently classified into four Ambler (molecular) classes (namely classes A, B, C, and D) based on differences in their protein sequences and their ability to hydrolyze specific β -lactam classes [22]. Classes A, C (AmpC), and D β -lactamases have serine-based active sites. Class B enzymes, known as metallo- β -lactamases, have zinc-based active sites. Carbapenemases are classified into three of the four Ambler classes: class A (e.g., KPC), class B (e.g., NDM, VIM, and IMP), and class D (e.g., OXA-48) enzymes. Currently KPCs have the greatest global distribution of all carbapenemases associated with Enterobacteriales [23, 24]. AmpC β -lactamases and ESBLs (a subset

of class A β -lactamases) may confer carbapenem resistance to isolates of Gram-negative bacilli when combined with porin loss/mutation, overexpression of efflux pumps, and/or alterations in PBPs. In *P. aeruginosa*, downregulation of the outer membrane porin OprD, which significantly reduces the uptake of β -lactams to the periplasmic space, in combination with an AmpC or class A or class D β -lactamase is the most common mechanism of carbapenem resistance [25].

Cefiderocol's novel mechanism of periplasmic entry via active iron transport systems has been shown to overcome β -lactam resistance associated with outer membrane permeability mutations in *P. aeruginosa*. Ito et al. studied OprD-deficient strains to assess the influence on the uptake of cefiderocol in *P. aeruginosa* PAO1 [26]. The minimum inhibitory concentration (MIC) of cefiderocol increased two-fold from 0.12 mg/L (wild-type PAO1) to 0.25 mg/L in the OprD-deficient mutant. The same study also examined the effect of PiuA iron transporter deficiency on the periplasmic uptake of cefiderocol *P. aeruginosa*. A mutation to the *piuA* transporter increased the cefiderocol MIC 0.12–2 mg/L [26], suggesting that *piuA* iron transporter mutations could be a potential mechanism of resistance development against cefiderocol in *P. aeruginosa*. Ito et al. also assessed the uptake of cefiderocol into a strain of *E. coli* (BW25113) with mutations in its *cirA* and *fliu* iron transporter genes [27]. Cefiderocol MICs were unchanged or increased twofold when mutations to each iron transporter gene were assessed individually (wild-type MIC = 0.06 mg/L; *cirA* mutation MIC = 0.06 mg/L; *fliu* mutation MIC = 0.12 mg/L). However,

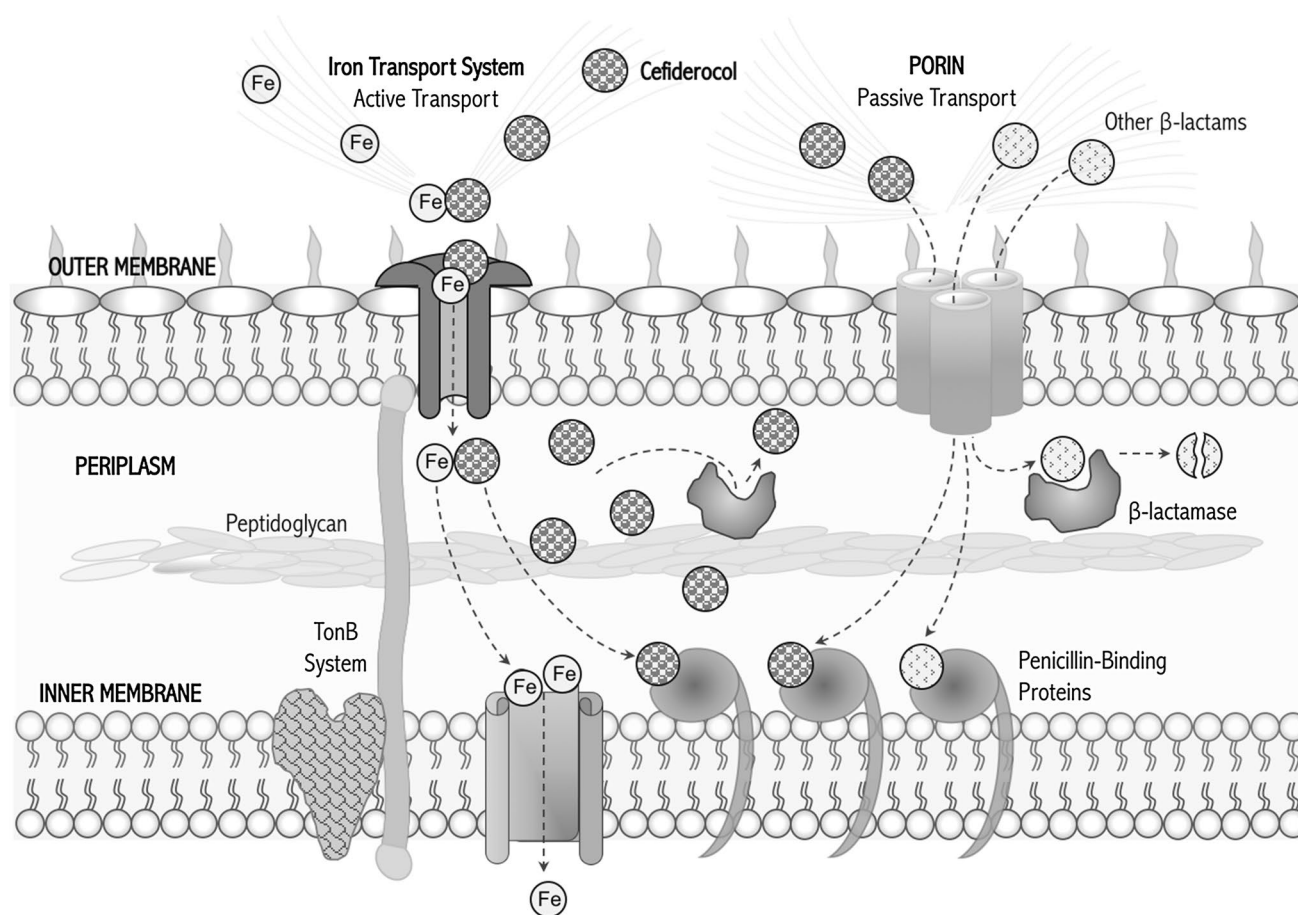


Fig. 3 Mechanism of action of cefiderocol against Gram-negative bacilli

a strain with mutations in both *cirA* and *fliu* transporter genes increased the cefiderocol MIC to 1 mg/L.

In addition to intrinsic and acquired plasmid-mediated resistance mechanisms, suboptimal exposure of bacterial cells to an antimicrobial agent may facilitate resistance development [28]. One method to assess potential resistance development with therapy is to perform serial passage studies in which bacteria grown in broth media are exposed to sub-MIC antimicrobial concentrations for multiple bacterial generations [29]. Kohira et al. conducted a ten-generation serial passage study using cefiderocol, ceftazidime, and meropenem, against three strains of *K. pneumoniae* (ATCC 13883, VA-357 and VA-364) and two strains of *P. aeruginosa* (PAO1 and SR27001) [30]. Cefiderocol MICs increased by fourfold or less against all five strains tested. The researchers reported that acquisition/selection of cefiderocol resistance was similar to that of ceftazidime and meropenem [30]. More data are required utilizing PD models to assess cefiderocol's resistance development potential compared to other agents as well as other siderophore candidates.

5 Microbiology

Cefiderocol is in development to target carbapenem-resistant and MDR Gram-negative bacilli including isolates producing ESBLs and carbapenemases (Tables 1, 2) [7, 8, 11, 16, 31–45]. The MIC values presented in these tables are modal MIC values compiled from a review of available in vitro studies using reference or defined antimicrobial susceptibility testing methods [46, 47]. It is important to state that in vitro susceptibility testing with cefiderocol is performed utilizing iron-depleted media. Clinical and Laboratory Standards Institute (CLSI) MIC methodology describes how to make iron-depleted media. The MICs of cefiderocol increase significantly if the iron is not depleted correctly. Performing cefiderocol MICs using iron-depleted media forces the bacteria to transport cefiderocol into the periplasmic space rather than compete with the superphysiological iron concentrations that occur in broth. These in vitro iron-depleted conditions mimic the clinical situation where patients with infectious diseases have very low free iron concentrations (the majority is bound to iron-binding proteins). Susceptible, intermediate and resistant breakpoints

Table 1 In vitro activity (MIC, mg/L) of cefiderocol, ceftazidime-avibactam and meropenem against Gram-negative aerobes Adapted from references [7, 8, 11, 32–44]

Gram-negative aerobes	Cefiderocol			Ceftazidime-avibactam		Meropenem	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter baumannii</i> (all)	0.12	1	≤0.002 to 64	16	> 64	32	> 64
Meropenem non-susceptible ^a	0.25	1	≤0.002 to 64	32	> 64	64	> 64
Multidrug-resistant ^b	0.25	8	0.015 to > 256	32	> 64	64	> 64
<i>Burkholderia cepacia</i>	0.008	0.016	0.002 to 0.016	NA	NA	4	8
<i>Citrobacter freundii</i>	0.06	0.25	≤0.002 to 1	0.12	0.5	≤0.06	≤0.06
<i>Citrobacter koseri</i>	0.25	0.5	0.06 to 2	0.12	0.12	≤0.06	≤0.06
<i>Enterobacter asburiae</i>	0.25	1	≤0.06 to 0.5	0.25	0.5	≤0.06	0.12
<i>Enterobacter cloacae</i>	0.25	1	≤0.03 to 64	0.25	1	≤0.06	0.125
Enterobacteriales (all)	0.12	1	≤0.002 to 8	0.12	0.5	≤0.06	0.12
Meropenem non-susceptible ^c	1	4	0.008 to 32	1	> 64	16	> 64
KPC-producers	1	4	0.004 to 32	1	4	32	> 64
<i>Escherichia coli</i>	0.06	0.5	≤0.002 to 4	0.12	0.25	≤0.06	≤0.06
<i>Klebsiella aerogenes</i>	0.12	0.5	≤0.004 to 8	0.25	0.5	≤0.06	0.12
<i>Klebsiella oxytoca</i>	0.06	0.25	≤0.002 to 2	0.12	0.25	≤0.06	≤0.06
<i>Klebsiella pneumoniae</i> (all)	0.12	2	≤0.06 to 8	0.25	1	≤0.06	8
Ceftazidime-avibactam non-susceptible ^d	2	4	0.25 to 16	64	64	32	64
Meropenem non-susceptible ^a	1	4	≤0.03 to 8	8	64	8	32
KPC-producers	1	2	0.03 to 64	2	4	> 16	> 16
<i>Pseudomonas aeruginosa</i> (all)	0.06	0.5	≤0.002 to 8	2	8	0.5	8
Multidrug-resistant	0.25	1	≤0.002 to 32	32	> 64	32	> 64
Ceftazidime-avibactam non-susceptible ^e	0.12	1	≤0.002 to 4	16	64	16	64
Ceftolozane-tazobactam non-susceptible ^f	0.25	4	0.004 to 8	8	64	16	32
Meropenem non-susceptible ^a	0.25	1	0.008 to 4	8	64	8	16
<i>Serratia liquefaciens</i>	0.06	0.12	0.015 to 0.25	0.25	0.5	≤0.06	0.12
<i>Serratia marcescens</i>	≤0.06	0.5	≤0.002 to > 64	0.12	0.5	≤0.06	0.12
<i>Stenotrophomonas maltophilia</i>	0.06	0.5	≤0.002 to 4	16	64	> 64	> 64
Ciprofloxacin non-susceptible ^g	0.06	0.5	0.002 to 2	NA	NA	NA	NA
Colistin non-susceptible ^h	0.12	0.5	0.002 to 2	NA	NA	NA	NA

KPC *Klebsiella pneumoniae* carbapenemase, MIC₅₀ minimum concentration (mg/L) to inhibit growth of 50% of isolates, MIC₉₀ minimum concentration (mg/L) to inhibit growth in 90% of isolates, NA data unavailable

^aMeropenem MIC ≥ 8 mg/L

^bResistant to carbapenems, fluoroquinolones and aminoglycosides

^cMeropenem MIC ≥ 4 mg/L

^dCeftazidime-avibactam > 8 mg/L

^eCeftazidime-avibactam MIC ≥ 16 mg/L

^fCeftolozane-tazobactam MIC ≥ 16 mg/L

^gCiprofloxacin MIC ≥ 1 mg/L

^hColistin MIC ≥ 1 mg/L

for cefiderocol against *A. baumannii*, Enterobacteriales, *P. aeruginosa* and *Stenotrophomonas maltophilia* were provisionally accepted by the CLSI Breakpoint Working Group in June 2018 (susceptible MIC ≤ 4 mg/L, intermediate MIC 8 mg/L, and resistant MIC ≥ 16 mg/L).

Table 1 shows the in vitro activities of cefiderocol, ceftazidime-avibactam, and meropenem against common Gram-negative aerobic pathogens [7, 8, 11, 31–44]. Also

included in the table are various resistant phenotypes/genotypes such as meropenem–non-susceptible isolates and KPC-producing isolates. The activity of cefiderocol against resistant subsets of Gram-negative bacilli is retained or enhanced compared to ceftazidime-avibactam and meropenem. Cefiderocol is more potent than both ceftazidime-avibactam and meropenem against *A. baumannii* including meropenem–non-susceptible and MDR

Table 2 In vitro (MIC, mg/L) activity of cefiderocol, ceftazidime-avibactam and meropenem versus specific Gram-negative bacillary β -lactamase genotypes Adapted from references [31, 40, 43, 45]

Organism	<i>n</i>	Cefiderocol			Ceftazidime-avibactam		Meropenem	
β -Lactamase enzyme		MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter baumannii</i>								
OXA-23	543	0.12	1	≤ 0.002 to 16	32	> 64	64	> 64
OXA-24	124	0.12	1	≤ 0.004 to 64	16	> 64	> 64	> 64
OXA-58	13	0.12	1	0.06 to 1	64	> 64	8	16
OXA-23, -40, -58 or -72	85	0.12	4	≤ 0.03 to 64	16	64	32	64
<i>Enterobacter</i> spp.								
OXA-48	136	0.5	4	0.015 to 4	1	> 64	8	> 64
VIM	99	1	4	0.06 to 8	> 64	> 64	8	> 64
NDM	117	4	8	0.25 to 32	> 64	> 64	64	> 64
NDM, VIM or IMP	29	1	4	≤ 0.03 to 64	> 64	> 64	16	64
<i>Escherichia coli</i>								
OXA-48	42	0.06	0.5	≤ 0.03 to 64	0.25	0.5	1	4
NDM, VIM or IMP	67	1	16	≤ 0.03 to 64	> 64	> 64	64	> 64
<i>Klebsiella pneumoniae</i>								
KPC-2, KPC-3, KPC-4	730	0.5	4	≤ 0.03 to 64	0.5	2	8	> 64
OXA-48	88	0.25	1	≤ 0.03 to 64	0.5	> 64	1	64
NDM, VIM or IMP	38	1	4	≤ 0.03 to 64	> 64	> 64	32	> 64
<i>Pseudomonas aeruginosa</i>								
VIM	101	0.12	0.5	0.015 to 2	32	> 64	64	> 64
IMP, KPC, VIM, SPM, or GIM	30	0.5	2	≤ 0.03 to 64	> 64	> 64	64	> 64

MIC₅₀ minimum concentration (mg/L) to inhibit growth of 50% of isolates, MIC₉₀ minimum concentration (mg/L) to inhibit growth in 90% of isolates

isolates. In addition, cefiderocol activity against meropenem–non-susceptible and KPC-producing Enterobacteriales is comparable or superior to ceftazidime-avibactam and consistently superior to meropenem. Cefiderocol is more active against ceftazidime-avibactam–non-susceptible, meropenem–non-susceptible, and KPC-producing *K. pneumoniae*. Cefiderocol was more active than both ceftazidime-avibactam and meropenem versus all resistance phenotypes of *P. aeruginosa* including ceftolozane-tazobactam–non-susceptible isolates. Finally, cefiderocol displayed potent in vitro activity versus *S. maltophilia* and *Burkholderia cepacia*.

Table 2 shows the activities of cefiderocol, ceftazidime-avibactam and meropenem versus specific Gram-negative bacillary β -lactamase genotypes [31, 40, 43, 45]. Cefiderocol demonstrated greater potency than ceftazidime-avibactam and meropenem against all β -lactamase genotyped isolates reported. It is clear that the unimpeded delivery of cefiderocol to the periplasmic space allows it to avoid β -lactamase interaction and confers upon it excellent activity against a variety of β -lactamase producing Gram-negative bacilli.

Tsuji et al. reported that the in vitro potencies of cefiderocol and ceftazidime-avibactam [minimum concentration to inhibit growth in 90% of isolates (MIC₉₀) 4 mg/L]

were similar against KPC-producing Enterobacteriales, but that cefiderocol MIC₉₀s against NDM- and VIM-positive Enterobacteriales, and VIM-positive *P. aeruginosa* (8, 4 and 0.5 mg/L, respectively) were significantly lower than for ceftazidime-avibactam (> 64 mg/L), suggesting cefiderocol was stable and active against isolates carrying class B β -lactamases [31]. Cefiderocol is active against Enterobacteriales carrying class D OXA-48-like β -lactamases (MIC₉₀ 4 mg/L) and OXA-23-like- (MIC₉₀ 2 mg/L) and OXA-24-like-positive (MIC₉₀ 8 mg/L) isolates of *A. baumannii* compared to MIC₉₀ values of > 64 mg/L for ceftazidime-avibactam for all isolates carrying class D β -lactamases [31]. Cefiderocol also retained its activity against isolates of *P. aeruginosa* engineered to overexpress class C β -lactamases (PW6111 and PW8615, cefiderocol MIC = 0.25 mg/L for both strains) compared to ceftazidime (PW6111 MIC = 16 mg/L and PW8615 MIC = 32 mg/L) [48]. The more potent in vitro activity of cefiderocol compared to ceftazidime-avibactam and meropenem against various β -lactamases indicates that cefiderocol has intrinsic structural stability against Ambler class A, B, C, and D β -lactamase-producing Gram-negative bacilli.

Limited data have been published describing the activity of cefiderocol against aerobic Gram-positive bacteria and

Table 3 Pharmacokinetics of cefiderocol

Study	Subjects	Renal function (mean eGFR, mL/min/1.73 m ²)	Dose (1-h infusion)	n	C _{max} ^a (mg/L)	AUC ^a (mg×h/L)	V _{ss} ^a (L)	t _{1/2} ^a (h)	CL ^a (L/h)	fe ^a (%)
[49]	Healthy adults, 20–60 years, mean BMI ^b 21.5–22.9 kg/m ²	101.4–132.2 ^b	100 mg×1	6	7.8±0.6	17.5±1.5 ^c	NA	2.0±0.1	5.7±0.5	68.4±2.2 ^e
			250 mg×1	6	18.9±0.9	41.9±2.6 ^c	NA	2.0±0.1	6.0±0.4	64.0±3.5 ^e
			500 mg×1	6	46.6±5.0	108.6±24.7 ^c	NA	2.1±0.3	4.6±1.0	65.8±10.7 ^e
			1000 mg×1	6	76.4±3.5	168.1±11.8 ^c	NA	2.3±0.1	6.0±0.4	68.3±4.1 ^e
			2000 mg×1	6	156.0±12.3	389.7±35.1 ^c	NA	2.7±0.3	5.1±0.5	61.5±6.5 ^e
			1000 mg q8 h×10 days	8	72.2±8.3	168.6±18.5 ^d	NA	2.2±0.1	5.9±0.1	64.7±8.3
[50]	Healthy adults, 27–74 years, mean BMI 29.6 kg/m ²	98.5 (normal ≥90) 72.1 (mild 60 to <90) 48.1 (moderate 30 to <60) 20.8 (severe <30) 7.5 (ESRD on HD)	2000 mg q8 h×10 days	8	153.0±19.7	366.5±51.3 ^d	NA	2.7±0.6	5.5±0.1	71.4±3.8
			1000 mg×1	8	81.0±22.2	213.4±56.6 ^e	13.5±4.1	2.8±0.5	4.7±1.3	68.8±11.9
			1000 mg×1	8	73.4±15.6	218.7±48.6 ^e	14.8±2.6	3.0±0.3	4.6±1.0	68.3±9.7
			1000 mg×1	7	78.0±24.3	312.3±120.0 ^e	15.4±4.4	4.1±0.5	3.2±1.2	55.5±2.1
			1000 mg×1	6	80.1±15.9	543.2±128.0 ^e	16.4±3.8	6.9±2.1	1.8±0.4	NA
			1000 mg×1	8	93.0±23.4	318.1±64.6 ^e	26.6±8.9	9.6±3.2	1.1±0.3	NA

AUC area under the concentration vs time curve, BMI body mass index, CL total drug clearance, C_{max} maximum plasma concentration, eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, fe fraction of dose excreted unchanged in the urine, HD hemodialysis, NA data not available, q8 h every 8 h, t_{1/2} half-life, V_{ss} volume of distribution at steady state

^aGeometric mean ± standard deviation

^bRange of means for each group

^cAUC from 0 to ∞

^dAUC from 0 to τ

^efe_{0–48} the urinary excretion ratio relative to the dose over 48 h

Gram-negative and Gram-positive anaerobic bacteria [16]. In general, cefiderocol demonstrates poor activity versus these organisms. It has been reported less active than ceftazidime-avibactam and meropenem against ATCC strains of aerobic Gram-positive bacteria including *Bacillus subtilis*, *Enterococcus faecalis*, *Lactobacillus casei* and *Staphylococcus aureus*, and against anaerobes including *Bacteroides* spp., *Clostridioides difficile*, *Fusobacterium*, *Veillonella*, and *Prevotella* [16].

6 Pharmacokinetics

The PK of cefiderocol were described in two phase I studies of single and multiple IV doses in healthy adults and single doses in adults with varying degrees of renal function (Table 3) [49, 50]. Saisho et al. characterized the PK of cefiderocol in healthy adults with single doses ranging from 100 mg to 2000 mg and multiple-dose regimens of 1000 mg every 8 h (q8 h) and 2000 mg q8 h for 10 days [49]. Cefiderocol demonstrated linear PK with a mean half-life ($t_{1/2}$) of 2.0–2.7 h and total drug clearance (CL) of 4.6–6.0 L/h, with 60–70% excreted unchanged in the urine. Katsube et al. investigated the influence of renal function on the PK of cefiderocol with a single 1000 mg dose in subjects with mild ($n=8$, estimated glomerular filtration rate (eGFR)=60 to <90 mL/min/1.73 m²), moderate ($n=7$, eGFR 30 to <60 mL/min/1.73 m²), and severe ($n=6$, eGFR <30 mL/min/1.73 m²) renal impairment [50]. Eight subjects with end-stage renal disease (ESRD) requiring hemodialysis were also studied. Compared with subjects with normal renal function, the ratios of area under the concentration versus time curve ($AUC_{0-\infty}$) with the 1000 mg dose were 1.0, 1.5, and 2.5 for subjects with mild, moderate, and severe renal impairment, respectively. In subjects undergoing hemodialysis, the cefiderocol CL was 7.5 ± 0.7 L/h, with 60% of drug removed over 3–4 h. The $AUC_{0-\infty}$ ratio was 4.1 in subjects with ESRD compared with those with normal renal function. Protein binding of cefiderocol, which ranged from 53% to 65%, was not affected by renal function.

Katsube et al. also conducted a population-PK analysis of cefiderocol using data from the two PK studies described above ($n=91$, 40.6 ± 15.7 years, 73.4 ± 17.3 kg, Creatinine clearance (CL_{CR}) 108.3 ± 48.2 mL/min) [51]. Cefiderocol PK were best described by a three-compartment covariate model with a CL of 4.83 L/h [relative standard error (RSE) 2.9%], a volume of distribution in the central compartment (V_1) of 7.58 L (RSE 2.7%), a V_2 of 5.54 L (RSE 2.5%), and a V_3 of 0.681 L (RSE 8.3%). Significant covariate relationships were described according to the following: $V_1 = 7.58 \times (\text{body weight}/70)^{0.575}$, $V_2 = 5.54 \times (\text{body weight}/70)^{0.730}$, and $CL = 4.83 \times [1 + 0.00880 \times (CL_{CR} - 100)]$ for $CL_{CR} < 100$ mL/min.

A second population-PK analysis was conducted using concentration data from the 91 healthy subjects (above) (although a few had renal impairment) and 238 patients with cUTIs or acute uncomplicated pyelonephritis (AUP) (55 ± 18.4 years, 76.6 ± 16.5 kg, CL_{CR} 90.0 ± 38.7 mL/min) [52]. Again, cefiderocol PK were best described by a three-compartment model, with significant covariate relationships between body weight and volume of distribution and between CL_{CR} and drug CL. In addition, the presence of infection was a significant covariate in the PK model where volume of distribution and CL were increased by 36% and 26%, respectively, compared with non-infected subjects. Currently, data regarding the PK of cefiderocol in special patient populations such as those who are obese, pregnant, or critically ill are not available.

7 Pharmacodynamics

The percentage of time that free drug concentrations exceed the MIC ($\%fT > MIC$) is an established PD index for the activity of β -lactams. Several in vivo animal studies by the same investigators confirmed the association between $\%fT > MIC$ and the antibacterial effects of cefiderocol [53–55]. Various dosing regimens were tested in neutropenic murine thigh and lung infection models of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* including carbapenem-resistant, β -lactamase-producing, and MDR strains (cefiderocol MICs of 0.125–16 mg/L). Overall, a 1 log₁₀ reduction in bacterial burden at 24 h was associated with a median $\%fT > MIC$ of 75%, although individual values ranged from 30 to 100% [53–55]. Ghazi et al. also studied the activity of cefiderocol in a neutropenic murine thigh infection model against *P. aeruginosa* ($n=8$, cefiderocol MICs of 0.063–0.5 mg/L) [56]. Eight dosing regimens from 4.2 to 166.7 mg/kg q8 h with $\%fT > MIC$ exposures ranging from 45% to 100% were tested. In this case, bacteriostasis, 1 log₁₀, and 2 log₁₀ of bacterial kill at 24 h were observed at mean $\%fT > MIC$ s of $76.3\% \pm 18.4\%$, $81.9\% \pm 18.3\%$, and $88.2\% \pm 15.9\%$, respectively.

Monogue et al. investigated potential MIC breakpoints for cefiderocol 2 g q8 h (3-h infusion) using a humanized dosing regimen for 24 h in a neutropenic murine thigh model [57]. Ninety-five isolates of *P. aeruginosa* ($n=21$), *A. baumannii* ($n=35$), and Enterobacteriales ($n=39$) with cefiderocol MICs of 0.12 mg/L to >256 mg/L were studied. For those with MICs of ≤ 4 mg/L ($n=67$), bacteriostasis or ≥ 1 log₁₀ of bacterial kill was observed for 85%, 88%, and 77% of *P. aeruginosa*, *A. baumannii*, and Enterobacteriales, respectively. Similar activity was observed in only 7% of isolates with MICs ≥ 8 mg/L ($n=28$). Based on their humanized PK data, the authors predicted that a

Table 4 In vivo activity of cefiderocol in various animal model studies

References	Animal model	Treatment protocol	Bacterial strain tested	Bacterial count on initiation of therapy	Bacterial count after treatment	Difference in bacterial count
[58]	Immunocompetent-rat respiratory tract infection	Dosing administered to recreate human PK of 2 g cefiderocol IV q8 h with 1-h infusion for 96 h total	<i>A. baumannii</i> 1485176	5.6 ± 0.7 ^a	2.5 ^a	3.1 ^a
			<i>A. baumannii</i> 1485247		5.1 ^a	0.7 ^a
			<i>K. pneumoniae</i> VA-361	5.6 ± 0.7 ^a	3.8 ^a	1.8 ^a
			<i>K. pneumoniae</i> K12		1.8 ^a	3.7 ^a
			<i>P. aeruginosa</i> ATCC 27853	4.2 ± 0.5 ^a	1.2 ^a	3.0 ^a
			<i>P. aeruginosa</i> SR27001		1.2 ^a	3.0 ^a
		Dosing administered to recreate human PK of 2 g cefiderocol IV q8 h with 3-h infusion for 96 h total	<i>A. baumannii</i> 1485176	5.6 ± 0.7 ^a	2.1 ^a	3.5 ^a
			<i>A. baumannii</i> 1485247		2.5 ^a	3.1 ^a
			<i>K. pneumoniae</i> VA-361	5.6 ± 0.7 ^a	0.8 ^a	4.4 ^a
			<i>K. pneumoniae</i> K12		2.6 ^a	3.0 ^a
			<i>P. aeruginosa</i> ATCC 27853	4.2 ± 0.5 ^a	1.2 ^a	3.0 ^a
			<i>P. aeruginosa</i> SR27001		0.9 ^a	3.3 ^a
[60]	Rat lung infection	Dosing was administered to recreate human PK of 2 g cefiderocol IV q8 h with a 1-h infusion	<i>A. baumannii</i> 1484911	5.4 to 7.9 log ₁₀ /rat	NA	2.5 ^a
			<i>A. baumannii</i> 1485176			3.4 ^a
			<i>A. baumannii</i> 1515988			4.3 ^a
			<i>A. baumannii</i> 1485247			0.6 ^a
			<i>P. aeruginosa</i> ATCC27853			2.8 ^a
			<i>P. aeruginosa</i> SR27001			2.7 ^a
[61]	Neutropenic murine lung infection	10 mg/kg dose administered subcutaneously 2, 5 and 8 h after infection	<i>E. coli</i> EC-14	3 × 10 ⁴ to 1 × 10 ⁶ CFU/mouse	NA	3.5 ^a
			<i>E. coli</i> SR33971			3.2 ^a
			<i>E. coli</i> SR21182			2.8 ^a
			<i>K. pneumoniae</i> SR1			3.1 ^a
			<i>K. pneumoniae</i> SR34586			2.4 ^a
			<i>K. pneumoniae</i> SR34589			2.4 ^a
			<i>P. aeruginosa</i> SR24			2.0 ^a
		10 mg/kg dose administered subcutaneous 2, 4, 6, 8, 10 and 12 h after infection	<i>A. baumannii</i> SR38435			1.0 ^a
			<i>A. baumannii</i> SR38424			2.5 ^a
			<i>A. baumannii</i> SR38425			3.2 ^a
[61]	Murine urinary tract infection	10 mg/kg dose administered subcutaneously 4, 7 and 10 h after infection	<i>E. coli</i> EC-14	2 × 10 ⁴ to 6 × 10 ⁵ CFU/mouse	NA	3.7 ^b
			<i>E. coli</i> SR21432			3.1 ^b
			<i>E. coli</i> SR1459			3.1 ^b
			<i>K. pneumoniae</i> SR22232			3.2 ^b
			<i>K. pneumoniae</i> SR22203			3.5 ^b
			<i>K. pneumoniae</i> SR22202			3.3 ^b
		10 mg/kg dose administered subcutaneously 4, 6, 8, 10, 12 and 14 h after infection	<i>A. baumannii</i> SR27325			1.8 ^b
		10 mg/kg dose administered subcutaneously 2, 4, 6, 8, 10 and 12 h after infection	<i>A. baumannii</i> SR27323			2.9 ^b

Table 4 (continued)

References	Animal model	Treatment protocol	Bacterial strain tested	Bacterial count on initiation of therapy	Bacterial count after treatment	Difference in bacterial count
[61]	Murine subcutaneous infection	30 mg/kg dose administered subcutaneously 2, 5 and 8 h after infection	<i>A. baumannii</i> SR27316	2×10^4 to 2×10^6 CFU/mouse	NA	3.9 ^c
			<i>E. coli</i> EC-14			2.0 ^c
			<i>E. coli</i> SR33971			2.5 ^c
			<i>E. coli</i> SR21182			3.1 ^c
			<i>K. pneumoniae</i> SR1			2.0 ^c
			<i>K. pneumoniae</i> SR34866			3.9 ^c
[62]	Neutropenic murine thigh infection	100 mg/kg dose administered subcutaneously 2, 5 and 8 h after infection	<i>A. baumannii</i> SR27323	10^6 /CFU per thigh	NA	2.9 ^c
		15, 20, 25, 10, and 5 mg/kg administered at 0, 1, 2, 4, and 6 h, repeated q8 h	<i>P. aeruginosa</i> 1403			> 2 ^d
			<i>P. aeruginosa</i> 1401			> 2 ^d
			<i>P. aeruginosa</i> JJ8-16			> 2 ^d
			<i>P. aeruginosa</i> JJ5-35			> 2 ^d
			<i>P. aeruginosa</i> AZ8-18			> 1 ^d
			<i>P. aeruginosa</i> AZ32-13			> 2 ^d
			<i>P. aeruginosa</i> JJ\$-36			> 2 ^d
			<i>P. aeruginosa</i> JJ11-54			> 2 ^d

Results represent mean approximations of bacterial cell counts from available data

CFU colony forming units, IV intravenous, NA data not available, PK pharmacokinetics, q8 h every 8 h

^alog₁₀ CFU/lung

^blog₁₀ CFU/kidney

^clog₁₀ CFU/abscess

^dlog₁₀ CFU/thigh

%fT > MIC of 96.2% would be achieved against isolates with MICs ≤ 4 mg/L.

Matsumoto et al. (discussed in greater detail in the animal models section) studied cefiderocol in an immunocompetent rat lung infection model of *P. aeruginosa* (*n* = 2), *A. baumannii* (*n* = 2), and *K. pneumoniae* (*n* = 2) [58]. The authors suggested the influence of %fT > MIC where 3-h infusions would achieve 100% fT > MIC and 1-h infusions would achieve 75% fT > MIC and 50% fT > MIC against isolates with MICs of 4 mg/L and 8 mg/L, respectively.

Katsube et al. predicted the probability of target attainment for cefiderocol using Monte Carlo simulations and their population-PK data in healthy adults with varying renal function [51]. They incorporated cefiderocol MICs from 1260 clinical isolates of *P. aeruginosa*, *A. baumannii*, and Enterobacteriales where values ranged from 0.25 to 16 mg/L and 98% were ≤ 4 mg/L [11, 59]. In simulated subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m²), 2 g q8 h (3-h infusion) achieved ≥ 75% fT > MIC in at least 90% of cases. Lower doses of 1.5 g q8 h (3-h infusion) and 1 g q8 h (3-h infusion)

reached ≥ 75% fT > MIC in at least 90% of simulated subjects with moderate (eGFR 30 to < 60 mL/min/1.73 m²) and severe (eGFR 15 to < 30 mL/min/1.73 m²) renal impairment, respectively. A cefiderocol dose of 0.75 g q12 h (3-h infusion) achieved ≥ 75% fT > MIC in at least 90% of simulated subjects with ESRD on hemodialysis, whereas 2 g q6 h (3-h infusion) was required for target attainment in those with augmented renal function (CL_{CR} ≥ 120 mL/min/1.73 m²). Although the study found acceptable target attainment with 1-h infusions, the authors supported the prolonged, 3-h infusion based on the potential use of cefiderocol for severe infections, including in critically ill patients. Kawaguchi et al. also predicted target attainment using simulation methods, their population-PK data that included infected patients, and cefiderocol MICs of Gram-negative pathogens that ranged from 0.004 mg/L to 8 mg/L (MIC₅₀ = 0.06 mg/L, MIC₉₀ = 1 mg/L) [52]. In this case, the target of ≥ 75% fT > MIC was achieved in all subjects with simulated dosages of 2 g q8 h (1-h infusion) that were adjusted for body weight and renal function.

Table 5 Clinical trials of cefiderocol

Trial description	n	Treatment regimen	Primary outcome measure	Secondary outcome measure
Completed: phase II treatment of cUTI, with or without pyelonephritis or AUP [12, 63]; ClinicalTrials.gov ID: NCT02321800	452	Experimental: cefiderocol, 2000 mg IV (<i>t</i> 1 h) q8 h×7–14 days Comparator: imipenem/cilastatin, 1000/1000 mg IV (<i>t</i> 1 h) q8 h×7–14 days	Composite ^a of clinical cure and microbiological eradication at TOC in the MITT population Results <i>n/N</i> (%) Cefiderocol: 183/252 (72.6) Imipenem/cilastatin: 65/119 (54.6)	Microbiological ^b and clinical ^c response per patient/pathogen at EA/EOT/TOC/FUP in the MITT population Safety: adverse events, plasma and urine concentrations of cefiderocol at steady state Results (%) Microbiological response per patient at EA/EOT/TOC/FUP Microbiological response per pathogen (<i>n</i> cefiderocol, imipenem/cilastatin) at EA/EOT/TOC/FUP: <i>E. coli</i> (152, 79) <i>K. pneumoniae</i> (48, 25) <i>P. aeruginosa</i> (18, 5) <i>P. mirabilis</i> (17, 2) Clinical response per patient at EA/EOT/TOC/FUP Clinical response per pathogen (<i>n</i> cefiderocol, imipenem/cilastatin) at EA/EOT/TOC/FUP: <i>E. coli</i> (146, 77) <i>K. pneumoniae</i> (46, 25) <i>P. aeruginosa</i> (15, 4) <i>P. mirabilis</i> (13, 1)
				Cefiderocol: 92.1/96.8/73.0/57.1 Imipenem/cilastatin: 90.8/95.8/56.3/43.7 Cefiderocol: 92.8/98.7/75.0/59.9 Imipenem/cilastatin: 94.9/97.5/58.2/41.8 Cefiderocol: 89.6/97.9/75.0/58.3 Imipenem/cilastatin: 88.0/92.0/52.0/52.0 Cefiderocol: 94.4/88.9/44.4/27.8 Imipenem/cilastatin: 80.0/100/60.0/20.0 Cefiderocol: 88.2/94.1/76.5/64.7 Imipenem/cilastatin: 100/100/50.0/0 Cefiderocol: 90.5/98.0/89.7/81.3 Imipenem/cilastatin: 90.8/99.2/87.4/72.3 Cefiderocol: 91.8/97.9/89.7/82.9 Imipenem/cilastatin: 96.1/98.7/88.3/72.7 Cefiderocol: 82.6/100/89.1/82.6 Imipenem/cilastatin: 88.0/100/84.0/68.0 Cefiderocol: 93.3/93.3/73.3/53.3 Imipenem/cilastatin: 75.0/100/75.0/75.0 Cefiderocol: 84.6/100/100/84.6 Imipenem/cilastatin: 100/100/100/100

Table 5 (continued)

Trial description	n	Treatment regimen	Primary outcome measure	Secondary outcome measure
In progress: phase III treatment of serious infections (HAP, VAP, HCAP, cUTI or BSI/sepsis) caused by carbapenem-resistant Gram-negative pathogens; ClinicalTrials.gov ID: NCT02714595	~150	Experimental: cefiderocol, 2000 mg IV (<i>t</i> ' 3 h) q8 h × 7–14 days Comparator: best available IV therapy × 7–14 days	Clinical outcome per patient at TOC for HAP/VAP/HCAP or BSI/sepsis Microbiological outcome (Gram-negative pathogens) per patient at TOC for cUTI	Clinical outcome: Per patient at EOT/FUP and per pathogen at EOT/TOC/FUP for HAP/VAP/HCAP or BSI/sepsis Per patient/pathogen at EOT/TOC/FUP for cUTI Microbiological outcome: Per patient/pathogen at EOT/TOC/FUP for HAP/VAP/HCAP or BSI/sepsis Per patient at EOT/FUP and per pathogen at EOT/TOC/FUP for cUTI For documented carbapenem-resistant Gram-negative bacteremia at EOT/TOC/FUP Participants with positive clinical/microbiological outcome at EOT/TOC/FUP All-cause mortality (days 14 and 28) and survival time for HAP/VAP/HCAP and BSI/sepsis; SOFA score and CPIS at EOT/TOC for HAP/VAP/HCAP; composite endpoint of survival and no change in antimicrobial treatment; adverse events
In progress: phase III treatment of nosocomial pneumonia caused by Gram-negative pathogens, including HAP, VAP and HCAP; ClinicalTrials.gov ID: NCT03032380	~300	Experimental: cefiderocol, 2000 mg IV q8 h × 7–14 days plus linezolid, 600 mg IV (<i>t</i> ' 30 min–2 h) q12 h for ≥ 5 days Comparator: meropenem, 2000 mg IV q8 h × 7–14 days plus linezolid, 600 mg IV (<i>t</i> ' 30 min–2 h) q12 h for ≥ 5 days	All-cause mortality at day 14	Percentage of participants in each treatment arm with: Clinical cure at EA/TOC/EOT/FUP Microbiological eradication at EA/TOC/EOT/FUP All-cause mortality at day 28 and all over the full study duration; number of treatment days; adverse events

AUP acute uncomplicated pyelonephritis, *BSI* bloodstream infection, *CFU* colony forming units, *CPIS* clinical pulmonary infection score, *cUTI* complicated urinary tract infection, *EA* early assessment (3–4 days after start of treatment), *EOT* end of treatment (last day of study treatment, day 7–14), *FUP* follow-up (14 days after end of treatment), *HAP* hospital-acquired pneumonia, *HCAP* healthcare-associated pneumonia, *IV* intravenous, *MITT* microbiological intent to treat (patients who received at least 1 dose of study drug and had a Gram-negative uropathogen at baseline), *q8 h* every 8 h, *q12 h* every 12 h, *SOFA* sequential organ failure assessment, *TOC* test of cure (7 days after end of treatment), *t'* infusion time, *VAP* ventilator-associated pneumonia

^aComposite outcome measure defined as resolution/improvement of symptoms of cUTI present at trial entry (with no new symptoms) and reduction of bacterial pathogen identified at trial entry to fewer than 10⁴ CFU/mL from urine culture at TOC

^bMicrobiological eradication defined as a urine culture demonstrating that the bacterial pathogen identified at baseline has decreased from ≥ 10⁵ CFU/mL to < 10⁴ CFU/mL

^cClinical cure defined as the resolution of cUTI signs and symptoms or a return to pre-infection baseline

8 Animal Models

The efficacy of cefiderocol has been evaluated in various animal infection models [58, 60, 61]. These studies are summarized in Table 4, with the MIC values of isolates tested in each model included.

Matsumoto et al. evaluated the in vivo efficacy of cefiderocol versus carbapenem-resistant strains of *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* in an immunocompetent rat respiratory infection model [58]. Cefiderocol was administered to anesthetized rats to recreate human plasma concentrations achieved with IV administration of 2 g of cefiderocol given q8 h, with 1-h or 3-h infusion times for a total of 96 h. Ceftazidime was used as a comparator and was administered to recreate human plasma concentrations achieved with IV administration of 1 g of ceftazidime q8 h with 0.5-h infusion for a total of 96 h. At the end of treatment, cefiderocol administered to recreate the human PK with a 3-h infusion demonstrated greater efficacy than cefiderocol administered to recreate human PK with a 1-h infusion ($3.04\text{--}4.41 \log_{10}$ colony forming units (CFU)/lung reduction with 3-h infusion and $0.7\text{--}3.7 \log_{10}$ CFU/lung reduction with 1-h infusion). Ceftazidime at the end of treatment demonstrated efficacy only against the *P. aeruginosa* strain ATCC 27853, with a reduction of approximately $2.7 \log_{10}$ CFU/lung. Similar results were reported in a study performed by Horiyama et al., which examined the in vivo efficacy of cefiderocol against strains of *A. baumannii* and *P. aeruginosa* in a rat lung infection model [60]. Cefiderocol was administered to recreate human plasma PK profiles observed with IV administration of 2 g of cefiderocol q8 h with a 1-h infusion time for a total of 96 h. After treatment, bacterial inocula were reduced by $0.7\text{--}4.3 \log_{10}$ CFU/lung for all isolates of *A. baumannii* and *P. aeruginosa*.

Nakamura et al. evaluated the in vivo efficacy of cefiderocol in lung, urinary tract and subcutaneous murine infection models [61]. In the murine lung infection model, neutropenic mice were infected by nasal inoculation of 0.07 mL of various bacterial suspensions and were administered cefiderocol or comparator cefepime subcutaneously starting 2 h after infection (Table 4). A viable bacterial count was performed 24 h post-infection for all strains except *P. aeruginosa* SR24888, where viable bacterial cell count was performed at 10 h post-infection. Post-treatment, cefiderocol displayed greater in vivo efficacy against the EBSL-producing *E. coli* strain SR21182 compared to cefepime ($2.7 \log_{10}$ CFU/lung reduction for cefiderocol, and $0.7 \log_{10}$ CFU/lung increase for cefepime) and the *A. baumannii* strain SR38435 ($1.0 \log_{10}$ CFU/lung bacterial reduction for cefiderocol and $0.7 \log_{10}$ CFU/lung increase for cefepime). For all other bacterial

strains, cefiderocol was comparable to cefepime. In the murine urinary tract infection model, mice were infected by transurethral inoculation of 0.1 mL of various bacterial suspensions (Table 4). Mice had their urethral meatus clamped for 2–4 h to prevent urine flow, prior to subcutaneous administration of cefiderocol and a cefepime comparator 2–4 h post-infection. A viable bacterial cell count in the kidneys was performed 24 h post-infection. Post-treatment, cefiderocol displayed comparable efficacy to cefepime for all bacterial strains. In the subcutaneous murine infection model, neutropenic mice were infected subcutaneously with 0.2 mL of various bacterial suspensions containing dextran based micro beads to create an abscess. Cefiderocol and the comparator cefepime were administered subcutaneously 2 h post-infection, and a viable bacterial cell count in the abscess was assessed 24 h post-treatment. After treatment, a notable difference in efficacy between cefiderocol and cefepime was observed in the EBSL-producing *E. coli* strain SR21182 ($3.2 \log_{10}$ CFU/abscess reduction for cefiderocol, and $2.8 \log_{10}$ CFU/abscess increase for cefepime), suggesting that cefiderocol may have increased activity against EBSL-producing strains of *E. coli*.

Ghazi et al. used a neutropenic murine thigh infection model to study the effect of cefiderocol against eight *P. aeruginosa* strains that had previously demonstrated a propensity to develop resistance to non-catechol siderophore antimicrobials [62]. Cefiderocol displayed potent in vivo activity against all *P. aeruginosa* strains, including those resistant to cefepime, levofloxacin and non-catechol siderophore compounds.

In summary, the in vivo efficacy of cefiderocol has been studied in a variety of murine and rat models of infection which try to simulate the limited free iron conditions that occur in humans with infectious diseases. In these studies, cefiderocol performed similarly to, or has been superior to, comparator agents including ceftazidime and cefepime.

9 Clinical Trials

Clinical trials for cefiderocol are summarized in Table 5, including one completed phase II trial for the treatment of cUTI (with or without pyelonephritis) or AUP (NCT02321800), and two phase III trials for the treatment of serious infections caused by carbapenem-resistant Gram-negative pathogens and nosocomial pneumonia caused by Gram-negative pathogens (NCT02714595 and NCT03032380).

9.1 Phase II Trial

The efficacy and safety of cefiderocol has been studied for the treatment of cUTI (with or without pyelonephritis) and AUP in a multicenter, double-blind, randomized, active-controlled phase II trial (APEKS-cUTI, NCT02321800) [12, 63]. A total of 452 patients were randomly assigned (2:1) to receive cefiderocol (2000 mg) or imipenem/cilastatin (1000/1000 mg) administered intravenously [infusion time (t') 1 h], each q8 h for a duration of 7–14 days, with dose adjustment for reduced renal function and/or low body weight. No oral antimicrobial stepdown therapy was permissible in this study. Hospitalized patients ≥ 18 years of age with a clinical diagnosis of either cUTI (with or without pyelonephritis) or AUP, with evidence of pyuria, a urine culture with a carbapenem-susceptible Gram-negative pathogen, and at least two UTI signs and symptoms (temperature ≥ 38 °C, chills, flank or back pain, nausea or vomiting, urinary frequency or urgency, costo-vertebral angle tenderness) were enrolled in the study. A cUTI diagnosis also required a patient history of at least one of the following: indwelling catheter or recent instrumentation of the urinary tract, urinary retention, obstructive uropathy or azotemia caused by intrinsic renal disease. Patients were excluded from the study if they had a baseline urine culture with more than two uropathogens, a known carbapenem-resistant Gram-negative uropathogen at baseline, a confirmed fungal UTI, a creatinine clearance of < 20 mL/min or had received hemodialysis or peritoneal dialysis.

The primary outcome of the APEKS-cUTI trial was a composite of clinical cure and microbiological eradication at the test-of-cure (TOC) assessment (7 days after completion of treatment) in the microbiological intent-to-treat (MITT) population. The composite outcome measure was defined as the resolution or improvement of symptoms of cUTI present at trial entry (with no new symptoms) and reduction of bacterial pathogen identified at trial entry to $< 10^4$ CFU/mL from urine culture at TOC. The MITT population included all randomized patients who had a Gram-negative uropathogen at baseline and received at least one dose of study drug; this population comprised 371 patients (82.1% of the 452 patients that originally underwent randomization), including 252 in the cefiderocol arm and 119 in the imipenem/cilastatin arm. Non-inferiority for the primary outcome was assessed using two-sided 95% confidence intervals (CIs) with 20% and 15% inferiority margins, which provided $> 90\%$ and 80% power, respectively, to determine the non-inferiority of cefiderocol compared to imipenem/cilastatin. The composite microbiological and clinical responses at TOC (primary endpoint) for cefiderocol and imipenem/cilastatin were 72.6% and 54.6%, respectively, a difference of 18.58 (95% CI 8.23–28.92) (Table 5). Therefore, cefiderocol was at least non-inferior and perhaps superior to imipenem/

cilastatin at the specified 20% and 15% margins for the primary outcome. Composite results in the microbiologically evaluable population (eligible and compliant MITT patients) were consistent with the primary endpoint.

Secondary endpoints included microbiological and clinical responses per patient and per pathogen at early assessment (EA; 3–4 days after start of treatment), end of treatment (EOT; day 7–14), TOC, and follow-up (FUP; 14 days after end of treatment) in the MITT population. Microbiological eradication was higher in the cefiderocol group at TOC in comparison with imipenem/cilastatin (73.0% vs 56.3%, difference 17.25, 95% CI 6.92–27.58), as well as at FUP (Table 5). Rates of clinical cure for cefiderocol and imipenem/cilastatin at TOC were similar between groups (89.7% vs 87.4%, difference 2.39, 95% CI –4.66 to 9.44); however, clinical cure was higher for cefiderocol at FUP (81.3% vs 72.3%, difference 9.02, 95% CI –0.37 to 18.41). Overall, the most frequently isolated Gram-negative uropathogens at baseline were *E. coli* ($n = 231$), *K. pneumoniae* ($n = 73$), *P. aeruginosa* ($n = 23$) and *Proteus mirabilis* ($n = 19$). Microbiological results for *E. coli* and *K. pneumoniae* for the cefiderocol and imipenem/cilastatin treatment groups were consistent with the results of the overall population (for *E. coli*, 75.0% vs 58.2%, difference 16.77, 95% CI 3.90–29.64; for *K. pneumoniae*, 75.0% vs 52.0%, difference 23.00, 95% CI –0.10 to 46.10) (Table 5). Statistical comparisons could not be completed for the *P. aeruginosa* and *P. mirabilis* subgroups, as they occurred at a low frequency (< 10) in one of the treatment groups. Results for additional time points and clinical outcome results for these four pathogens are listed in Table 5. Additionally, the composite response at TOC for extended-spectrum β -lactamase-producing pathogens was consistent with previous outcomes between the cefiderocol and imipenem/cilastatin groups (62.9% vs 47.2%, difference 16.66, 95% CI –3.08 to 36.40). Adverse events observed in the APEKS-cUTI study will be discussed in Sect. 10.

9.2 Phase III trials

Cefiderocol is currently being studied in two phase III clinical trials. The first, CREDIBLE-CR (NCT02714595), compares cefiderocol (2000 mg) administered intravenously (t' 3 h) q8 h for a duration of 7–14 days against the best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative pathogens. Serious infections include clinically documented cases of HAP, VAP, HCAP, cUTI, bloodstream infections (BSIs) and sepsis. The primary outcomes are clinical cure per patient at TOC for HAP/VAP/HCAP or BSI/sepsis, and microbiological eradication per patient at TOC for cUTI. Secondary outcomes are listed in Table 5. The CREDIBLE-CR trial has an estimated study completion date of early 2019.

The second phase III clinical trial underway is APEKS-NP (NCT03032380), comparing the combined treatment of IV cefiderocol (2000 mg) q8 h for 7–14 days plus IV linezolid (600 mg) (*t'* 1 h) q12 h for at least 5 days against the combination of IV meropenem (2000 mg) q8 h for 7–14 days plus IV linezolid (600 mg) (*t'* 1 h) q12 h for at least 5 days for the treatment of nosocomial pneumonia (HAP, VAP, HCAP) caused by Gram-negative pathogens. All patients included in this trial must fulfill the clinical screening requirements of nosocomial pneumonia and demonstrate at least one pneumonia sign or symptom. The primary outcome for the APEKS-NP study is all-cause mortality at day 14; secondary outcomes include microbiological eradication and clinical cure at EA, EOT, TOC and FUP (Table 5). The APEKS-NP trial has an estimated study completion date of late 2019.

10 Adverse Effects

The safety and tolerability of cefiderocol from phase I and phase II studies has been reviewed [12, 49, 50, 63]. Drug-related adverse effects were considered mild in severity and not clinically serious across 84 subjects in two phase I PK studies [49, 50].

Following single doses of cefiderocol (100–2000 mg IV with a 3-h infusion) in healthy subjects [49], nine adverse effects were reported from 30 subjects. The adverse effects were mild in severity and included diarrhea (two events/two subjects), rash (two events/two subjects), and one event each of abdominal pain, blood present in the urine, urine testing positive for red blood cells, increased plasma white blood cell (WBC) count and urine testing positive for WBCs. All adverse effects were classified as not clinically significant. Following a 10-day multi-dose regimen of cefiderocol (1000 or 2000 mg administered q8 h with a 3-h infusion) in 16 healthy subjects [49], a total of 22 adverse effects were reported. The adverse effects were considered mild in severity and included rash, abdominal pain, headache, oropharyngeal pain, pyrexia, increases in the liver enzymes alanine aminotransferase and aspartate aminotransferase from baseline, increase in plasma WBC count from baseline, increase in blood creatinine phosphokinase concentrations from baseline, and urine testing positive for WBCs. Data from eight healthy subjects who received the 1000-mg multi-dose regimen of cefiderocol were excluded from discussion, as it was discovered that the study drug was contaminated with 0.36% iodine, which could have possibly affected the adverse effect profile [49].

In the second phase I trial, conducted by Katsube et al., which assessed the safety of cefiderocol in 30 subjects with varying degrees of renal impairment, no serious adverse effects were reported [50]. The most common adverse effects reported were contact dermatitis (three events/30 subjects)

and nausea (two events/30 subjects). Other adverse events reported included phlebitis, flushing, urticaria, macropapular rash, polyuria, headache, dizziness and flank pain. No apparent differences in adverse effects were observed with increasing degrees of renal impairment. Overall, the nature and incidence of adverse effects reported in the phase I studies did not appear to be dose dependent and no dose-limiting toxicities were identified. No serious adverse effects or deaths were reported in either study.

In a phase II clinical trial (NCT02321800) [12, 63] evaluating the efficacy and safety of cefiderocol versus imipenem/cilastatin in cUTIs, a total of 27 subjects (9.0%) reported treatment-emergent adverse effects (TEAEs) out of 300 subjects in the cefiderocol trial arm. The TEAEs with a >2% incidence in each treatment arm included (from most to least prevalent) diarrhea, hypertension, constipation, infusion site pain, headache, nausea, cough, vomiting, hypokalemia, insomnia, renal cyst, infusion site erythema, upper abdominal pain, cardiac failure, *C. difficile* colitis and vaginal infection. A total of 14 serious adverse effects were reported, and one death was reported in the cefiderocol treatment arm, but the investigators considered the death to be unrelated to the drug. The adverse effect profile for imipenem/cilastatin was similar to cefiderocol, with 17 (11.5%) out of 148 subjects reporting TEAEs as listed above. Limited data suggest that *Clostridium difficile* infection was substantially lower in the cefiderocol-treated patients. Overall the investigators noted that cefiderocol was generally well tolerated, with a similar adverse effect rate profile to imipenem/cilastatin, and no unexpected safety concerns were identified.

Based on the limited phase I and phase II data, the adverse effect profile of cefiderocol does not appear to be different to that of other β -lactams. Only limited data are currently available about the interaction of cefiderocol with other drugs (i.e., drug interactions), but the expectation would be that the drug-interaction profile would be similar to the profiles of ceftazidime and cefepime. Ongoing clinical trials are needed to fully describe both the drug-interaction and adverse effect profile of cefiderocol.

11 Place in Therapy

Cefiderocol is a siderophore cephalosporin targeted for activity against carbapenem-resistant and MDR Gram-negative bacilli including ESBL- and carbapenemase-producing strains. Cefiderocol demonstrates microbiological activity against Gram-negative bacilli that is equal to and frequently superior compared to ceftazidime-avibactam and meropenem. Cefiderocol has intrinsic structural stability against a variety of Ambler class A, C, and D β -lactamases, and it

is the first agent with activity versus class B β -lactamases; this confers upon it activity against MDR Gram-negative bacilli, including MDR Enterobacteriales, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, all while possessing a safety and tolerability profile similar to other cephalosporins. The potent activity against resistant Gram-negative bacilli, including *P. aeruginosa*, due to its unique mechanism of siderophore-like periplasmic penetration and avoidance of β -lactamase inactivation, makes cefiderocol a potentially important compound for the treatment of a variety of infections resistant to other antimicrobial classes. Phase II clinical trials have demonstrated that cefiderocol is non-inferior (and likely superior) to imipenem/cilastatin for the treatment of cUTI including pyelonephritis, providing clinicians with a safe and effective option for treatment of such infections caused by resistant Gram-negative bacilli. Phase III trials are currently underway for the treatment of hospital-acquired, healthcare-associated, and ventilator-acquired pneumonia, as well as in the treatment of serious infections caused by carbapenem-resistant Gram-negative pathogens. If cefiderocol proves to be microbiologically and clinically efficacious in seriously ill patients with infections caused by carbapenem-resistant Gram-negative pathogens, this may open up its use to treat a variety of such infections, including respiratory, urinary, intra-abdominal infections and sepsis. Although ongoing clinical trials will help to further define the safety and efficacy of cefiderocol and the exact clinical role of this novel siderophore cephalosporin, its potential as a treatment for infections caused by MDR Enterobacteriales, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* is welcome as infections caused by carbapenem-resistant and MDR Gram-negative bacilli continue to increase.

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Compliance with Ethical Standards

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