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REVIEW

Cefiderocol: A Novel Agent for the Management of Multidrug-Resistant Gram-Negative Organisms

Janet Y. Wu · Pavithra Srinivas · Jason M. Pogue

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ABSTRACT

Cefiderocol, formerly S-649266, is a first in its class, an injectable siderophore cephalosporin that combines a catechol-type siderophore and cephalosporin core with side chains similar to cefepime and ceftazidime. This structure and its unique mechanism of action confer enhanced stability against hydrolysis by many β-lactamases, including extended spectrum β-lactamases such as CTX-M, and carbapenemases such as KPC, NDM, VIM, IMP, OXA-23, OXA-48-like, OXA-51-like and OXA-58. Cefiderocol's spectrum of activity encompasses both lactose-fermenting and non-fermenting Gram-negative pathogens, including carbapenem-resistant Enterobacterales. Cefiderocol recently received US Food and Drug Administration approval for the treatment of complicated urinary tract infections, including pyelonephritis, and is currently being evaluated in phase III trials for nosocomial pneumonia and infections caused by carbapenem-resistant Gram-negative pathogens. The purpose of this article is to review existing data on the mechanism of action, microbiology, pharmacokinetics, pharmacodynamics, efficacy, and safety of cefiderocol to assist clinicians in determining its place in therapy.

Keywords: Cefiderocol; Cephalosporin; CRE; Siderophore

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J. Y. Wu (✉) · P. Srinivas
Department of Pharmacy, Cleveland Clinic, Cleveland, OH, USA
e-mail: wuj5@ccf.org

J. M. Pogue
College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

Key Summary Points

Cefiderocol is a first in its class, an injectable siderophore cephalosporin with potent in vitro activity against carbapenem-resistant Enterobacteriaceae and drug-resistant non-fermenting Gram-negative bacilli.

Cefiderocol was recently US FDA-approved for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, and is being evaluated for the treatment of nosocomial pneumonia and carbapenem-resistant infections.

Its unique mechanism of action allows for high intracellular penetration into the periplasmic space and increased stability to many β-lactamases including both serine-type (KPC, OXA) and Ambler class B metallo-β-lactamases (VIM, IMP, NDM).

Cefiderocol has an important place in therapy for cUTI, but further data are necessary to determine its place in therapy for other systemic infections, such as pneumonia and bloodstream infections.

INTRODUCTION

The emergence of carbapenem resistance in Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* is an urgent threat to global public health [1]. These Gram-negative organisms are common pathogens in a variety of serious infections, including intra-abdominal infections, pneumonia, urinary tract infections, and bloodstream infections (BSI) [2]. The presence of multi-drug resistance complicates the management of these infections due to the limited treatment options available. Historically, antibiotic options for multi-drug resistant (MDR) Gram-negative infections have included aminoglycosides, polymyxins, and/or tigecycline. Unfortunately, these agents possess significant disadvantages, including toxicities, sub-optimal pharmacokinetics at target sites of infection, and poor outcome data [3]. While the antimicrobial pipeline has recently produced a number of game-changing agents, gaps in the armory are still present. Most recent additions to the armamentarium have targeted activity against MDR *P. aeruginosa* (ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam), and KPC-producing (ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/relebactam) and OXA-48-like (ceftazidime/avibactam) carbapenem-resistant Enterobacterales (CRE). Additionally, plazomicin, a novel aminoglycoside, displays enhanced activity against Enterobacterales, including CRE. However, antibacterials with activity against Ambler Class B metallo β-lactamases (NDM, VIM, IMP) are lacking. Furthermore, the novel β-lactamase inhibitor combinations provide no clinically relevant protection for the parent β-lactam compound against other class D carbapenemases, such as OXA-23, OXA 40, OXA-51-like, which are the predominant enzymes driving carbapenem resistance in *A. baumannii* [4]. Compounding the problem, non-β-lactamase-mediated mechanisms of resistance, such as mutations causing porin channel depletion or efflux pump up-regulation, are becoming a growing threat in the development of carbapenem resistance, and the novel agents do not fully address this need [5, 6]. Similarly, the recent additions to the armamentarium fail to address other problematic non-fermenting Gram-negative bacilli, such as *Stenotrophomonas maltophilia* and *Burkholderia* spp., which are inherently associated with high rates of β-lactam resistance.

Cefiderocol is a newly US FDA-approved, first in its class, siderophore cephalosporin with potent in vitro activity against CRE and drug-resistant non-fermenting Gram-negative bacilli. The purpose of this article is to review existing data on the mechanism of action, microbiology, pharmacokinetics, pharmacodynamics, efficacy and safety of cefiderocol.

DATA SOURCES

Literature for this review was obtained through a search of MEDLINE for all materials containing the name "S-649266" or "cefiderocol". Additional sources were obtained through clinicaltrials.gov, FDA briefing document, and conference proceedings and published abstracts. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CHEMISTRY AND MECHANISM OF ACTION

To appreciate the unique mechanism(s) of action of cefiderocol, it is important to understand the role of iron in host immunity and infection. Iron, in its insoluble ferric form (Fe^{3+}), is an essential nutrient for various cellular processes such as respiration and DNA replication. Under physiological conditions in humans, iron metabolism and distribution is a tightly regulated process. The majority of iron is complexed with hemoglobin within erythrocytes. Any extracellular iron is tightly bound to proteins, such as transferrin, or with a lower affinity to albumin, citrate, and amino acids when transferrin-binding capacity may be exceeded. In the setting of an infection, iron sequestration is further increased by lactoferrin, a protein that maintains iron-binding capacity in acidic environments, as well as peptides, such as hepcidin, and cytokines, such as interferon gamma, tumor necrosis factor alpha, interleukin-1 and Interleukin-6 [7].

Similar to humans, microorganisms also require iron for important cellular redox processes. In order to survive under iron-depleted conditions in human hosts, pathogens possess various pathways for heme uptake and non-heme iron-acquisition mechanisms. One such mechanism is the production and subsequent extracellular release of molecules called siderophores that scavenge for free ferric iron and undergo re-uptake into the cell as a siderophore–iron complex via iron transporter channels. Siderophores are classified into three general types: hydroxamate, carboxylate, and catecholate. Hydroxamate- and carboxylate-type siderophores are commonly produced by fungi and some bacteria, while catecholate siderophores are primarily produced by bacteria. For example, the enteric Gram-negative bacteria, *Escherichia coli*, produces enterobactin, a catechol siderophore with a high affinity for Fe^{3+}, while *P. aeruginosa* produces a combination of pyoveridine, a hydroxamate-type, and pyochelin, a catecholate-type, siderophores [8].

Cefiderocol (S-649266), a novel combination of a catechol-type siderophore and a cephalosporin antibiotic, utilizes the siderophore–iron complex pathway to penetrate the outer membrane of Gram-negative organisms in addition to normal passive diffusion through membrane porins. The chemical structure of cefiderocol contains a cephalosporin core with side chains similar to ceftazidime and cefepime. The aminothiazole ring and carboxypropyl-oxyimino group attached to the 7-position side chain confer enhanced activity against Gram-negative bacilli, including *P. aeruginosa* and *A. baumannii*. A catechol 2-chloro-3,4-dihydroxybenzoic acid moiety on the 3-position of the R2 side chain functions as the siderophore mimic, by chelating extracellular iron and by facilitating enhanced uptake into bacterial periplasmic space via iron transporter channels in the outer membrane. Additionally, a pyrridoline ring bound to the catechol moiety confers zwitterionic properties, similar to those of cefepime, that enhance water solubility of the molecule [9, 10]. Once within the periplasmic space, cefiderocol dissociates from the iron and binds to penicillin-binding proteins (PBP), primarily PBP3, to inhibit peptidoglycan synthesis. Compared to ceftazidime, cefiderocol has demonstrated significantly lower IC_{50}s (50% inhibitory concentrations) and a higher affinity for PBP3 in strains of *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa* and *A. baumannii*. Furthermore, the combined structure of a cephalosporin and a catechol moiety appears to confer enhanced stability against hydrolysis by many β-lactamases, including extended spectrum β-lactamases (ESBLs), such as CTX-M, and carbapenemases, such as KPC, NDM, VIM, IMP, OXA-23, OXA-51-like and OXA-58 [11].

IN VITRO ACTIVITY

Cefiderocol has potent in vitro activity against various lactose-fermenting enteric Gram-negative bacilli, including *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Providencia* spp. *Salmonella* spp., *Yersinia* spp., and *Vibrio* spp., as well as non-fermenting organisms, such as *Acinetobacter* spp., *Pseudomonas* spp., *Burkholderia* spp., and *Stenotrophomonas maltophilia*. Cefiderocol has also demonstrated in vitro activity against *Haemophilus* spp., *Moraxella catarrhalis*, and *Bordetella parapertussis*, and the intrinsically multidrug-resistant *Elizabethkingia meingoseptica*. However, activity against aerobic Gram-positive and anaerobic organisms is comparatively weaker. High minimum inhibitory concentrations (MICs) have been observed against most aerobic Gram-positive and anaerobic Gram-positive and Gram-negative organisms [11].

Cefiderocol is currently being evaluated in clinical trials for the treatment of carbapenem-resistant Gram-negative infections, including Enterobacterales, *P. aeruginosa* and *A. baumannii*. MICs of cefiderocol required to inhibit growth in 50% (MIC_{50}) and 90% (MIC_{90}) of Gram-negative isolates range from 0.12 to 0.5 μg μg/mL and from 0.5 to 4 μg μg/mL, respectively. A comparison of cefiderocol MIC_{50} and MIC_{90} to meropenem, ceftazidime/avibactam (CAZ/AVI) and ceftolozane/tazobactam (TOL/TAZ) against various Gram-negative isolates is summarized in Table 1. Overall, cefiderocol MICs ranged from ≤ 0.002 to 128 μg/mL for all Enterobacterales, compared to 0.008–8 μg/mL for a subset of carbapenem-resistant Enterobacterales from a compilation of worldwide isolates. In surveillance studies, cefiderocol demonstrated more potent in vitro activity against carbapenem-resistant Enterobacterales, *A. baumannii* and *P. aeruginosa*, compared to meropenem, CAZ/AVI and TOL/TAZ [10]. Cefiderocol inhibited > 98% of CAZ/AVI and TOL/TAZ non-susceptible Enterobacterales and all CAZ/AVI and TOL/TAZ non-susceptible *P. aeruginosa* isolates at MICs ≤ 4 μg/mL, the provisional susceptibility breakpoint from the Clinical and Laboratory Standards Institute (CLSI) [12]. Additionally, cefiderocol has also demonstrated potent in vitro activity against *S. maltophilia* with an MIC_{90} of 0.25 μg/mL, and low MICs against *Burkholderia cepacia* (MIC_{90} 0.12–0.5) [12, 13].

As previously stated, the CLSI has established provisional MIC breakpoint standards of ≤ 4 (susceptible), 8 (intermediate), and ≥ 16 μg/mL (resistant) for cefiderocol against Enterobacterales, *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia*. One key differentiating feature of susceptibility testing for cefiderocol is that it requires an iron-depleted medium, typically an iron-depleted cation -adjusted Mueller–Hinton broth (ID-CAMHB) [14]. The presence of iron in CAMHB may interfere with organism uptake of cefiderocol in vitro, thereby resulting in increased cefiderocol MICs. Use of an iron-depleted medium mimics the physiological state of iron-depletion in the human host, and has demonstrated good correlation with in vivo efficacy [15].

In vitro studies of the stability of cefiderocol against clinically relevant carbapenemases have demonstrated that the compound is relatively stable to hydrolysis by NDMs, KPC-3 and OXA-23. The K_{cat} (i.e., the enzyme turnover rate) of cefiderocol with IMP-1, VIM-2 and L1 was 0.92 s^{-1}, 1.0 s^{-1} and 12 s^{-1}, respectively, and was found to be four- to sevenfold lower than that of meropenem. The K_m (i.e., the enzyme affinity) of cefiderocol to IMP-1, VIM-2 and L1 was 190 mcM, 200 mcM and 510 mcM, respectively, compared to meropenem that demonstrated a 58- to 83-fold higher affinity for the metallo-β-lactamases. The catalytic efficiency (K_{cat}/K_m), (i.e., the rate of enzyme–substrate turnover versus the affinity of the enzyme and substrate) for cefiderocol against metallo-β-lactamases (L1, VIM-2, and IMP-1) was 260- to 417-fold lower than that for meropenem, and the lowest among all antibacterials tested. The affinity (K_m) of cefiderocol to KPC-3 and OXA-23 enzymes was shown to be > 1600 mcM and 4800 mcM, respectively, suggesting weak binding of cefiderocol to these enzymes. Comparatively, the K_m of meropenem to KPC-3 and OXA-23 was 6.5 mcM and 0.028 mcM, respectively, suggesting 250- to 100,000-fold higher affinity of these enzymes for meropenem

Table 1 In vitro activity of cefiderocol, meropenem, ceftazidime/avibactam and ceftolozane/tazobactam against Enterobacterales and non-fermenting Gram-negative bacilli, adapted from references [12, 13]

Organism (no. of isolates)	Antimicrobial	N. American isolates			European isolates			Combined/worldwide isolates		
		MIC50	MIC90	Range	MIC50	MIC90	Range	MIC50	MIC90	Range
Enterobacterales, all (6013)	Cefiderocol	0.12	0.5	≤ 0.002–128	0.25	1	≤ 0.002–8			
	MER	≤ 0.06	≤ 0.06	≤ 0.06 to > 64	≤ 0.06	0.12	≤ 0.06 to > 64			
	CAZ/AVI	0.12	0.5	≤ 0.06–32	0.25	0.5	≤ 0.06 to > 64			
	TOL/TAZ	0.25	1	≤ 0.06 to > 64	0.25	8	≤ 0.06 to > 64			
MER-resistant (246)	Cefiderocol							1	4	0.008–8
	MER							16	> 64	2 to > 64
	CAZ/AVI							1	> 64	0.12 to > 64
	TOL/TAZ							> 64	> 64	0.25 to > 64
CAZ/AVI-resistant (57)	Cefiderocol							1	4	0.12–8
	MER							32	> 64	≤ 0.06 to > 64
	CAZ/AVI							> 64	> 64	16 to > 64
	TOL/TAZ							> 64	> 64	0.12 to > 64
TOL/TAZ-resistant (597)	Cefiderocol							1	2	0.008–128
	MER							0.12	64	≤ 0.06 to > 64
	CAZ/AVI							1	8	≤ 0.06 to > 64
	TOL/TAZ							32	> 64	4 to > 64
K. pneumoniae, all (1528)	Cefiderocol	0.12	0.5	≤ 0.002–4	0.25	2	≤ 0.002–2			
	MER	≤ 0.06	≤ 0.06	≤ 0.06 to > 64	≤ 0.06	16	≤ 0.06 to > 64			
	CAZ/AVI	0.12	0.5	≤ 0.06 to 8	0.25	1	≤ 0.06 to > 64			
	TOL/TAZ	0.25	1	≤ 0.06 to > 64	0.5	> 64	≤ 0.06 to > 64			

Table 1 continued

Organism (no. of isolates)	Antimicrobial	N. American isolates			European isolates			Combined/worldwide isolates		
		MIC50	MIC90	Range	MIC50	MIC90	Range	MIC50	MIC90	Range
MER-resistant (165)	Cefiderocol							1	4	0.015–4
	MER							16	> 64	2 to > 64
	CAZ/AVI							1	> 64	0.25 to > 64
	TOL/TAZ							> 64	> 64	1 to > 64
E. coli (1830)	Cefiderocol	0.12	0.5	≤ 0.002 to 4	0.12	1	≤ 0.002–8			
	MER	≤ 0.06	≤ 0.06	≤ 0.06 to 16	≤ 0.06	≤ 0.06	≤ 0.06 to > 64			
	CAZ/AVI	0.12	0.25	≤ 0.06–8	0.12	0.25	≤ 0.06 to > 64			
	TOL/TAZ	0.25	0.5	≤ 0.06 to > 64	0.25	0.5	≤ 0.06 to > 64			
E. cloacae (594)	Cefiderocol	0.25	1	0.008–128	0.5	1	≤ 0.002 to 4			
	MER	≤ 0.06	0.12	≤ 0.06 to 32	≤ 0.06	0.12	≤ 0.06 to 64			
	CAZ/AVI	0.25	1	≤ 0.06 to 8	0.25	1	≤ 0.06 to > 64			
	TOL/TAZ	0.25	16	0.12 to > 64	0.5	16	≤ 0.06 to > 64			
E. aerogenes (244)	Cefiderocol	0.12	0.5	0.004 to 2	0.12	0.5	≤ 0.002 to 4			
	MER	≤ 0.06	0.12	≤ 0.06 to 16	≤ 0.06	0.12	≤ 0.06 to 4			
	CAZ/AVI	0.25	0.5	≤ 0.06 to 8	0.25	1	≤ 0.06 to 8			
	TOL/TAZ	0.25	4	≤ 0.06 to 32	0.5	8	≤ 0.06 to >64			
C. freundii (252)	Cefiderocol	0.12	1	0.004–4	0.12	1	≤ 0.002 to 8			
	MER	≤ 0.06	≤ 0.06	≤ 0.06 to 16	≤ 0.06	≤ 0.06	≤ 0.06 to 16			
	CAZ/AVI	0.12	0.5	≤ 0.06 to 8	0.25	1	≤ 0.06 to > 64			
	TOL/TAZ	0.25	8	≤ 0.06 to > 64	0.25	16	0.12 to > 64			

Table 1 continued

Organism (no. of isolates)	Antimicrobial	N. American isolates			European isolates			Combined/worldwide isolates		
		MIC50	MIC90	Range	MIC50	MIC90	Range	MIC50	MIC90	Range
C. koseri (169)	Cefiderocol	0.5	1	0.015 to 8	0.5	0.5	0.12 to 1			
	MER	≤ 0.06	≤ 0.06	≤ 0.06	0.5	16	≤ 0.06 to > 64			
	CAZ/AVI	0.12	0.25	≤ 0.06 to 0.5	0.12	0.25	≤ 0.06 to 4			
	TOL/TAZ	0.25	0.5	≤ 0.06 to 1	0.25	0.5	≤ 0.06 to 16			
S. marcescens (776)	Cefiderocol	0.12	0.5	0.015–32	0.12	0.5	0.015–2			
	MER	≤ 0.06	0.12	≤ 0.06 to > 64	≤ 0.06	0.12	≤ 0.06 to > 64			
	CAZ/AVI	0.25	0.5	≤ 0.06–16	0.25	0.5	≤ 0.06 to > 64			
	TOL/TAZ	0.5	1	0.12 to > 64	0.5	1	0.12 to > 64			
A. baumannii, all (837)	Cefiderocol	0.25	2	0.008 to >256	0.25	2	≤ 0.002 to > 256			
	MER	8	>64	≤ 0.06 to > 64	64	>64	≤ 0.06 to > 64			
	CAZ/AVI	8	>64	0.5 to > 64	32	>64	≤ 0.06 to > 64			
	TOL/TAZ	4	>64	≤ 0.06 to > 64	16	>64	≤ 0.06 to > 64			
MER-resistant (558)	Cefiderocol							0.5	2	≤ 0.002 to > 256
	MER							64	> 64	4 to > 64
	CAZ/AVI							64	> 64	1 to > 64
	TOL/TAZ							32	> 64	1 to > 64
MDR (368)	Cefiderocol							0.25	8	0.015 to > 256
	MER							64	> 64	< 0.06 to > 64
	CAZ/AVI							32	> 64	≤ 0.06 to > 64
	TOL/TAZ							32	> 64	0.5 to > 64

Table 1 continued

Organism (no. of isolates)	Antimicrobial	N. American isolates			European isolates			Combined/worldwide isolates		
		MIC50	MIC90	Range	MIC50	MIC90	Range	MIC50	MIC90	Range
P. aeruginosa, all (1540)	Cefiderocol	0.12	0.5	≤ 0.002 to 4	0.12	0.5	≤ 0.002 to 8			
	MER	0.5	8	≤ 0.06 to > 64	0.5	16	≤ 0.06 to > 64			
	CAZ/AVI	2	8	0.12 to > 64	2	16	≤ 0.06 to > 64			
	TOL/TAZ	0.5	2	≤ 0.06 to > 64	0.5	8	≤ 0.06 to > 64			
MER-resistant (395)	Cefiderocol							0.25	1	≤ 0.002 to 8
	MER							8	> 64	4 to > 64
	CAZ/AVI							4	64	0.25 to > 64
	TOL/TAZ							1	> 64	0.25 to > 64
CAZ/AVI-resistant (280)	Cefiderocol							0.25	1–2	0.008–32
	MER							64	> 64	0.12 to > 64
	CAZ/AVI							32	> 64	16 to > 64
	TOL/TAZ							> 64	> 64	0.5 to > 64
TOL/TAZ-resistant (310)	Cefiderocol							0.25	1–2	0.004–32
	MER							64	> 64	0.12 to > 64
	CAZ/AVI							32	> 64	1 to > 64
	TOL/TAZ							> 64	> 64	0.5 to > 64
MDR (262)	Cefiderocol							0.25	1	≤ 0.002–32
	MER							32	> 64	≤ 0.06 to > 64
	CAZ/AVI							32	> 64	0.5 to > 64
	TOL/TAZ							> 64	> 64	0.5 to > 64

Table 1 continued

Organism (no. of isolates)	Antimicrobial	N. American isolates			European isolates			Combined/worldwide isolates		
		MIC50	MIC90	Range	MIC50	MIC90	Range	MIC50	MIC90	Range
S. maltophilia (340)	Cefiderocol	0.12	0.5	0.004–64	0.12	0.25	≤ 0.002–64			
	MER	> 64	> 64	0.25 to > 64	> 64	> 64	0.5 to > 64			
	CAZ/AVI	16	64	0.5 to > 64	16	64	0.5 to > 64			
	TOL/TAZ	16	>64	0.25 to > 64	16	> 64	0.25 to > 64			
B. cepacia complex (93)	Cefiderocol	0.015	0.12	≤ 0.002–32	0.015	0.5	≤ 0.002–32			
	MER	4	8	0.12–32	4	16	1–64			
	CAZ/AVI	4	8	0.5–32	4	8	0.25–32			
	TOL/TAZ	4	32	0.25 to > 64	2	32	0.25 to > 64			
MER-resistant [31]	Cefiderocol							0.06	8	≤ 0.002–32
	MER							8	162	8–64
	CAZ/AVI							4	8	0.25–32
	TOL/TAZ							4	32	0.5 to > 64

MER meropenem, *CAZ/AVI* ceftazidime/avibactam, *TOL/TAZ* ceftolozane/tazobactam, *MIC50* minimum concentration (mg/L) to inhibit growth of 50% of isolates, *MIC90* minimum concentration (mg/L) to inhibit growth of 90% of isolates

compared to cefiderocol. Steady-state kinetics demonstrated 3–10 times lower hydrolysis velocity of cefiderocol with NDM-1 compared to meropenem, ceftazidime and cefepime [16]. Cefiderocol has also demonstrated low-level hydrolysis by the IMP-type metallo-carbapenemases, IMP-1 and IMP-6, the latter of which can confer imipenem-susceptible, meropenem-resistant phenotypes to Enterobacterales strains [17]. Against Ambler class-D carbapenemases, OXA-48, OXA-23, and OXA-40, cefiderocol maintained full susceptibility with no changes to the MIC compared to aminopenicillins and carboxypenicillins that demonstrated high-level resistance, and imipenem that demonstrated intermediate-level resistance in *E. coli* isolates modified with bla_{OXA-48}, bla_{OXA-23} and bla_{OXA-40} genes [18].

In addition to carbapenemases, cefiderocol has also demonstrated stability and low induction potential against chromosomal Amp-C β-lactamases. In an in vitro assessment of cefiderocol activity, stability and propensity for Amp C induction in *P. aeruginosa* and *Enterobacter cloacae*, MICs for ceftazidime, cefepime and aztreonam in AmpC-producing isolates were $\geq$ 16-fold higher than the parental strains, whereas MICs for cefiderocol were $\leq$ 4-fold different. AmpC enzyme affinities for cefiderocol in *P. aeruginosa* were 40- and 17-fold lower than for ceftazidime and cefepime, respectively. In *E. cloacae*, enzyme affinities were > 940- and > 8-fold lower for cefiderocol than for ceftazidime and cefepime, respectively. Double disc diffusion assays performed to detect the propensity for ampC induction of cefiderocol compared to imipenem demonstrated that cefiderocol did not induce ampC β-lactamases in *P. aeruginosa* or *E. cloacae* [19].

Mutations causing alteration or loss of porin channels, such as in OmpK35-36 in *K. pneumoniae*, do not appear to significantly impact the in vitro activity of cefiderocol [11, 16, 17]. Additionally, *P. aeruginosa* PAO1 strains with a transposon insertion in *oprD* leading to porin loss demonstrated only a twofold increase in cefiderocol MIC (0.25 μg/mL) over the parent strain compared to an eightfold increase in imipenem MIC (8 μg/mL). On the other hand, two- to fourfold lower MICs in *P. aeruginosa* strains without functional *mexB* or *oprM* genes suggest that cefiderocol may be a substrate of the MexAB-OprM efflux pump [11]. However, overproduction of these efflux pumps only slightly increased MICs, suggesting a limited effect an efflux pump mechanism on the activity of cefiderocol. MICs to cefiderocol against *P. aeruginosa* strains with over-expression of the MexAB-OprM efflux pump were only twofold higher than the PAO1 parent strain, as opposed to ceftazidime, aztreonam and ciprofloxacin that demonstrated fourfold higher MICs [11]. In vitro frequency of resistance analyses in *P. aeruginosa* PAO1 strains have demonstrated lower mutational frequencies with cefiderocol (2.9×10^{-8} and $< 7.1 \times 10^{-9}$ colonies per inoculum) compared to ceftazidime (3.1×10^{-7} and 3.4×10^{-7} colonies per inoculum), at 4-times and 10-times the MIC, respectively. Whole genome sequencing identified mutations in the promoter regions of *pvdS*, which increases pyoverdine production, and *fecI*, which increases expression of the FecA OMP iron transporter, leading to a fourfold increase in cefiderocol MICs and suggesting that these mutations may contribute to cefiderocol resistance in *P. aeruginosa* [20].

Limited data suggest poor activity of cefiderocol against aerobic Gram-positive organisms and anaerobes, both Gram-positive and Gram-negative. Cefiderocol has demonstrated significantly higher MICs to most aerobic Gram-positive organisms compared to piperacillin/tazobactam, cefepime, and meropenem except for *Streptococcus pneumoniae* ATCC 49619 and *Streptococcus pyogenes* ATCC 10389, which demonstrated MICs of 2 and 1 μg/mL, respectively. However, activity of cefiderocol against these strains of Streptococci were still weaker than other β-lactams tested. For anaerobic organisms, although cefiderocol has demonstrated some in vitro activity against strains of *Bacteroides* spp., *Prevotella* spp., and *Clostridium* spp., consistency has not been observed across multiple clinical isolates and it is less potent compared to meropenem and metronidazole [11].

PHARMACOKINETICS AND PHARMACODYNAMICS

Cefiderocol appears to display linear pharmacokinetics, as examined in phase I and II studies. At steady-state, cefiderocol 2 g given as a 60-min infusion every 8 h in healthy adults achieved a peak serum concentration (C_{max}) of 153 μg/mL, elimination half-life ($t_{½}$) of 2.72 h, and systemic clearance (Cl) of 3.89 L/h (Table 2). Cefiderocol is predominantly excreted unchanged via the kidneys [21].

Cefiderocol was also examined in 38 individuals with varying degrees of renal impairment (mild, moderate, or severe and end-stage renal disease (ESRD) requiring hemodialysis). Ratios of $AUC_{0–inf}$ in mild, moderate, severe renal impairment and ESRD compared to normal renal function were 1, 1.5, 2.5, and 4.1, respectively. This is indicative that cefiderocol exposure increases as renal function decreases. Patients with ESRD requiring hemodialysis had a mean drug clearance of 3.1 L/h with approximately 60% of the dose removed by hemodialysis. Plasma protein binding ranged from 53% to 65% and was similar between groups [22]. In a population pharmacokinetic analysis of healthy patients and patients with complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP), cefiderocol pharmacokinetics were best described by a three-compartment model [23]. Effects of disease state on clearance and volume were observed with infected patients having 26% higher total clearance and 36% higher central compartment volume of distribution compared to healthy patients.

Similar to other cephalosporins, the pharmacokinetic/pharmacodynamic (PK/PD) index that best predicts activity is percentage of a 24-h time period that the unbound drug concentration exceeds the MIC ($fT > MIC$) [24–27]. Various dosing regimens were tested in murine thigh and lung infection models caused by Gram-negative bacteria, including *E. coli, K. pneumoniae, P. aeruginosa, A. baumannii,* and *S. maltophilia*. Mean % $fT > MIC$ for a 1 $\log_{10}$ reduction was 73.3% for Enterobacterales and 77.2% for *P. aeruginosa* in thigh infection models. In lung infection models, the mean % $fT > MIC$ for Enterobacterales, *P. aeruginosa, A. baumannii*, and *S. maltophilia* were 64.4%, 70.3%, 88.1%, and 53.9%, respectively [27]. Ghazi et al. characterized cefiderocol PK/PD in a neutropenic murine thigh infection model. MICs in this study were determined by broth microdilution, using iron-depleted medium to mimic the environment of acute infection. Eight clinical isolates of *P. aeruginosa* with MICs ranging from 0.063 to 0.5 μg/mL were used in this study. Targets for bacteriostasis, 1 $\log_{10}$, and 2$\log_{10}$ reductions in bacteria were observed at mean % $fT > MIC$ of 76.3, 81.9, and 88.2, respectively [28]. Based on these animal infection models, a % $fT > MIC$ of 75% was selected as the target for cefiderocol [25, 26].

Monte Carlo simulations based on the pharmacokinetics observed in patients with cUTI or AUP revealed that the $fT > MIC$ values were > 75% in all patients at the dose administered in this study. Patients with normal renal function received 2-g doses as a 1-h infusion every 8 h and doses were adjusted for renal dysfunction. Furthermore, Katsube et al. created a pharmacokinetic model in patients with various degrees of renal function to determine the probability of target attainment (PTA) for $fT > MIC$. In patients with normal renal function, a 2-g dose given as a 3-h infusion every 8 h resulted in > 90% PTA for 75% $fT > MIC$ for an MIC ≤ 4 μg/mL. All dose-adjusted regimens for patients with renal impairment also met these criteria. Sensitivity analyses were performed evaluating PTA for 100% $fT > MIC$ and greater than 90% was still met for MIC ≤ 4 μg/mL. In patients with augmented renal function (CrCl ≥ 120 mL/min), a more frequent dose such as 2 g every 6 h may be necessary. As cefiderocol is removed by hemodialysis, a supplemental dose after intermittent hemodialysis should be considered to provide > 90% of PTA [29]. Table 3 shows the recommended renal dose adjustments from the package insert, which are based on this study [30].

The intrapulmonary pharmacokinetics of cefiderocol was evaluated in a phase I, single-center, open-label study in 20 healthy adult males. Each subject underwent one bronchoscopy in order to calculate cefiderocol

Table 2 Pharmacokinetics of cefiderocol[a] [21, 23]

Dose[b]	*n*	Demographics	CrCl (mL/min)	C_{max} (μg/mL)	t_{max} (h)[c]	AUC (μg·h/mL)	V_{ss} (L)	$t_{½}$ (h)	Cl (L/h)	Feu (%)	Fu (8 h)
1 g × 1	6	Healthy adult males, mean age 28.8 years, mean BMI 22.7 kg/m^2	147.5 ± 20.1[d]	76.4 (4.6)	1.0 (1.0–1.0)	168.1 (11.8)[e]		2.26 (5.8)	5.95 (7.0)	68.3 (4.1)	
1 g q8h × 10 days	8	Healthy adult males, mean age 32.6 years, mean BMI 22.89 kg/m^2	141.5 ± 22.6[d]	69.8 (13.3)	1.0 (1.0–1.0)	160.5 (13.5)[f]		2.35 (18.5)	6.23 (13.5)	70.0 (6.1)	
1 g q8h × 10 days	8	Healthy adult males, mean age 29.6 years, mean BMI 21.9 kg/m^2	130.6 ± 17.1[d]	72.2 (11.5)	1.0 (1.0–1.25)	168.6 (11.0)[f]		2.19 (4.3)	5.93 (11.0)	64.7 (12.8)	
2 g × 1	6	Healthy adults, mean age 30.5 years, mean BMI 21.42 kg/m^2	131.3 ± 29.6[d]	156 (7.9)	1.0 (1.0–1.0)	389.7 (9.0)[e]		2.74 (10.2)	5.13 (9.0)	61.5 (10.6)	
2 g q8h × 10 days	8	Healthy adult males, mean age 34.1 years, mean BMI 22.39 kg/m^2	133.5 ± 23.0[d]	153 (12.9)	1.0 (1.0–1.25)	366.5 (14.0)[f]		2.72 (21.6)	5.46 (14.0)	71.4 (5.3)	
1 g × 1	8	Healthy adults, mean age 56.5, mean BMI 27.3 kg/m^2	100.5 (76.4–122.3)	81.0 (27.4)	1.0 (1.0–1.0)	213.4 (26.5)[e]	13.5 (30.2)	2.8 (16.5)	4.7 (26.5)	68.6 (17.3)	0.44 (9.8)
1 g × 1	8	Healthy adults, mild renal impairment, mean age 58.1, mean BMI 30.9 kg/m^2	78.2 (67.3–91.5)	73.4 (21.3)	1.0 (1.0–1.0)	218.7 (22.2)[e]	14.8 (17.7)	3.0 (8.4)	4.6 (22.2)	68.3 (14.0)	0.42 (19.1)

Table 2 continued

Dose[b]	*n*	Demographics	CrCl (mL/min)	C_{max} (μg/mL)	t_{max} (h)[c]	AUC (μg·h/mL)	V_{ss} (L)	$t_{½}$ (h)	Cl (L/h)	Feu (%)	Fu (8 h)
1 g × 1	8	Healthy adults, moderate renal impairment, mean age 60.1, mean BMI 29.4 kg/m^2	55.3 (38.6–79.3)	78.0 (31.1)	1.0 (1.0–1.0)	312.3 (38.4)[e]	15.4 (28.7)	4.1 (12.6)	3.2 (38.4)	55.5 (19.6)	0.45 (18.5)
1 g × 1	6	Healthy adults, severe renal impairment, mean age 51.8, mean BMI 29.4 kg/m^2	27.7 (15.6–39.1)	80.1 (19.8)	1.0 (1.0–1.0)	543.2 (23.6)[e]	16.4 (23.4)	6.9 (30.6)	1.8 (23.6)		0.44 (10.1)
1 g × 1	8	Healthy adults, ESRD, mean age 45.8, mean BMI 30.9 kg/m^2	ESRD without HD 11.7 (6.0–23.1)	93.0 (27.8)	1.0 (1.0–1.0)	880.7 (24.2)[e]	14.2 (22.5)	9.6 (33.4)	1.1 (24.2)		0.37 (27.0)
1 g × 1	8	Healthy adults, ESRD, mean age 45.8, mean BMI 30.9 kg/m^2	ESRD on HD	75.4 (31.1)	1.0 (1.0–1.5)	318.1 (20.3)[e]	26.6 (33.5)	9.5 (32.8)	3.1 (20.3)		0.42 (21.5)

Table 2 continued

Dose[b]	*n*	Demographics	CrCl (mL/min)	C_{max} (µg/mL)	t_{max} (h)[c]	AUC (µg·h/mL)	V_{ss} (L)	$t_{½}$ (h)	Cl (L/h)	Feu (%)	Fu (8 h)
0.75 g q6h	3	Adults with cUTI or AUP, mean age 60.5, mean weight 77.8 kg	83.0 ± 31.9[d]	69.3 (67.3–72.6)[g]		1003 (872.9–1181)[g, h]					
1 g q6h	40			79.9 (30.7–122)[g]		1026 (316.4–1686)[g, h]					
1.5 g q6h	8			102 (73.8–138)		862.0 (525.2–1227)					
1 g q8h	22			87.5 (57.0–161)		1108 (588.4–1719)					
1.5 g q8h	26			134 (79.0–292)		1186 (588.2–2505)					
2 g q8h	139			138 (29.5–460)		1184 (270.0–3562)					

CrCl creatinine clearance, C_{max} maximum plasma concentration, t_{max} time to C_{max}, *AUC* area under the curve, V_{ss} volume of distribution under steady-state conditions, $t_{½}$ terminal half-life elimination, *Cl* total drug clearance, *Feu* fraction of excreted dose unchanged in the urine, *Fu* fraction of total drug that is unbound in plasma

[a] Values expressed as geometric mean (% coefficient of variation) for all parameters unless specified

[b] Infusions given over 60 min

[c] Values expressed as median (range)

[d] Values expressed as mean ± standard deviation

[e] AUC from 0 to ∞

[f] AUC from 0 to τ

[g] Values expressed as mean (range)

[h] Daily AUC

Table 3 Cefiderocol Dose regimens based on renal function [30]

Renal function	Dose regimen[a]
Augmented (CG-CL_{CR}, ≥ 120 mL/min)	2 g q6h
Normal (CG-CL_{CR}, 90 to < 120 mL/min)	2 g q8h
Mild impairment (CG-CL_{CR}, 60 to < 90 mL/min)	2 g q8h
Moderate impairment (CG-CL_{CR}, 30 to < 60 mL/min)	1.5 g q8h
Severe impairment (CG-CL_{CR}, 15 to < 30 mL/min)	1 g q8h
ESRD (CG-CL_{CR}, < 15 mL/min)	0.75 g q12h
Intermittent hemodialysis	0.75 g q12h

CG-CL_{CR} creatinine clearance estimated by Cockcroft-Gault equation

[a] All doses given as a 3-h infusion

concentrations in the plasma, epithelial lining fluid (ELF), and alveolar macrophages (AM). Cefiderocol was administered as a single 2 g infusion over 60 min. ELF concentrations appear to parallel plasma concentrations, indicating rapid distribution from plasma to ELF. The geometric mean ELF concentration of cefiderocol was 13.8, 6.69, 2.78, and 1.38 mg/L at 1, 2, 4, and 6 h from the start of infusion. The AUC ratios in ELF to total plasma were 0.101 and 0.239 to free plasma, suggesting ~ 24% penetration into the ELF. AUC ratios in AMs to total plasma and free plasma were 0.0177 and 0.0419, respectively, suggesting much lower penetration into AMs [31]. Future work is needed to assess intrapulmonary penetration in infected patients, particularly those who are critically ill.

Drug–drug interaction potentials of cefiderocol were assessed in an open-label, randomized, crossover study of 3 study cohorts. Cohort 1 assessed the effect of cefiderocol on furosemide, an OAT1 and OAT3 substrate. Cohort 2 assessed metformin, an OCT1, OCT2, and MATE2-K substrate, and cohort 3 evaluated rosuvastatin, an OATP1B3 substrate. Furosemide and metformin exposures were not impacted by cefiderocol co-administration. Slight increases in rosuvastatin concentrations were observed with ratios of maximum plasma concentration and area under the plasma concentration–time curve of 1.28 and 1.21, respectively, when co-administered with cefiderocol [32].

ANIMAL EFFICACY MODELS

Cefiderocol has been studied in a variety of animal models to determine its clinical role against Gram-negative organisms. Cefiderocol humanized exposures (2 g every 8 h as a 3-h infusion) for 24 h was evaluated in a neutropenic murine thigh model. Isolates studied were *P. aeruginosa* ($n = 21$), *A. baumannii* ($n = 35$), and Enterobacterales ($n = 39$) with cefiderocol MIC ranges from 0.12 to > 256 mg/L. For isolates with MIC ≤ 4 mg/L, bacterial stasis or ≥ 1 $\log_{10}$ of bacterial kill was achieved in 85% of *P. aeruginosa* isolates, 88% of *A. baumannii* isolates, and 77% of Enterobacterales isolates. In 28 isolates with MIC ≥ 8 mg/L, this same observation only occurred in 2 strains. Bacterial-density studies using a subset of 15 Gram-negative isolates comparing cefiderocol, meropenem, and cefepime activities were also conducted. Even in isolates with high-level cefepime (MICs up to > 512 mg/L) or meropenem (MICs up to > 512 mg/L) resistance, cefiderocol was efficacious against all isolates. Cefiderocol bacterial reduction was 2.6 ± 0.5 and 2.1 ± 0.9 $\log_{10}$ CFU against cefepime- and meropenem-susceptible isolates, respectively, and was similar to those of cefepime (2.6 ± 0.5 $\log_{10}$ CFU) and meropenem (2.2 ± 0.6 $\log_{10}$ CFU). Mean bacterial kill of cefiderocol against cefepime- and meropenem-resistant isolates was 1.5 ± 0.4 $\log_{10}$ CFU [33].

The efficacy of cefiderocol against carbapenem-resistant Gram-negative bacilli was examined in immunocompetent-rat respiratory tract infection models [34]. Six total isolates were evaluated: 1 cephalosporin-susceptible *P. aeruginosa* isolate, 1 multidrug-resistant *P. aeruginosa* isolate, 2 multidrug-resistant *A. baumannii* isolates, and 2 carbapenem-resistant *K.*

pneumoniae isolates. A humanized exposure of cefiderocol 2 g every 8 h as a 3-h infusion for 4 days was compared to a humanized exposure of ceftazidime 1 g every 8 h as a 0.5-h infusion for 4 days. Cefiderocol resulted in a > 3 $\log_{10}$ reduction in CFU of all 5 carbapenem-resistant isolates. However, ceftazidime only demonstrated efficacy against the cephalosporin-susceptible *P. aeruginosa* isolate. Ghazi et al. showed similar results in a neutropenic murine thigh infection model using 8 *P. aeruginosa* isolates, including ones with resistance to 2 preclinical candidate siderophores, cefepime and levofloxacin. Cefiderocol resulted in > 1 $\log_{10}$ CFU reduction in all 8 isolates, including those with resistance to other siderophores [35].

Stainton et al. evaluated the in vivo efficacy of cefiderocol against 12 Gram-negative isolates (*P. aeruginosa*, *A. baumannii*, and Enterobacterales) in a murine thigh infection model. Cefiderocol MICs ranged from 0.5 to 16 μg/mL with elevated cefepime, meropenem, ceftazidime, and/or piperacillin/tazobactam MICs. Cefiderocol, administered at humanized exposures of 2 g every 8 h (3 h infusion), was compared to untreated control at 24, 48, and 72 h. Sustained kill with cefiderocol exposure over 72 h was observed in 9 isolates. It is important to note that while regrowth did occur in some isolates, the pattern of regrowth in their study was inconsistent with the emergence of resistance observed with other siderophores and the phenomenon of adaptive resistance was not observed over the 72 h period. In isolates that were retested for MICs after cefiderocol exposure, only one isolate (1/54 samples, 1.8%) demonstrated an increase in MIC from 1 to 4 μg/mL for an *E. coli* isolate at 72 h [36]. This is notable as adaptive resistance has been well documented in other siderophore compounds. For these compounds, bacterial growth was observed to be similar to that in control animals following supratherapeutic exposure to a siderophore-conjugated monobactam in *P. aeruginosa* with increases in MIC up to $\geq$ 16 fold [37].

Although the majority of organisms evaluated in these animal studies have been *P. aeruginosa*, *A. baumannii*, and Enterobacterales, Takemura et al. conducted an assessment of cefiderocol against *S. maltophilia* in a murine lung infection model. Four clinical isolates were used in this study with cefiderocol MICs ranging from 0.125 to 0.25 μg/mL. Cefiderocol administration resulted in > 3 $\log_{10}$ reduction in all isolates. The in vivo efficacies of cefiderocol were superior to those of ciprofloxacin and at least comparable or superior to those of tigecycline [38].

CLINICAL EFFICACY

The clinical efficacy of cefiderocol has been evaluated in a phase II study among adult patients with cUTI or AUP. This was a multicenter, double-blind, parallel-group, randomized, non-inferiority study comparing cefiderocol to imipenem/cilastatin. Adult patients with a diagnosis of cUTI or AUP were randomized 2:1 to receive cefiderocol 2 g every 8 h administered over 60 min or imipenem/cilastatin 1 g every 8 h for a duration of 7–14 days. Step-down or switch to oral antibiotics was not permitted in this study. Key exclusion criteria included baseline urine culture with more than 2 pathogens, fungal urinary tract infection, carbapenem-resistant pathogens, and CrCl < 20 mL/min [39].

The primary efficacy outcome was a composite end point of clinical response and microbiological response at the test of cure assessment 5–9 days after the last dose of study medication. Response was evaluated in the modified intention-to-treat (mITT) population, which included all randomly assigned participants who received at least one dose of study drug [39].

A total of 448 patients were randomized and received at least one dose of the study drug and 371 patients with a qualifying Gram-negative organism were included in the mITT population. Baseline demographics were similar between groups, with an average age of approximately 61 years and 55% female. Over 70% of patients in both arms had a diagnosis of cUTI with or without pyelonephritis, with *E. coli* being the most common pathogen isolated (60% in the cefiderocol arm vs. 66% in the imipenem/cilastatin arm). *P. aeruginosa* was isolated in 18 (7%) patients in the cefiderocol

group and 5 (4%) in the imipenem/cilastatin group [39].

The primary outcome of clinical and microbiological response was met in 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem/cilastatin group (adjusted treatment difference 18.58%; 95% CI 8.23–28.92; $p = 0.0004$) at test of cure. This met the pre-specified criterion for non-inferiority. At test of cure, microbiological response was higher in the cefiderocol group than the imipenem/cilastatin group (73% vs. 56%; 95% CI 6.92–27.58) with no differences in clinical response (90% vs. 87%; 95% CI − 4.66 to 9.44). This study was designed to demonstrate non-inferiority, but a post hoc analysis was consistent with superiority, with the adjusted treatment difference of 18.58% favoring cefiderocol and the lower limit of the CI exceeding zero.

Per-pathogen microbiological outcomes were also assessed. Treatment differences for patients with *E. coli* and *K. pneumoniae* were consistent with that in the mITT population. In patients with *P. aeruginosa* infectious, the primary outcome was met in 7/15 (47%) patients in the cefiderocol group and 2/4 (50%) patients in the imipenem/cilastatin group. Composite clinical and microbiological response rates for ESBL producing organisms were consistent with those for the overall cohort (62.9% vs. 47.2%; difference 16.66, 95% CI − 3.08 to 36.40) [39].

In addition to the published phase II study, multiple phase III trials are currently underway or awaiting publication of their results. These include one pneumonia study (NCT03032380), one BSI study (NCT03869437), and one study in severe infections caused by carbapenem-resistant Gram-negative pathogens (NCT02714595). Although one study is still enrolling, two of the studies have been completed with preliminary results presented at scientific conferences and/or at the FDA advisory committee meeting.

CREDIBLE-CR (NCT02714595) was a multicenter, randomized, open-label study of cefiderocol compared to best available therapy (BAT) for the treatment of severe infections caused by carbapenem-resistant Gram-negative pathogens and was presented to the US FDA as part of the application for drug approval [40]. The results have not yet been presented further at scientific meetings nor have they undergone peer-reviewed publication. Disease states included were healthcare-associated pneumonia (HCAP), hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP), cUTI, BSI, and sepsis. Cefiderocol 2 g every 8 h was given as a 3-h infusion and BAT was chosen by the investigator and consisted of up to 3 antibacterials. The primary outcome was a clinical outcome at test of cure for patients with HAP/VAP/HCAP, BSI/sepsis, and a microbiologic outcome for patients with cUTI. A total of 101 patients were randomized to the cefiderocol arm and 49 patients to the BAT arm (safety population), with 80 and 38, respectively, having central-laboratory-confirmed infections due to carbapenem-resistant Gram-negative bacilli. These 118 patients made up the CR-mITT population and were the primary efficacy population. Baseline demographics were similar with a mean age of 63 years and APACHE II score of 15. Forty-five percent of patients had APACHE II scores ≥ 16. The majority of patients had a baseline diagnosis of pneumonia (44.6% cefiderocol vs. 44.9% BAT). While most patients in the cefiderocol arm received monotherapy ($n = 66$, 82.5%), the majority of patients in the BAT arm received combination therapy ($n = 27$, 71.1%), largely with colistin-based regimens. In the CR-mITT population clinical cure rates at test of cure were comparable between groups overall (52.5% cefiderocol vs. 50% BAT) and for each individual disease state HAP/VAP/HCAP (50% cefiderocol vs. 52.6% BAT), BSI/Sepsis (43.5% vs 42.9%), and cUTI (70.6% vs. 60%). However, all-cause mortality at day 14, day 28, and day 49 was, respectively, numerically higher in the cefiderocol group (18.8%, 24.8%, 33.7%) compared to BAT (12.2%, 18.4%, 20.4%). The mortality imbalance was greatest at days 14, 28, and 49 for patients with HAP/VAP/HCAP (cefiderocol 24.4%, 31.1%, and 42.2% vs. BAT 13.6%, 18.2%, and 18.2%) and BSI/sepsis (cefiderocol 16.7%, 23.3%, and 36.7% vs. BAT 5.9%, 17.6%, 23.5%). The hazards ratio for time to death with cefiderocol was 1.77, however the 95% confidence interval (0.87–3.57) crossed 1, with a p value of 0.11. Concerningly, the greatest imbalance with deaths at day 49 were

in patients with *A. baumannii* [cefiderocol 19/39 (49%) vs. BAT 4/17 (24%)], and those with APACHE II scores ≥ 16 [21/46 (46%) vs. 5/22 (23%]. Although numbers were small, concerns were also noted with other non-fermenters. Day 49 mortality rates for *P. aeruginosa* were 6/17 (35%) for cefiderocol and 2/12 (17%) for BAT. Further, all five patients in the study with *S. maltophilia* infections were randomized to cefiderocol with 4 (80%) demonstrating day 49 mortality [40].

APEKS-NP (NCT03032380) was a phase III, double-blind, randomized, active-controlled, non-inferiority trial of cefiderocol for the treatment of HAP, VAP, or HCAP caused by Gram-negative pathogens. Patients were randomized to cefiderocol 2 g every 8 h or meropenem 2 g every 8 h, both as a 3-h infusion. Linezolid was administered in both arms for a duration of at least 5 days and cefiderocol or meropenem for 7–14 days [41]. The primary endpoint was all-cause mortality at day 14 for the mITT population with a non-inferiority margin of 12.5%. Cefiderocol was non-inferior with respect to all-cause mortality to meropenem at day 14 [12.4% vs. 11.6% (difference 0.8%; 95% CI − 6.6 to 8.2%)] and day 28 [21.2% vs. 20.1% (difference 1.1%; 95% CI − 8.0 to 10.3)]. Mortality was also similar between groups at day 14, day 28, and end of study in the intention-to-treat population [40].

Real-world clinical use of cefiderocol has also been documented in a few case reports. The first case was in a 78-year-old female with extremely drug-resistant (XDR) *P. aeruginosa* native aortic valve endocarditis. This isolate was found to harbor a $bla_{(\text{Vietnam ESBL})}$ gene and susceptible to only gentamicin, amikacin, and colistin. The patient was also found to be rectally colonized with OXA-48 *K. pneumoniae* and OXA-23/OXA-51 *A. baumannii*. Despite combination therapy with colistin and gentamicin or colistin and meropenem, the patient was persistently bacteremic on days 56, 62, and 68, and the decision was made to request cefiderocol for compassionate use. Blood cultures cleared after 2 days of cefiderocol therapy, 1 day prior to valve surgery. Cefiderocol and colistin combination therapy was continued for an additional 3 weeks. An episode of transient neutropenia occurred near the end of therapy, but neutrophil counts returned to the normal range within a few days of stopping antibiotics [42]. Another case of compassionate cefiderocol use occurred in an adult male patient with XDR *A. baumannii* (susceptible to colistin) and carbapenemase-producing *K. pneumoniae* (susceptible to colistin, gentamicin, and ceftazidime/avibactam) BSI and VAP. Cefiderocol was initiated on day 35 after persistent fevers and worsening lung infiltrates on various colistin-based combination therapies. After 14 days of cefiderocol therapy, chest X-rays showed complete resolution of lung infiltrates, and the patient was discharged to a rehabilitation department [43]. Cefiderocol was also used to successfully treat a 46-year-old patient with MDR *P. aeruginosa* intra-abdominal infection susceptible only to amikacin, cefiderocol, colistin, and gentamicin. After 28 days of cefiderocol and metronidazole therapy, CT of the abdomen demonstrated complete resolution of the intra-abdominal abscess and the patient was ultimately discharged to independent living [44]. Lastly, cefiderocol treatment for 14 weeks resulted in clinical and radiological cure in a 15-year-old male with chronic osteomyelitis caused by XDR *P. aeruginosa* carrying $bla_{\text{NDM-1}}$ and ESBL *K. pnemoniae*. Combination therapy with aztreonam and cefiderocol was originally used, but aztreonam was discontinued after 2 weeks due to increasing liver function markers. Intermittent episodes of decreased white cell count with nadir at 1200/mm^3 was noted on cefiderocol therapy and resolved spontaneously without any adjustments [45].

SAFETY AND TOLERABILITY

The available body of evidence from phase I and phase II studies suggests that cefiderocol is well tolerated and has a safety profile similar to that of other cephalosporins. In a phase I, dose-ascending study in 40 patients, no serious or clinically significant adverse events were observed. Cefiderocol was administered at doses of 100–2000 mg in the single-dose study and 1–2 g every 8 h in the multiple-dose study. In the single-dose study group, 9 adverse events

were reported in 6/30 (20%) of patients with diarrhea (2 events in 2 subjects) and rash (2 events in 2 subjects) being the most common. In the 10-day multiple-dose study, 22 adverse events were reported by 16 subjects. These included alanine aminotransferase (ALT) level increase ($n = 4$), aspartate aminotransferase (AST) level increase ($n = 4$), creatine phosphokinase increase ($n = 3$), white blood cell increase ($n = 2$), rash ($n = 2$), and one case each of diarrhea, pyrexia, abdominal pain, headache, oropharyngeal pain, and urine positive for white blood cells. Allergy tests were conducted for the two participants who reported rash in the 2000-mg group. Levels were almost within normal ranges and measurement of cefiderocol-specific immunoglobulin G and immunoglobulin E showed nondetectable levels. One participant in the multiple-dose group withdrew due to pyrexia [21].

In the second phase I trial, safety and tolerability of cefiderocol was assessed in 30 participants with varying levels of renal impairment. No serious adverse events or deaths were reported in this study. The most frequently reported adverse event was contact dermatitis (7.9%), which were assessed as unrelated to the study drug. Drug-related adverse events were noted in 5 patients (13.2%), including nausea, maculopapular rash, urticaria, myalgia, and polyuria. There was no correlation between the incidence of adverse events and the degree of renal impairment. One patient discontinued treatment due to urticaria [22].

Adverse events in the phase II cUTI or AUP study were similar between the cefiderocol and imipenem/cilastatin groups (41% vs. 51%). Treatment emergent adverse events were also similar (9% vs. 11%). Adverse events with rates > 2% in the cefiderocol group were diarrhea (4%), hypertension (4%), constipation (3%), and infusion site pain (3%). A total of 14 serious adverse events were reported in the cefiderocol group, including 1 case of *C. difficile* colitis. One death was reported in the cefiderocol group due to cardiac arrest, although this was considered unrelated to the study drug by the investigator [39].

The rate of adverse events in the CREDIBLE-CR study were similar, with over 90% of patients in the cefiderocol arm and BAT arm experiencing at least 1 adverse event. The incidence of adverse events considered to be treatment-related were 14.9% in the cefiderocol arm and 22.4% in the BAT arm. The most common overall adverse events reported in the cefiderocol arm (≥ 10%) were diarrhea, increased ALT, increased AST, pleural effusion, and chest pain [40].

The effect of cefiderocol on QT and corrected QT (QTcF) interval was also evaluated in a phase I study in healthy adult subjects. Cefiderocol was administered as a 3-h infusion in normal doses of 2 g and supratherapeutic doses of 3 g and 4 g compared to moxifloxacin 400 mg as the positive control. No clinically significant effect was found on the QTcF interval or other ECG parameters with any cefiderocol dose. Moxifloxacin resulted in a prolongation of the QTcF interval for all time points [46].

To summarize, the limited data available from phase I and phase II studies have not demonstrated significant safety concerns for cefiderocol; however publication of the phase III data have yet to occur. Further studies will need to be conducted to comprehensively assess drug–drug interactions. It is also unclear if there is a significant cross-reactivity between penicillins or cephalosporins and cefiderocol. While cefiderocol does not appear to share a similar side with any penicillins, it shares the same R1 side chain with aztreonam and ceftazidime and a similar R2 side chain with cefepime [47].

CONCLUSION AND PLACE IN THERAPY

Cefiderocol is a first-in-class siderophore cephalosporin with broad coverage against many drug-resistant Gram-negative bacteria. Its unique mechanism of action allows for high intracellular penetration into the periplasmic space and increased stability to many β-lactamases, including both serine-type (KPC, OXA) and Ambler class B metallo-β-lactamases (VIM, IMP, NDM). Additionally, due to its ability to penetrate the cells by mechanisms independent of classic porin channels, cefiderocol may remain active when β-lactam resistance is

driven by porin channel mutations. Data from global surveillance studies demonstrate potent in vitro activity against a wide variety of Gram-negative pathogens, including *P. aeruginosa*, *A. baumannii*, Enterobacterales, and *S. maltophilia*.

The PK/PD target best associated with efficacy for cefiderocol is $fT > MIC$, similar to other cephalosporins. Cefiderocol is mainly renally excreted and requires dose adjustments for both renal impairment and augmented renal clearance. Based on pharmacodynamic analyses, a dosage of 2 g every 8 h as a 3-h infusion was selected. In vivo efficacy of cefiderocol has been studied in various animal models, including murine and rat infection models, and has performed similarly to or superior to comparator drugs, such as tigecycline, ciprofloxacin, and cefepime.

Cefiderocol has an important place in therapy for cUTI and AUP, particularly in infections due to MDR Gram-negative organisms. The adverse event profile, low risk of drug interactions, and the ability to largely avoid all 3 mechanisms of carbapenem resistance in Gram-negative pathogens make cefiderocol an important antibiotic to have in our armamentarium. In the cUTI study, with a primary composite endpoint of microbiological eradication and clinical response at test of cure, cefiderocol was non-inferior to imipenem/cilastatin [40]. Outside of the cUTI study, clinical data for cefiderocol are limited to phase II and unpublished phase III studies.

The place in therapy of cefiderocol for systemic infections such as pneumonia and BSI due to drug-resistant pathogens remains unclear. The all-cause mortality imbalance in CREDIBLE-CR study is concerning. Even more concerning is that the imbalance was driven by the very pathogens (*A. baumannii*, *P. aeruginosa*, *S. maltophilia*), disease states (pneumonia, BSI), and patient types (high severity of illness) where cefiderocol is most needed. While it is encouraging that clinical cure rates were similar between cefiderocol and BAT, this does not offset the mortality concerns. Cefiderocol is coming to market at a time when either RCT or real-world clinical data are available that strongly suggest the superiority of ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, ceftolozane/tazobactam, and plazomicin over this same comparator [48–53]. Therefore, the lack of an improvement in clinical cure combined with a signal for potentially increased mortality is suboptimal. However, it is important to note that CREDIBLE-CR does represent a different population than those in the aforementioned studies, with nearly half the patients having *A. baumannii* infections (compared to zero in the other datasets such as those studies targeted CRE or *P. aeruginosa*), and a larger proportion of patients being treated for pneumonia (large proportions of the CRE trials were BSI or cUTI.) Conversely, there are the high-level results of APEKS-NP, a study focused on nosocomial pneumonia with an impressive comparator arm of high-dose, extended infusion meropenem. This study demonstrated no difference between cefiderocol and meropenem with regards to all-cause mortality. This increases confidence that the preclinical excitement of cefiderocol can hold true in the clinical setting; however, additional details related to these data are needed before further judgment can be made.

So where does this leave the clinician? Given the unknowns and concerns, at this point, cefiderocol should not be placed in the same category as other novel β-lactam therapies (ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, and imipenem/relebactam), and these agents should be given preferential placement above cefiderocol for resistant pathogens susceptible to both. Once further data become available, it will be appropriate to revisit this stance, but current evidence does not support putting them on equal grounds. Further, until more data are available, it would be prudent to continue to prefer non-β-lactam options (trimethoprim-sulfamethoxazole, tetracyclines, fluoroquinolones) to cefiderocol for less commonly encountered non-fermenters, such as *S. maltophilia* and *Burkholderia* spp. unless resistance or intolerance prevents this. In scenarios where there are no good alternatives (e.g., polymyxin-only susceptible pathogens), a firm recommendation cannot be made. Until further data are available, clinicians will need to weigh the risks and benefits of cefiderocol, and consideration

should be given to combination therapy. Full publication of CREDIBLE-CR and APEKS-NP, as well as completion of the GAME CHANGER trial (NCT03869437) comparing cefiderocol and standard therapy for all comer Gram-negative BSI, will help further place cefiderocol. Additionally, clinicians should be encouraged to publish their real-world experience, both good and bad, to help inform this decision.

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