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REVIEW ARTICLE

Cefiderocol, a New Siderophore Cephalosporin for the Treatment of Complicated Urinary Tract Infections Caused by Multidrug-Resistant Pathogens: Preclinical and Clinical Pharmacokinetics, Pharmacodynamics, Efficacy and Safety

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Abstract

Cefiderocol (Fetroja®) is a siderophore cephalosporin and has demonstrated potent activity against extended-spectrum beta-lactamases producing *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae*, and nonfermenting Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii, Burkholderia cepacia*, and *Klebsiella pneumoniae*. However, cefiderocol has limited activity against Gram-positive bacteria and anaerobes like *Bacterodies fragilis*. In the APEKS-cUTI study, 183 (73%) of 252 patients in the cefiderocol group versus 65 (55%) of 119 patients in the imipenem-cilastatin group achieved the composite outcome of clinical and microbiological eradication of Gram-negative bacteria (treatment difference of 18.58%; 95% CI 8.23–28.92, p = 0.0004) in complicated urinary tract infections (cUTIs). Cefiderocol was non-inferior to imipenem-cilastatin in cUTIs caused by Gram-negative bacteria such as *E. coli, K. pneumoniae, P. aeruginosa, Proteus mirabilis, Enterobacter cloacae, Morganella morganii,* and *Citrobacter freundii*. Cefiderocol required dose adjustment in patients with renal impairment and percentage of time that free drug concentrations above the minimum inhibitory concentration (%fT > MIC) best correlated with clinical outcomes. The most common adverse events with cefiderocol were gastrointestinal symptoms such as diarrhea, constipation, nausea, vomiting, or upper abdominal pain. Two phase III clinical trials, the CREDIBLE-CR study and the APEKS-NP study, investigated the efficacy and safety of cefiderocol for the treatment of pneumonia or cUTI, and both studies showed higher all-cause mortality associated with cefiderocol. Therefore, the use of cefiderocol should be limited only to the treatment of cUTIs from Gram-negative bacteria, especially in patients who have limited or no alternative treatment options.

1 Introduction

According to the Centers for Disease Control and Prevention (CDC), infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) organisms are associated with high mortality rates in inpatient healthcare settings up to 50% [1]. CRE can result in bloodstream infections, ventilator-associated pneumonia, intra-abdominal abscesses, and urinary tract infections due to exposure to healthcare and antibiotics [1, 2]. Hence, it is imperative to develop a new antibiotic to overcome antimicrobial resistance. Cefiderocol was developed in line with US Food and Drug Administration (FDA)-guided streamlined development for antibiotics to treat life-threatening infections caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) [3]. Cefiderocol, a new parenteral siderophore cephalosporin, has demonstrated potent activities against Gram-negative pathogens such as carbapenem-resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii, Burkholderia cepacia*, and *Stenotrophomonas maltophilia* that are MDR and carbapenem-resistant isolates by producing carbapenemases and β-lactamases [4–7]. Cefiderocol is approved for the treatment of complicated urinary tract infection (cUTI) with limited or no alternative treatment options [8].

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Key Points

Cefiderocol (Fetroja®) is a siderophore cephalosporin that results in an iron-depleted environment of Gram-negative bacteria via the "Trojan horse" strategy.

Cefiderocol has demonstrated time-dependent bactericidal activity against Gram-negative bacteria, especially those with multidrug-resistant organisms, including carbapenem-resistant *Enterobacteriaceae* (CRE).

Cefiderocol has received the US Food and Drug Administration approval for the treatment of complicated urinary tract infections (cUTIs) from Gram-negative bacteria, especially in patients who have limited or no alternative treatment options.

Due to an increase in all-cause mortality in patients treated with cefiderocol compared to those treated with best available therapy, cefiderocol is reserved for cUTIs in carbapenem-resistant Gram-negative bacterial infections.

2 Methods of Literature Review

A literature search from PubMed (1996-March 2020) and EMBASE (1947-March 2020) was conducted using terms including "cefiderocol," "S-649266," or "multi-drug resistant pathogens." Results were limited to primary literature published in English. Additional information was gathered from Shionogi Inc. website and clinicalTrials.gov. provided by the US National Library of Medicine.

3 Mechanism of Action

Cefiderocol is a siderophore cephalosporin with a catechol group (Fig. 1), which is important for antibacterial activities against multi-drug resistant GNB such as *P. aeruginosa* and *A. baumannii* [5, 9]. The carboxylic acid of the C-7 side chain improves cefiderocol permeability into the outer membrane, and the chlorocatechol group of the C-3 side chain chelates iron. This chelating activity is responsible for antibacterial activities of cefiderocol, resulting in an iron-depleted environment and the uptake of cefiderocol [10]. By inhibiting mainly penicillin-binding protein 3 (PBP3) of *Enterobacteriaceae* and nonfermenting GNB, the antibacterial action of cefiderocol results in morphological changes of filamentous cells [4]. Active transport of cefiderocol into GNB and its stability against clinically relevant carbapenemases have shown a dual antimicrobial activity of this siderophore cephalosporin [10].

4 Spectrum of Activity

Cefiderocol has demonstrated potent activity against a range of GNB such as *Enterobacteriaceae*, *A. baumannii*, *P. aeruginosa*, *B. cepacia*, and *S. maltophilia*, including MDR and carbapenem-resistant isolates that produce carbapenemases and β-lactamases [6, 7]. In the SIDERO-CR study, cefiderocol demonstrated efficacy against isolates of Gram-negative bacilli that are not susceptible to ceftazidime-avibactam, ceftolozane-tazobactam, and colistin [11]. Compared to cefepime or meropenem, cefiderocol has shown weak activity against multiple clinical isolates of anaerobic bacteria such as *Bacteroides* spp., *Prevotella* spp., or *Clostridioides difficile* [4]. The antibacterial activity of cefiderocol was superior to that of comparators, including cephalosporins, carbapenems, fluoroquinolones, and monobactams against MDR Gram-negative pathogens, except for colistin and tigecycline, with equivalent efficacy against certain subgroup organisms [12]. However, another study found that cefiderocol showed lower minimum inhibitory concentrations (MICs) compared to ten antibiotics against carbapenem-resistant GNB, including strains resistant to colistin and aminoglycoside. It has demonstrated that isolates producing carbapenemases or β-lactamases cannot develop resistance to cefiderocol [13]. Seven studies investigated in vitro activities of cefiderocol against MDR Gram-negative pathogens. Dobias et al. demonstrated excellent cefiderocol activity against *K. pneumoniae* carbapenemase (KPC), OXA, inosine-5′-monophosphate (IMP), Verona integron-mediated metallo-β-lactamase (VIM), New Delhi metallo-β-lactamases (NDM)-producing Enterobacteriaceae and carbapenemase- [IMP, KPC, VIM, São Paulo metallo-β-lactamase (SPM), Germany imipenemase (GIM)] producing *P. aeruginosa* [12]. Kazmierczak et al. demonstrated

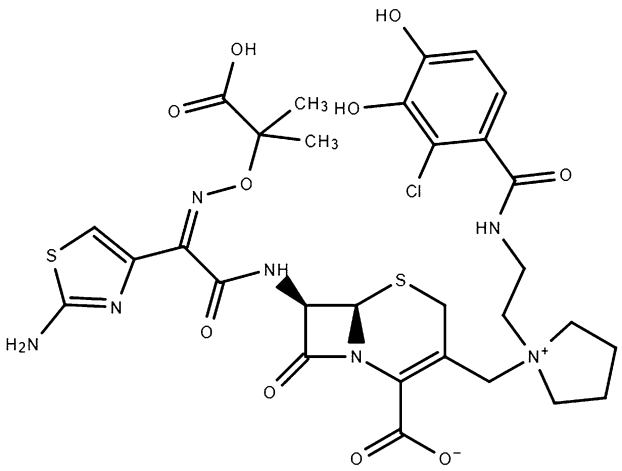

Fig. 1 The chemical structure of cefiderocol

excellent cefiderocol activity against IMP, OXA, KPC, VIM, and NDM producing resistant *Enterobacteriaceae* [14]. Jacobs et al. demonstrated excellent cefiderocol activity against MDR *A. baumannii, S. maltophilia, P. aeruginosa*, and *Enterobacteriaceae* [15]. Cefiderocol demonstrated potent in vitro activity against 231 isolates of MDR GNB, and 98% of which were MICs of 4 mg/L shown to be superior to comparators [16]. Five isolates were not susceptible to cefiderocol (MIC > 4 mg/L), including three ST2/OXA-24/40-producing *A. baumannii*, one ST114/VIM-1-producing *E. cloacae*, one ST114/VIM-1, and OXA-48-producing *E. cloacae* [16]. All KPC-3-producing *K. pneumoniae* resistant to ceftazidme/avibactam were inhibited by cefiderocol (MIC < 4 mg/L). *P. aeruginosa* and *S. maltophilia* isolates were inhibited by cefiderocol (both at MICs < 4 mg/L), which were not susceptible to ceftolozane/tazoactam and levofloxacin, respectively [16]. Golden et al. reported that all 800 isolates of Gram-negative bacilli from intensive care units (ICUs), including of extended-spectrum β-lactamases (ESBL)-producing ($n = 40$), AmpC-producing ($n = 6$), and carbapenem-nonsusceptible ($n = 21$) *Enterobacterales*, carbapenem-nonsusceptible ($n = 54$) and MDR ($n = 29$) *P. aeruginosa*, *S. maltophilia* ($n = 66$), and *A. baumannii* ($n = 11$) were susceptible to cefiderocol with an MIC ≤ 4 μg/mL of which 99% (600/606) met FDA breakpoints of MIC ≤ 2 μg/mL [17]. Notably, cefiderocol demonstrated a fourfold potent antimicrobial activity to *P. aeruginosa* than compactors, including ceftazidime/avibactam, ceftolozane/tazobactam, colistin, meropenem, and piperacillin/tazobactam, which is a pathogen responsible for pneumonia in critically ill patients in ICUs [17]. Cefiderocol had potent in vitro activity against 97.5% of 478 GNB isolates from cancer patients with MIC90 ≤ 4 mg/L [18]. It has demonstrated activity against isolates of ESBL-positive *Enterobacteriaceae*, CRE, and nonfermenting Gram-negative bacilli, including *P. aeruginosa, S. maltophilia*, and *Acinetobacter* [18]. Against non-CRE, ceftazidime-avibactam, meropenem, and tigecycline had a comparable activity to cefiderocol; however, cefiderocol alone was active against MDR *P. aeruginosa* isolates [18]. Cefiderocol and trimethoprim-sulfamethoxazole had appreciable activity against *S. maltophilia* isolates [18]. Overall, cefiderocol demonstrated the lowest level of resistance to GNB [18].

While neither resistance pattern to cefiderocol nor the underlying mechanisms have been studied, Kawai et al. reported reduced susceptibility to cefiderocol in AmpC beta-lactamases with R2 loop deletion that increased hydrolysis of cefiderocol and ceftazidime-avibactam [19]. This finding explained the evolving survival strategy of MDR GNB to beta-lactam agents under selective pressure, and warrants further studies [19].

Table 1 summarizes data of the MIC50 and MIC90 of the antibiotics against bacterial isolates.

5 Pharmacokinetics and Pharmacodynamics

A phase I, randomized, double-blind, placebo-controlled study was conducted to evaluate the pharmacokinetics, safety, and tolerability of cefiderocol in healthy subjects [20]. A single ascending-dose study included doses of 100, 250, 500, 1,000, or 2000 mg cefiderocol, and a multiple ascending-dose study evaluated doses of 1000 and 2000 mg cefiderocol every 8 h over 60-min intravenous infusions [20]. Dose-dependent increases appeared in the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) following single and multiple intravenous infusions of 100–2000 mg [20]. This study demonstrated that cefiderocol was safe and well tolerated in patients administered 2000 mg every 8 h [20]. No clinically significant adverse reactions were reported except one patient receiving 1000 mg every 8 h was withdrawn due to fever [20]. Cefiderocol was excreted in the urine mostly unchanged (60–70%), and no accumulation of cefiderocol and cefiderocol metabolites were observed after a 1-h intravenous infusion of 1000 mg cefiderocol in healthy subjects [20, 21]. Pharmacokinetic parameters including C_{max}, AUC, total clearance (CL), and terminal half-life ($t_{1/2}$) of the multiple dosing every 8 h were similar to those of the single-dose study, indicating there was no change in pharmacokinetics [20].

Since most cefiderocol is renally excreted, another study evaluated pharmacokinetics and safety of cefiderocol in subjects with renal impairment [22]. A single intravenous infusion of 1000 mg over 1 h was administered to subjects with mild, moderate, or severe renal impairment and end-stage renal disease (ESRD) with or without hemodialysis [22]. Cefiderocol was given twice for subjects with hemodialysis-dependent ESRD [22]. In comparison to a normal renal function group, there was increased cefiderocol exposure in subjects with moderate, severe renal impairment and those with ESRD without hemodialysis, as evidenced by increased AUC and the mean plasma $t_{1/2}$ [22]. The study found that renal impairment impacted AUC, CL, and $t_{1/2}$ with little change in C_{max} [22]. Ratios of AUC in mild, moderate, severe, and ESRD groups to those with normal renal function were 1.0, 1.5, 2.5, and 4.1, respectively; however, ratios of C_{max} were similar between groups, as shown 0.9, 0.9, 1.0, and 1.1, respectively [22]. Due to the significant removal of cefiderocol with hemodialysis, dose adjustment is suggested in patients with renal impairment [22].

Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol were conducted to determine dose adjustment based on renal function [23]. Using plasma, urine, and dialysate data in two phase I studies, population pharmacokinetic models were proposed using a nonlinear mixed-effect model [23]. The pharmacodynamic index,

Table 1 Antimicrobial activity of cefiderocol and comparator antimicrobial agents against Gram-negative organisms

Organism	Cefiderocol		Ceftazidime		Meropenem		Levofloxacin		Cefepime		PIPC-TAZ		CAZ-AVI		CFT-TAZ		Ciprofloxacin		Colistin		Tigecycline		Amikacin		References
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	
A. baumannii	0.06	0.5	> 64	> 64	64	> 64	–	–	> 16	> 16	–	–	32	64	32	> 64	> 4	> 4	1	8	1	2	> 64	> 64	[13]
	0.5	2	–	–	64	> 64	–	–	64	> 64	–	–	64	> 64	32	> 32	> 8	> 8	0.5	> 8	–	–	–	–	[7]
	0.063	–	8	–	1	–	–	–	16	–	16	–	16	–	2	–	1	–	0.5	–	–	–	16	–	[4]
	0.12	1	64	> 64	2	> 64	–	–	16	> 16	–	–	16	> 64	8	> 64	> 4	> 4	≤0.5	2	1	2	≤4	> 64	[15]
	0.125	2	> 32	> 32	> 16	> 16	> 8	> 8	32	> 32	–	–	–	–	–	–	–	–	–	–	–	–	–	–	[6]
	–	4	–	> 64	–	> 64	–	–	–	> 16	–	–	–	32	–	> 64	–	> 4	–	2	–	2	–	16	[18]
	0.06	–	–	–	0/5	–	–	–	–	–	4	–	16	–	1	–	–	–	0.5	–	–	–	–	–	[17]
	0.25	4	64	> 64	64	> 64	–	–	> 16	> 16	–	–	32	64	16	> 64	> 4	> 4	1	4	2	4	64	> 64	[16]
OXA-58-positive	0.06	1	–	–	8	16	–	–	16	> 64	–	–	64	> 64	16	> 64	> 8	> 8	1	1	–	–	–	–	[14]
OXA-23-positive	0.12	1	–	–	64	>64	–	–	64	>64	–	–	32	>64	16	>64	>8	>8	1	>8	–	–	–	–	[14]
OXA-24-positive	0.12	1	–	–	>64	>64	–	–	32	>64	–	–	16	>64	8	> 64	> 8	> 8	0.5	1	–	–	–	–	[14]
P. aeruginosa	0.12	0.5	32	> 64	32	> 64	–	–	16	> 16	–	–	16	> 64	> 64	> 64	> 4	> 4	≤ 0.5	1	> 4	> 4	64	> 64	[13]
	0.25	1	–	–	8	> 64	–	–	16	64	–	–	4	64	1	> 64	8	> 8	1	1	–	–	–	–	[7]
	0.5	–	2	–	0.25	–	–	–	2	–	2	–	2	–	0.5	–	0.25	–	0.5	–	–	–	4	–	[4]
	≤0.063	1	4	> 32	0.5	> 16	1	> 8	4	32	–	–	–	–	–	–	–	–	–	–	–	–	–	–	[6]
	0.25	0.5	64	> 64	32	64	–	–	> 16	> 16	–	–	64	> 64	> 64	> 64	> 4	> 4	1	1	> 4	> 4	64	> 63	[15]
	0.06	0.5	–	–	1	16	–	–	–	–	8	128	2	8	1	2	–	–	1	2	–	–	–	–	[17]
P. aeruginosa, MDR	–	1	–	> 64	–	> 64	–	–	–	> 16	–	–	–	>64	–	> 64	–	–	–	8	–	> 4	–	64	[18]
	0.12	–	–	–	16	–	–	–	–	–	128	–	16	–	2	–	–	–	1	–	–	–	–	–	[17]
Meropenem-non-susceptible *P. aeruginosa*	0.12	1	–	–	16	32	–	–	–	–	16	256	8	> 16	1	4	–	–	1	2	–	–	–	–	[17]
VIM-positive	0.25	2	–	–	> 64	>64	–	–	32	>64	–	–	64	>64	>64	>64	>8	>8	1	2	–	–	–	–	[14]
IMP-positive	–	2	–	–	>64	>64	–	–	>64	> 64	–	–	>64	>64	>64	>64	>8	>8	–	2	–	–	–	–	[14]
S. maltophilia	0.125	–	>32	–	> 32	–	–	–	32	–	> 32	–	32	–	32	–	0.25	–	1	–	–	–	4	–	[4]
	0.125	0.5	32	> 32	> 16	> 16	1	8	32	> 32	–	–	–	–	–	–	–	–	–	–	–	–	–	–	[6]
	0.06	0.25	> 64	> 64	–	–	–	–	> 16	> 16	–	–	64	> 64	> 64	> 64	2	> 4	1	8	0.5	2	> 64	> 64	[15]
	–	0.25	–	> 64	–	> 64	–	–	–	> 16	–	–	–	> 64	–	> 64	–	> 4	–	> 8	–	> 4	–	> 64	[18]
	0.12	0.5	–	–	> 32	> 32	–	–	–	–	256	> 512	> 16	> 16	32	> 64	–	–	4	> 16	–	–	–	–	[17]
	0.25	0.5	> 64	> 64	> 64	> 64	≤1	4	–	–	–	–	32	> 64	32	> 64	–	–	> 8	> 8	0.5	2	> 64	> 64	[16]

Table 1 (continued)

Organism	Cefiderocol		Ceftazidime		Meropenem		Levofloxacin		Cefepime		PIPC-TAZ		CAZ-AVI		CFT-TAZ		Ciprofloxacin		Colistin		Tigecycline		Amikacin		References
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	
Enterobacteriaceae	1	4	–	–	16	> 64	–	–	> 64	> 64	–	–	1	> 64	> 64	> 64	> 8	> 8	0.5	> 8	–	–	–	–	[7]
	0.5	4	> 64	> 64	8	> 64	–	–	> 16	> 16	–	–	0.5	2	64	> 64	> 4	> 4	0.5	4	0.5	1	16	32	[15]
Escherichia coli	≤ 0.03	0.5	–	–	≤ 0.03	≤ 0.03	–	–	–	–	2	16	0.12	0.25	0.25	0.5	–	–	0.25	0.5	–	–	–	–	[17]
ESBL-producing *E. coli*	0.25	–	–	–	≤ 0.03	–	–	–	–	–	4	–	0.25	–	0.5	–	–	–	0.25	–	–	–	–	–	[17]
Amp C-producing *E. Coli*	≤ 0.03	–	–	–	≤ 0.03	–	–	–	–	–	8	–	0.25	–	0.5	–	–	–	0.25	–	–	–	–	–	[17]
Ertapenum-non-susceptible *Enterobacteriaceae*	0.25	–	–	–	0.25	–	–	–	–	–	128	–	1	–	16	–	–	–	0.25	–	–	–	–	–	[17]
VIM-positive	1	4	–	–	16	64	–	–	64	> 64	–	–	> 64	> 64	> 64	> 64	> 8	> 8	0.5	> 8	–	–	–	–	[14]
	1	4	> 64	> 64	32	> 64	–	–	> 16	> 16	–	–	> 64	> 64	> 64	> 64	> 4	> 4	≤ 0.5	1	≤ 0.25	1	8	> 64	[12]
OXA-48-positive	0.5	4	–	–	8	64	–	–	> 64	> 64	–	–	1	4	> 64	> 64	> 8	> 8	0.5	> 8	–	–	–	–	[14]
	0.25	2	64	> 64	1	32	–	–	> 16	> 16	–	–	0.5	4	32	> 64	> 4	> 4	≤ 0.5	1	≤ 0.25	1	≤ 4	16	[12]
	0.25	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	[15]
B. cepacian	0.06	8	–	–	8	162	–	–	64	> 64	–	–	4	8	4	32	4	> 8	> 8	> 8	–	–	–	–	[7]
	≤ 0.031	–	4	–	4	–	–	–	32	–	32	–	2	–	2	–	1	–	> 32	–	–	–	> 32	–	[4]
K. pneumoniae	0.5	1	> 64	> 64	32	> 64	–	–	> 16	> 16	–	–	1	> 64	> 64	> 64	> 4	> 4	≤ 0.5	> 8	0.5	2	16	> 64	[13]
	≤ 0.031	–	0.125	–	0.063	–	–	–	0.063	–	2	–	0.25	–	0.25	–	0.063	–	0.25	–	–	–	1	–	[4]
	1	4	–	–	16	> 64	–	–	> 64	> 64	–	–	1	> 64	> 64	> 64	> 8	> 8	0.5	> 8	–	–	–	–	[7]
	–	2	–	> 64	–	0.125	–	–	–	> 16	–	–	–	0.5	–	32	–	> 4	–	> 8	–	> 4	–	16	[18]
	≤ 0.03	0.25	–	–	≤ 0.03	0.06	–	–	–	–	4	8	0.25	0.5	0.25	1	–	–	0.25	1	–	–	–	–	[17]
	0.5	2	> 64	> 64	8	> 64	–	–	> 16	> 16	–	–	1	4	> 64	> 64	> 4	> 4	≤ 0.5	> 8	1	2	8	64	[16]
ESBL-producing *K. pneumoniae*	1	–	–	–	0.06	–	–	–	–	–	32	–	0.5	–	2	–	–	–	0.25	–	–	–	–	–	[17]
KPC-positive	1	2	–	–	64	> 64	–	–	> 64	> 64	–	–	1	4	64	> 64	> 8	> 8	1	> 8	–	–	–	–	[14]
	1	2	> 64	> 64	32	> 64	–	–	> 16	> 16	–	–	1	4	64	> 64	> 4	> 4	≤ 0.5	> 8	0.5	1	16	32	[12]
KPC-3	0.25	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	[15]

percentage of time that free drug concentrations above the minimum inhibitory concentration (%fT > MIC), was best correlated with clinical outcomes [8]. Hence, Monte-Carlo simulations were used to calculate the probability of target attainment (PTA) for the MIC range of 0.25–16 µg/mL [23]. Adjusted dose regimens were determined based on C_{max} and daily AUC per renal function group using the MDRD-eGFR covariate model [23]. For subjects with normal renal function and mild renal impairment, a dose of 2,000 mg cefiderocol every 8 h with 3-h infusion achieved 90% PTA where 75% fraction of time was against strains with MIC < 4 µg /mL [23]. More frequent dosing every 6 h is desirable for patients with augmented renal function based on CG-CL_{CR} [23]. Moderate and severe renal impairment requires 1.5 and 1 g, respectively, every 8 h with 3-h infusion; 0.75 g every 12 h with 3-h infusion in ESRD patients with or without hemodialysis [23].

A summary of pharmacokinetic data is available in Table 2.

6 Efficacy

6.1 In Vitro Activity

Six in vitro studies have been conducted to demonstrate the antimicrobial activity of cefiderocol against isolates, including MDR and carbapenem-resistant GNB [7, 11, 13, 24]. In the SIDERO-WT-2014 study, MIC to inhibit the growth of 90% isolates (MIC90) was determined for the 9,205 clinical isolates of GNB, such as *Enterobacteriaceae, P. aeruginosa, A. baumannii, S. maltophilia, and B. cepacian* from North America and Europe [24]. In this study, the in vitro activity of cefiderocol was superior to that of antibiotic comparators, including colistin, ceftazidime-avibactam, and ceftolozane-tazobactam against isolates of meropenem-resistant and MDR GNB, which limits current treatment options for MDR infections [24]. Cefiderocol was effective against isolates of CRE, MDR *P. aeruginosa*, MDR *A. baumannii, S. maltophilia,* and *B. cepacian*, as evidenced by MICs ≤ 4 µg/mL [11, 24].

In another study comparing the efficacy of cefiderocol against MDR Gram-negative isolates with comparators, including ceftolozane-tazobactam (CT), meropenem (MEM), ceftazidime (CAZ), ceftazidime-avibactam (CZA), colistin (CST), aztreonam (ATM), amikacin (AMK), ciprofloxacin (CIP), cefepime (FEP), and tigecycline (TGC) [8]. Cefiderocol (MIC90 2–4 mg/L) demonstrated more potent efficacy compared to other comparators (MIC90 > 4 to > 64 mg/L) against all isolates, except colistin and tigecycline, having comparable efficacy to cefiderocol [12].

In the study conducted by Falagas, cefiderocol achieved an MIC90 of 0.5 mg/L against meropenem intermediate

Table 1 (continued)

MIC minimum inhibitory concentration (µg/mL), *PIPC–TAZ* piperacillin-tazobactam, *CAZ-AVI* ceftazidime-avibactam, *VIM* Verona integron-mediated metallo-β-lactamase, *IMP* active-on-imipenem, *ESBL* extended-spectrum β-lactamases, *Amp C* ampicillin C, *A. baumannii: Acinetobacter baumannii, P. aeruginosa MDR:* multidrug-resistant *Pseudomonas aeruginosa*, *S. maltophilia: Stenotrophomonas maltophilia, B. cepacian: Burkholderia cepacian, K. pneumoniae: Klebsiella pneumoniae, KPC: Klebsiella pneumoniae carbapenemase*

isolates and MIC90 of 1 mg/L against meropenem-resistant isolates of *Enterobacteriaceae, A. baumannii, P. aeruginosa, P. stuartii, K. pneumoniae*, and *E. cloacae,* which was superior to tigecycline and colistin [13]. Again, the potent antibacterial activity of cefiderocol was confirmed with MICs less than 4 µg/mL against isolates of GNB that are not susceptible to ceftazidime-avibactam, ceftolozane-tazobactam, and colistin [7, 11]. Against meropenem susceptible isolates from North America and Europe, cefiderocol exhibited an MIC90 of 0.5 and 1 mg/L for *Enterobacteriaceae*; 0.5 and 0.5 mg/L for *P. aeruginosa*; 1 and 2 mg/L for *Acinetobacter* spp.; 0.5 and 0.25 mg/L for *S. maltophilia*; 0.12 and 0.5 mg/L for *B. cepacia complex* spp., respectively [7]. Against meropenem-resistant isolates, cefiderocol had an MIC90 ≤ 4 mg/L for 99.6% (245/246) of *Enterobacteriaceae*, 99.7% (394/395) of *P. aeruginosa*, 96.1% (540/562) of *Acinetobacter* spp., and 87.1% (27/31) of *B. cepacia complex* spp. [7].

As part of SIDERO-WT-2014 surveillance study, isolates of carbapenemase-producing, and carbapenemase-negative and meropenem-resistant isolates of *Enterobacteriaceae, P. aeruginosa, A. baumannii* were tested for susceptibility to cefiderocol [14]. Cefiderocol suppressed the growth of 97.7% of isolates with an MIC less than 4 µg/mL, including those carrying additional ESBL or AmpC producing GNB [14]. The study results confirmed that cefiderocol MIC elevation is not necessarily due to carrying beta-lactamases but possibly related to the disruption of iron transport proteins or upregulation of efflux transporter [14]. Cefiderocol has demonstrated excellent activity in Gram-negative organisms including carbapenemase-producing organisms. Also, in vitro studies showed the superiority of cefiderocol to currently available antibiotics, including new agents such as ceftazidime-avibactam, ceftolozane-tazobactam, and colistin. However, cefiderocol is not active against Gram-positive bacteria and anaerobes [14]. Detailed study information is available in Table 3.

6.2 Animal Studies

A rat respiratory tract infection model was used to evaluate the antibacterial efficacy of cefiderocol that simulates human pharmacokinetic profiles [25]. Unlike murine thigh infection models, this model utilizes the immunocompetent rat and requires longer treatment of 4 days to eradicate bacterial infections [25]. Administering cefiderocol 2 g every 8 h as a 3-h infusion for 4 days achieved a greater than 3 log10 reduction in cells of carbapenem-resistant isolates of *P. aeruginosa, A. baumannii*, and *K. pneumoniae* in lung infection [25]. As with other beta-lactam antibiotics, the efficacy of cefiderocol correlates closely with the time that the free drug concentration is above the MIC (%fT > MIC) [25, 26]. Prolonged 3-h infusion of cefiderocol maintained 100 %fT > MIC for MIC of 4 µg/mL as compared to 75

Table 2 Pharmacokinetic data for cefiderocol [20, 22]

Parameters	Healthy group							Renal function group					
	Single dose				Multiple dose			Normal	Mild RI	Moderate RI	Severe RI	ESRD (without HD)	ESRD (with HD)
Dose (mg)	100	250	500	1000	2000	1000 1st	1000 2nd	2000	1000				
C_{max} (µg/mL)	7.76	18.9	46.6	76.4	156	72.2	68.1	141	81.0	73.4	78.0	80.1	93.0	75.4
AUC $_{(0-t)}$ (µg·h/mL)	17.03	41.41	108.0	167.3	388.9	176.4	171.0	337.2	212.0	217.8	311.0	540.3	872.5	314.9
CL (L/h)	5.72	5.96	4.60	5.95	5.13	5.64	5.81	5.91	4.7	4.6	3.2	1.8	1.1	3.1
$t_{1/2}$ (h)	2.00	1.98	2.12	2.26	2.74	2.37	2.25	2.40	2.8	3.0	4.1	6.9	9.6	9.5

C_{max} maximum plasma concentration, $AUC_{(0-t)}$ area under the plasma concentration-time curve from 0 to the time of the last quantifiable concentration after dosing, *CL* total clearance, $t_{1/2}$ terminal half-life, *ESRD* end-stage renal disease, *HD* hemodialysis, *RI* renal impairment

%fT > MIC with a 1-h infusion [25]. This study suggests the use of cefiderocol in the treatment of lung infections caused by carbapenem-resistant GNB [25]. Another study described the pharmacokinetics, pharmacodynamics, and 24-h efficacy of cefiderocol in a neutropenic murine thigh infection model [27]. Six neutropenic mice were infected with *P. aeruginosa* to estimate pharmacokinetic parameters using mean serum concentration data, which showed a mean $t_{1/2}$ of 0.86 h and similar pharmacokinetics in the range of doses tested (4, 100, and 250 mg/kg) with a one-compartment model [27]. In pharmacodynamic assessments, the efficacy of cefiderocol was investigated based on %fT > MIC and the change of bacterial density expressed in log10 CFU/mL after 24-h exposures [27]. The pharmacodynamics of cefiderocol showed sigmoidal dose-response curves as greater bacterial killing is achieved with increasing doses [27]. The study demonstrated that antibacterial effects were observed with %fT > MIC greater than 80%, as evidenced by 76.3, 81.9, and 88.2% to result in bacterial stasis, 1 log10, and 2 log10 CFU reductions, respectively [27]. Unlike other siderophore beta-lactams, cefiderocol produced a sustained bacterial killing with 2 log10 CFU reductions in 24-h treatment against *P. aeruginosa* [27]. Furthermore, cefiderocol exhibited potent activity against all *P. aeruginosa* isolates, which were resistant to cefepime and levofloxacin [27].

The third study investigated the in vivo efficacy of cefiderocol against *Enterobacteriaceae and P. aeruginosa* in neutropenic thigh models and *Enterobacteriaceae, P. aeruginosa, A. baumannii, and S. maltophilia* in lung infection models [26]. Compared to cefepime, which showed %fT > MIC of 61.7% and 87.7% to reach a bacterial stasis and a 1 log10 CFU reduction, cefiderocol demonstrated lower values of %fT > MIC of 47.5% and 57.6%, respectively [26]. To achieve a 1-log10 reduction, %fT > MIC for *Enterobacteriaceae* and *P. aeruginosa* in the thigh infection models were 73.3% and 77.2%, respectively [26]. Against *Enterobacteriaceae, P. aeruginosa, A. baumannii,* and *S. maltophilia* in the lung infection model, %fT > MIC were 64.4%, 70.3%, 88.1%, and 53.9%, respectively [26]. *A. baumannii* required higher %fT > MIC values than those for *Enterobacteriaceae and P. aeruginosa*, which demonstrated similar efficacy in both thigh and lung infection models [26]. These results indicate cefiderocol as being the treatment option for MDR Gram-negative bacterial infections [25–27].

6.3 Clinical Trials

The phase II, randomized, double-blind, parallel-group non-inferiority trial (APEKS-cUTI) evaluated the efficacy and safety of cefiderocol against imipenem-cilastatin for the treatment of cUTIs caused by GNB [28]. This study included hospitalized patients ≥ 18 years old who met the FDA diagnostic criteria for UTI and diagnosed with cUTI with or without pyelonephritis, or acute uncomplicated pyelonephritis, including immunosuppressed patients with renal transplant [28]. Patients with acute uncomplicated pyelonephritis were limited to 30% in this study to assess more complicated MDR infections in older patients with complex co-morbidities, including renal impairment [28]. 448 patients were randomized 2:1 to receive either cefiderocol 2 g or imipenem-cilastatin 1 g/1 g 1-h intravenous infusion every 8 h for 7–14 days with renally adjusted doses [28].

Uropathogens, including *E. coli, K. pneumoniae*, *P. aeruginosa, Proteus mirabilis, Enterobacter cloacae, Morganella morganii,* and *Citrobacter freundii,* have different resistance patterns against antibiotics classes [28]. The most common pathogens were beta-lactamase producing *E. coli,* which are extensively drug-resistant and pandrug-resistant bacteria, and the leading cause of community-acquired and hospital-acquired infections [28].

At 7 days after the end of treatment, 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem-cilastatin group achieved the composite outcome of clinical and microbiological response in the modified intention-to-treat population (mITT) [treatment difference of 18.58%; 95% CI 8.23–28.92, $p = 0.0004$, number needed to treat (NNT) = 6] [28]. This difference is clinically meaningful since it is consistent within all efficacy populations and resulted from microbiological eradication of GNB to $< 10^4$ CFU/mL from initial $\geq 10^5$ CFU/mL [28]. Therefore, cefiderocol was non-inferior to imipenem-cilastatin for primary endpoints [28]. Notably, cefiderocol demonstrated superiority to imipenem-cilastatin for the composite primary outcome in the post hoc analysis [28].

The pathogen-specific, randomized, prospective, phase III clinical study, the CREDIBLE-CR study, was conducted to investigate the efficacy and safety of cefiderocol for the treatment of carbapenem-resistant (CR) Gram-negative infections [29]. According to European Medicines Agency (EMA), patients with a confirmed diagnosis of HAP/VAP/HCAP, BSI or sepsis, or cUTI caused by CR Gram-negative infections, were randomized 2:1 to receive 2 g of cefiderocol every 8 h for a 3-h infusion or best available therapy (BAT) [29]. BAT as defined by a maximum of three antibiotics in combination or subsequent de-escalation at the early assessment (EA) time point was selected by the site investigator, considering the clinical condition of the patient [29].

The treatment duration for HAP/VAP/HCAP or BSI/sepsis was 7–14 days and 5 days for cUTIs, and can be extended to 21 days to achieve clinical cure [29]. The primary endpoints included clinical cure rates at the time of cure (TOC) in patients with HAP/VAP/HCAP, BSI or sepsis, and microbiological outcomes at TOC in patients with cUTI in the CR-micro intention-to-treat (ITT) population [29]. Secondary endpoints of the study were clinical outcome at the end of therapy (EOT) and follow-up (FUP) time

Table 3 Summary of in vitro and animal studies

Year	*N*	Authors	Inclusion	Results
2017	9205	Hackel et al. [24]	Gram-negative bacilli collected in SIDERO-WT-2014 Study	MICs ≤ 4 μg/mL for 99.9% of all *Enterobacteriaceae* (MIC_{90}: 0.5–1 μg/mL), for 97.0% of meropenem-nonsusceptible *Enterobacteriaceae* (MIC_{90}: 1–4 μg/mL), for 99.9% of all *P. aeruginosa* isolates (MIC_{90}: 0.5 μg/mL), for 100% of meropenem-nonsusceptible *P. aeruginosa* isolates (MIC_{90}: 0.5 μg/mL), for 97.6% of all *A. baumannii* isolates (MIC_{90}: 1 μg/mL), for 96.9% of meropenem-nonsusceptible *A. baumannii* isolates (MIC_{90}: 1 μg/mL), for 100% of isolates of *S. maltophilia* (MIC_{90}: 0.25–0.5 μg/mL), and for 93.8% of *B. cepacia* isolates
2017	753	Dobias et al. [12]	MDR Gram-negative isolates collected from hospitals worldwide were tested against cefiderocol and antibiotic comparators	MIC_{90} of 2 mg/L for cefiderocol, MIC_{90} > 64 mg/L for CT, MEM, CAZ, CZA, and AMK, > 32 mg/L for ATM, > 16 mg/L for FEP, 8 mg/L for CST, and 2 mg/L for TGC MIC_{50} of 0.5 mg/L for cefiderocol, MIC_{50} > 64 mg/L for CAZ, 64 mg/L for CT, >32 mg/L for ATM, >16 mg/L for FEP, 8 mg/L for MEM and AMK, >4 mg/L for CIP, 1 mg/L for CZA, 0.5 mg/L for TGC, and <0.5 mg/L for CST
2017	471	Falagas et al. [13]	Carbapenem-resistant Gram-negative bacteria	MIC_{90} of 0.5 mg/L for *A. baumannii and P. aeruginosa, P. stuartii*, respectively MIC_{90} of 0.5–1 μg/mL For *Enterobacteriaceae* MIC_{90} of 1 mg/L For *K. pneumoniae, E. cloacae*, respectively
2018	1873	Hackel et al. [11]	Carbapenem-nonsusceptible *Enterobacteriaceae*, MDR *Acinetobacter baumannii*, MDR *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*	MICs ≤4 μg/mL for 89.7%, 99.2%, and 100% of isolates of MDR *A. baumannii*, MDR *P. aeruginosa*, and *S. maltophilia,* respectively MIC_{90} of 4 μg/mL for 90% of carbapenem-nonsusceptible *Enterobacteriaceae* MICs of 0.004–8 for *B. cepacian*
2019	8954	Karlowsky et al. [7]	Gram-negative bacilli (GNB) in SIDERO-WT-2015 Study	MICs ≤ 4 mg/L for 99.9% of *Enterobacteriaceae*, 99.9% of *P. aeruginosa*, 96.4% of *Acinetobacter* spp., 99.4% of *S. maltophilia*, and 94.4% of *B. cepacia complex* spp. MICs ≤4 mg/L for 99.6% of *Enterobacteriaceae*, 99.7% of *P. aeruginosa*, 96.1% of *Acinetobacter* spp., and 87.1% of *B. cepacia complex* spp. resistant to meropenem

Table 3 (continued)

Year	*N*	Authors	Inclusion	Results
2019	1272	Kazmierczak et al. [14]	Meropenem-non-susceptible isolates of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* collected as part of the SIDERO-WT-2014 surveillance study	MIC ≤ 4 μg/mL for 97.7% of isolates, including 100% of IMP-positive, OXA-58-positive, KPC-positive, VIM-positive, and OXA-48-like-positive isolates; 99.3% of carbapenemase-negative isolates (MIC_{90}: 1 μg/mL); 97.2% of OXA-23-positive isolates (MIC_{90}: 1 μg/mL); 95.2% of OXA-24-positive isolates (MIC_{90}: 1 μg/mL); 91.7% of GES-positive isolates (MIC_{90}: 4 μg/mL); and 64.3% of NDM-positive isolates (MIC_{90}: 8 μg/mL). MIC ≥8 μg/mL for 29 isolates (2.3%; 15 OXA-23-producers, 6 OXA-24-producers, five NDM-producers, and three carbapenemase-negative isolates)
2017	181	Matsumoto et al. [25]	Immunocompetent-rat respiratory tract infection models	2 g every 8 h as a 3 h infusion of cefiderocol for 4 days resulted a > 3 log10 reduction in the number of cells of carbapenem-resistant isolates in the lungs
2018	6	Ghazi et al. [27]	Murine thigh infection model	Without cefiderocol, *P. aeruginosa* bacterial density increased from 5.54 ± 0.23 to 8.68 ± 0.57 log10 CFU in 24 h With cefiderocol, > 1 log10 CFU reduction in all eight isolates
2019	5	Nakamura et al. [26]	Neutropenic thigh and lung infection models	%fT > MIC best correlates with efficacy of cefiderocol in iron-depleted conditions

P. aeruginosa: *Pseudomonas aeruginosa*, *A. baumannii*: *Acinetobacter baumannii, S. maltophilia: Stenotrophomonas maltophilia*, *B. cepacian: Burkholderia cepacian, P. stuartii: Providencia stuartii*, *K. pneumoniae*: *Klebsiella pneumoniae*, *KPC: Klebsiella pneumoniae carbapenemase, E. cloacae: Enterobacter cloacae*, *CT* ceftolozane–tazobactam, *CAZ* ceftazidime, *CZA* ceftazidime–avibactam, *FEP* cefepime, *MEM* meropenem, *CIP* ciprofloxacin, *ATM* aztreonam, *AMK* amikacin, *CST* colistin, *TGC* tigecycline, *IMP* imipenemase metallo-β-lactamase, *VIM* Verona integron-mediated metallo-β-lactamase, *NDM* New Delhi metallo-β-lactamases, *OXA* oxacillin carbapenemases, *MIC* minimum inhibitory concentration (μg/mL), *MDR* multidrug resistant, *CFU* colony-forming units, *%fT > MIC* percentage of time that free drug concentrations above the minimum inhibitory concentration

points and microbiological outcomes (EOT, TOC, FUP), all-cause mortality in patients with HAP/VAP/HCAP, BSI or sepsis at days 14 and 28, as well as microbiological and clinical outcome (EOT, TOC, FUP), and composite clinical and microbiological outcome (EOT, TOC, FUP) for patients with cUTIs [29]. Safety and pharmacokinetic parameters of cefiderocol and BAT were assessed [29]. The all-cause mortality was higher in the cefiderocol group (18.0%, 24.8%, and 33.7%) versus the BAT group (12.2%, 18.4%, and 18.4%) at Days 14, 28, and end of study (EOS), respectively [30].

Another phase III clinical trial (APEKS-NP study) investigated cefiderocol versus meropenem against GNB for the treatment of hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, or healthcare-associated bacterial pneumonia [31]. The primary endpoint was all-cause mortality at 14 days after administering 2 g of cefiderocol or meropenem every 8 h for 7–14 days intravenously and 600 mg of linezolid intravenously every 12 h at least for 5 days [31]. The all-cause mortality was 12.4%, 21.2%, and 26.9% for cefiderocol versus 11.6%, 20.1%, and 22.8% for meropenem at Day 14, Day 28, and EOS, respectively [30].

Hence, there are safety concerns in the treatment of pneumonia with increased all-cause mortality related to cefiderocol, as evidenced by both the CREDIBLE-CR study and the APEKS-NP study [29–31].

A phase II clinical trial for bloodstream infection versus the best available therapy is recruiting now.

6.4 Safety

The phase I study evaluated the safety, tolerability, and pharmacokinetics of cefiderocol in patients with renal impairment after administering a single 1000-mg intravenous infusion over 10 days [22]. There was no mortality or serious adverse events (AEs) in 38 subjects [22]. One patient with moderate renal impairment had to withdraw from the medication due to urticaria with underlying lactose intolerance and seasonal allergies [22]. This urticaria was unrelated to cefiderocol since no antibodies against cefiderocol were detected in any blood samples [22]. The most common AE was mild contact dermatitis (7.9%) in one patient in each mild, severe, and end-stage renal disease (ESRD) group followed by mild nausea in one patient with moderate disease and ESRD without hemodialysis [22].

The phase II, randomized, double-blind, parallel-group non-inferiority trial (APEKS-cUTI) also evaluated safety, clinical responses assessed by the investigator, and microbiological responses evaluated by quantitative urinalysis early, at TOC, and at14 days after the end of treatment [28]. The safety of cefiderocol was conducted for an extended treatment period without having confounding factors such as step-down oral treatment [28]. AEs reported were 122 (41%) of 300 patients in the cefiderocol group and 76 (51%) of 148 patients in the imipenem-cilastatin group [28]. The most common AEs in both treatment groups involved gastrointestinal symptoms such as diarrhea, constipation, nausea, vomiting, or upper abdominal pain (35 [12%] patients in the cefiderocol group and 27 [18%] patients in the imipenem-cilastatin group) [28]. However, there was less incidence of diarrhea and *C. difficile* infection in the cefiderocol group (4%; 13/300) compared to the imipenem-cilastatin group (6%; 9/148) since cefiderocol does not have activity against anaerobes or Gram-positive bacteria, preventing the increased risk of *C. difficile* colitis by using broad-spectrum imipenem [28].

Still, there is a possibility of developing *C. difficile*-associated diarrhea (CDAD) with any systemic antibiotics, including cefiderocol, ranging from mild diarrhea to fatal colitis that may require colectomy [8]. Beta-lactam antibacterial drugs can cause hypersensitivity reactions, including serious skin reactions to life-threatening anaphylactic reactions [8]. Therefore, care must be taken before starting cefiderocol for patients with the previous history of allergic reactions to beta-lactams such as penicillin, cephalosporins, or other beta-lactam antibiotics [8]. Special precautions are required for the use of cephalosporins, such as cefiderocol in patients with a history of epilepsy or renal impairment to prevent seizures and other central nervous system adverse reactions [8]. Since there is limited information about cerebrospinal fluid (CSF) penetration of cefiderocol available, we were not able to find the CSF penetration information.

In the CREDIBLE-CR study, all-cause mortality was increased in critically ill patients who have carbapenem-resistant GNB infections such as nosocomial pneumonia, bloodstream infections, or sepsis, and treated with cefiderocol compared to BAT [8, 29]. The all-cause mortality in the cefiderocol group was higher than the BAT group through Day 28 and Day 49, as evidenced by [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (− 8.6, 19.2)], and [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (− 2.5, 26.9)], respectively [8, 29]. The main cause of death was the worsening of underlying diseases or infections caused by nonfermenters such as *A. baumannii, S. maltophilia,* and *P. aeruginosa*; however, the cause of the higher mortality is still unclear [8, 29].

7 Place in Therapy

The WHO defines priority 1 pathogens as critical for research and development of new antibiotic drugs to treat carbapenem-resistant *A. baumannii*, *P. aeruginosa*, and carbapenem-resistant or third-generation cephalosporin-resistant *Enterobacteriaceae* (CRE) [32]. CDC emphasizes CRE infections in healthcare settings due to its high mortality rates associated with bloodstream infections and high levels

of resistance to many antibiotic options [2]. CRE infections include bloodstream infections, ventilator-associated pneumonia, intra-abdominal abscesses, and most commonly urinary tract infections from urinary retention or a urinary catheter [1].

Cefiderocol (Fetroja®) received FDA approval on 14 November 2019 for the treatment of cUTIs such as pyelonephritis for patients 18 years and older due to Gram-negative pathogens, including *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* and *Enterobacter cloacae* complex [8]. To have potent efficacy of cefiderocol without developing the risk of antimicrobial resistance, its use should be limited to treat or prevent proven and probable infections caused by GNB listed above [8].

Since the safety and efficacy of cefiderocol for the treatment of nosocomial pneumonia, bloodstream infections, or sepsis need further investigation, cefiderocol use should be reserved for cUTI treatment if no other alternatives are available [8, 29, 31].

The recommended dosing for cUTIs is 2 g IV over 3 h at 8-h intervals for 7–14 days with creatinine clearance (CLcr) of 60–119 mL/min [8]. Dose adjustment is required in patients with renal impairment if CLcr is less than 60 mL/min or greater than 120 mL/min [8]. Patients with CLcr 30–59 mL/min should receive 1.5 g IV over 3 h at 8-h intervals, and patients with CLcr 15–29 mL/min should receive 1 g IV over 3 h at 8-h intervals, and ESRD patients with CLcr 15 mL/min or less should receive 0.75 g over 3 h at 12-h intervals [8]. If CLcr is 120 mL/min or greater, patients should receive 2 g IV over 3 h at 6-h intervals [8]. The current average wholesale price (AWP) for the current standard of therapy of imipenem/cilastatin is approximately US$135 per IV patient treatment day, and the AWP for imipenem/cilastatin/relebactam, ceftazidime/avibactam, and cefiderocol is approximately US$1284, $1292, and $1320, respectively, per IV patient treatment day [33–36].

8 Conclusion

Cefiderocol has demonstrated excellent activity against GNB, including *Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii, B. cepacia*, and *S. maltophilia.*

Until further investigation is completed in other MDR Gram-negative infections, cefiderocol should be considered only as a treatment option for the treatment of cUTIs from GNB, especially in patients who have limited or no alternative treatment options.

Compliance with Ethical Standards

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Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals For this type of review formal consent is not required.

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