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REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Cefiderocol

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Abstract

Cefiderocol is a new broad-spectrum cephalosporin antibiotic with promising activity against various Gram-negative bacteria including carbapenem-resistant strains. A chlorocatechol group in the C-3 side chain provides cefiderocol with a siderophore activity, improving its stability against β-lactamases and facilitating the transportation of cefiderocol across outer bacterial membranes. Cefiderocol shows linear pharmacokinetics over a broad range of clinically relevant doses, with unchanged renal excretion constituting the main route of elimination. Geometric means (coefficient of variation) of the volume of distribution and clearance in individuals with normal kidney function were 15.8 (15%) L and 4.70 (27%) L/h, respectively. In patients with end-stage renal disease, clearance was 1.10 (24%) L/h. Time above the minimum inhibitory concentration is the main predictor of efficacy. There is no evidence for clinically relevant interactions of cefiderocol with other drugs mediated by metabolizing enzymes or drug transporters. Simulations based on population pharmacokinetic modeling suggest that dosing regimens should be adjusted based on kidney function to optimize therapeutic exposure to cefiderocol. Clinical efficacy trials indicated that cefiderocol is non-inferior to imipenem/cilastatin in the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis, and to meropenem in the treatment of nosocomial pneumonia. In the one study currently available, cefiderocol performed similarly to the best available therapy in the treatment of severe carbapenem-resistant Gram-negative infections regarding clinical and microbiological efficacy. In summary, cefiderocol shows favorable pharmacokinetic/pharmacodynamic properties and an acceptable safety profile, suggesting that cefiderocol might be a viable option to treat infections with bacteria resistant to other antibiotics.

Key Points

Cefiderocol is a siderophore cephalosporin providing promising activity against Gram-negative bacteria, resistant to other antibiotics.

The drug shows linear pharmacokinetics and a kidney function-dependent elimination, supporting respective dose adjustments.

Clinical efficacy trials indicate that cefiderocol might be valuable to treat infections with bacteria resistant to other antibiotics.

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1 Introduction

Cefiderocol, formerly known as S-649266, is a novel catechol-substituted siderophore cephalosporin antibiotic developed by Shionogi & Co., Ltd, Japan. Siderophores are iron-chelating agents produced by bacterial species that facilitate the uptake of iron into the bacterial cell, which is needed for survival and growth. Similar to bacterial siderophores, cefiderocol binds to iron transport channels and thereby enters the periplasmic space of bacteria. This is called a "trojan horse" mechanism. Inside the cell, cefiderocol dissociates from the iron transport channel and exerts its antibacterial activity [1]. The cefiderocol molecule comprises functional groups that improve the stability against β-lactamases, facilitate the transport across the outer membrane of Gram-negative bacteria, and provide cefiderocol with its siderophore activity [2]. The strong activity of cefiderocol is a result of its stability against serine and metallo-type carbapenemases, and extended-spectrum β-lactamases [3]. Consequently, cefiderocol shows a solid in vitro activity against carbapenem-resistant (CR)

Gram-negative bacteria, including carbapenem-resistant *Enterobacterales* and non-fermenters [4].

Cefiderocol has been approved in the USA in 2019 for the treatment of complicated urinary tract infections (cUTIs), including kidney infections caused by susceptible Gram-negative microorganisms with limited or no alternative treatment options, and for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia [5]. In Europe, approval was granted in 2020 for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options [6]. Despite the approval of several new antibiotics to treat carbapenem-resistant Gram-negative infections, randomized clinical trials including the target pathogens of cefiderocol have been limited to carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Pseudomonas aeruginosa*. Randomized trials for the treatment of carbapenem-resistant infections including *Acinetobacter baumannii* have been limited to mostly colistin-based generic antibiotics. Recently, Bassetti et al. [4] compared cefiderocol to the best available therapy (BAT) in a heterogeneous patient population with infections caused by carbapenem-resistant Gram-negative bacteria in a randomized phase III study (CREDIBLE-CR). In this trial, cefiderocol was found to have similar clinical and microbiological efficacy compared to the BAT. The authors concluded that cefiderocol might be an option for the treatment of carbapenem-resistant infections in patients with limited treatment options. Furthermore, the broad-spectrum activity of cefiderocol coupled with the preserved efficacy irrespective of carbapenem resistance makes cefiderocol a good candidate for investigations in serious infections involving multiple infection sites. Thus, the target populations for cefiderocol treatment will be particularly patients who are immunocompromised, have relevant co-morbidities, and are critically ill. Recently, an extensive review of the drug has been provided by Abdul-Mutakabbir et al. [7].

The present review provides a comprehensive summary of the clinical pharmacokinetics (PK) and pharmacodynamics of cefiderocol. Studies evaluated include in vivo animal studies as well as recent phase II and III trials. The discussion refers primarily to studies carried out between 2017 and 2021. The literature for this review was obtained through a comprehensive search of PubMed, PubChem, and Google Scholar, including the terms "cefiderocol," "cefiderocol pharmacokinetics", "cefiderocol pharmacodynamics", and "cefiderocol clinical trials" from 2010 until May 2021. PubMed was queried using the terms "cefiderocol chemical structure" and "cefiderocol antimicrobial activity" without restricting the date of publication to a certain range. The US Food and Drug Administration and European Medicines Agency briefing documents for cefiderocol were also included in this review.

2 Chemical and Antimicrobial Overview

Cefiderocol is a novel antimicrobial compound developed by Shionogi & Co, Ltd., Japan [2]. The basis of this molecule is a cephalosporine nucleus coupled with an amino thiazolyl acetic acid derivative as a C-7 side chain. Quaternization with a tertiary amine as a C-3 side chain resulted in a precursor molecule, and the removal of all protective groups resulted in a novel cephalosporine derivative [2]. C-3 and C-7 side chain substituents were specifically chosen to achieve a potent antibacterial activity against multi-drug-resistant (MDR) Gram-negative bacteria. Important chemical characteristics of the cefiderocol molecule are shown in Fig. 1, and a comprehensive description of the chemical properties of cefiderocol has been provided by Aoki et al. [2]. Cefiderocol belongs to the group of siderophore cephalosporines. The name "siderophore" derives from the Greek term for "iron carrier", describing the capability of siderophore molecules to carry iron into cells via siderophore transport systems [8]. Certain microorganisms, such as bacteria and fungi, release siderophore molecules into their environment to ensure a sufficient iron supply to the cell [9]. Siderophores combined with chemical moieties with antibacterial activity are called sideromycins. Although the vast majority of sideromycins is synthetic, a small number of natural sideromycins has been discovered including albomycin and salmycin [10]. Sideromycins make use of the siderophore transport systems to enrich inside bacterial cells, resulting in a pronounced antibacterial activity even at low extracellular concentrations [11].

In comparison to antibiotics such as meropenem or ceftazidime-avibactam, cefiderocol has been shown to provide a superior in vitro activity against a selection of Gram-negative bacteria compared with cephalosporines, fluoroquinolones, monobactams, and carbapenems. This includes MDR strains of *A. baumanii*, *Enterobacteriaceae*, and *P. aeruginosa* [1, 12]. For example, cefiderocol showed a higher in vitro potency against these three strains compared with meropenem [13], and an increased stability to *Klebsiella pneumoniae* carbapenemases (KPC) compared with meropenem and cefepime [14]. The Clinical and Laboratory Standards Institute recently reported cefiderocol breakpoints of 4 (susceptible), 8 (intermediate), and 16 mg/L (resistant) for *P. aeruginosa*, *A. baumannii*, *Stenophomonas maltophilia,* and *Enterobacteriaceae* including *K. pneumoniae* and *Escherichia coli*. In the SIDERO-WT-2015 trial conducted by Karlowsky et al., 8954 clinical isolates of Gram-negative bacteria from various clinical laboratories in North America and Europe were collected and assessed according to the Clinical and Laboratory Standards Institute guidelines [15]. For *Enterobacteriaceae, Klebsiella* spp., and *E. coli*, the MIC_{90} was 0.5 mg/L for samples collected in North America

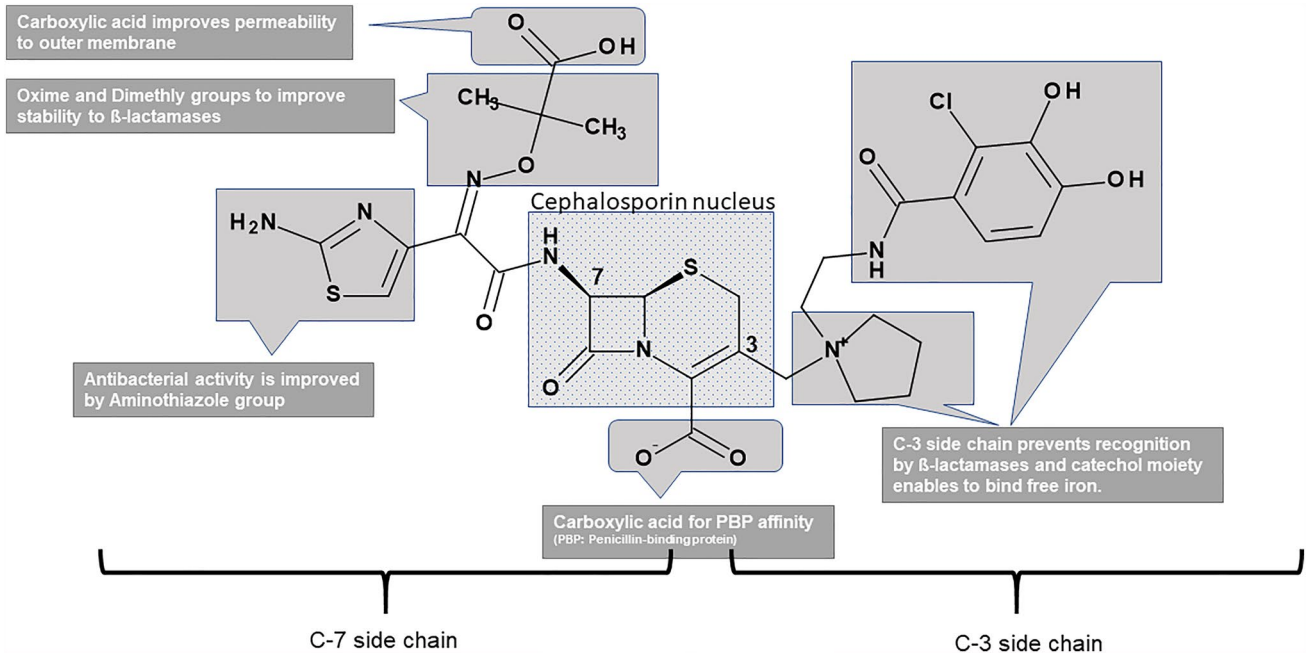

Fig. 1 Illustration of important functional groups in the cefiderocol molecule [1]. The cephalosporin nucleus is complemented by five functional groups in the C-3 and C-7 side chains, resulting in an improved outer membrane permeability, antibacterial activity, beta-lactamase stability, and the capability to bind free iron. Based on [1]

and 1 mg/L for samples collected in Europe. The MIC_{90} for *Acinetobacter* spp. was 2 mg/L in both regions, while the MIC_{90} for *S. maltophilia* was 0.5 mg/L and 0.25 mg/L for North America and Europe, respectively. In the case of *P. aeruginosa*, the MIC_{90} was 0.5 mg/L in both regions. For *Bacteroides* spp., *Clostridium difficile*, and *Prevotella* spp., the MIC_{90} of cefiderocol was > 32 mg/L [3]. Overall, currently available data show that cefiderocol provides a strong activity against a selection of clinically relevant MDR Gram-negative bacteria in vitro.

3 PK

3.1 PK in Healthy Volunteers

Cefiderocol has demonstrated linear PK in a randomized, double-blind, single ascending dose (SAD) and multiple (MAD) ascending dose phase I study in healthy Japanese and Caucasian volunteers [17]. A total of 54 volunteers received cefiderocol (30 in the SAD, 24 in the MAD part), while 16 volunteers received placebo (ten in the SAD, six in the MAD part). The SAD part covered doses of 100–2000 mg, while the MAD part comprised two groups receiving 1000 mg and a third group receiving 2000 mg every 8 h (q8h) for 10 days. The infusion duration was 60 min. Based on observed plasma concentration profiles, steady state was achieved within 24 h. Both data from the SAD and the MAD part indicated dose-proportional increases in maximum plasma concentrations (C_{max}) and areas under the concentration–time curve (AUC) with increasing dose, with no statistically significant dose dependency of half-life and clearance. Maximum plasma concentration (geometric mean) of cefiderocol ranged from 7.76 mg/L at 100 mg to 156 mg/L at 2000 mg in the SAD part, and from 72.2 at 1000 mg to 153 mg/L at 2000 mg on day 10 of the MAD part, respectively. The AUC from time zero to the last quantifiable concentration ($AUC_{0–last}$) was 389 mg•h/L in SAD and 337 mg•h/L in MAD for a 2000-mg dose, respectively, as shown in Table 1. Maximum plasma concentration, $AUC_{0–last,}$ and the AUC from time zero to infinity ($AUC_{0–inf}$) indicated a limited inter-individual variability for plasma exposure in all dose groups. By administering single intravenous doses of 1000 mg of radio-labeled cefiderocol to healthy volunteers, Miyazaki et al. explored the fate of cefiderocol in the human body using radiolabeled cefiderocol. This included partitioning into red blood cells, urinary excretion, and the formation of metabolites [18]. Cefiderocol was found to only marginally partition into red blood cells, with a blood-to-plasma ratio range from 0.53 to 0.56. Unchanged excretion in urine constituted the main route of elimination, with 90.6% of the administered dose being recovered in urine on average. Metabolism contributed less than 10% to overall elimination. Metabolites were mainly excreted via urine, while fecal excretion was negligible. In

an additional study in 15 healthy volunteers, Katsube et al. [19] evaluated the penetration of cefiderocol into epithelial lining fluid and alveolar macrophages, concluding that cefiderocol penetrated lung tissues with exposure ratios (based on AUC) with a range from 0.0927 to 0.116 for epithelial lining fluid and a range from 0.00496 to 0.104 for alveolar macrophages. Data on the penetration of cefiderocol into cerebrospinal fluid are currently missing [20]. Finally, limited data on protein binding of cefiderocol are available. The protein binding ratio in mice was found to be 38% [21], while in vitro plasma protein binding (primarily to albumin) of cefiderocol in humans was 57.8% [22]. In summary, pharmacokinetic studies in healthy volunteers indicate linear PK over a range of doses and time, with unchanged urinary excretion constituting the main route of elimination. Renal function is the main predictor of the PK of cefiderocol and should be considered for dosing considerations.

3.2 PK in Subjects with Impaired Kidney Function

Katsube et al. [23] evaluated the PK and the safety of cefiderocol in subjects with various levels of kidney dysfunction. Thirty-eight subjects were recruited and 37 completed the study. Eight control subjects with normal renal function were identified based on an evaluation of Cockcroft-Gault creatinine clearance ($CGCL_{CR}$), which was defined to be ≥ 90 mL/min in subjects with normal renal function. The Modification of Diet in Renal Disease (MDRD) formula was used to estimate the glomerular filtration rate (eGFR), which served as a criterion to distinguish between mild (eGFR 60 to < 90 mL/min/1.73 m^2), moderate (eGFR 30 to < 60 mL/min/1.73 m^2), and severe (eGFR < 30 mL/min/1.73 m^2) kidney impairment, and end-stage renal disease (ESRD) with and without hemodialysis. The PK of cefiderocol following a single intravenous infusion of 1000 mg was compared between subjects with normal and impaired renal function based on a non-compartmental analysis. As expected based on the predominating renal excretion of cefiderocol, the $AUC_{0–last}$ differed clearly between different renal function

Table 1 Summary pharmacokinetic parameters of cefiderocol in plasma following an intravenous infusion [17, 18, 22]

Pharmacokinetic parameters	Phase I PK, safety, and tolerability study				[^{14}C] CF-study[a]	Phase I study in renally impaired subjects		
	Single IV infusion		Multiple IV infusion day 1			Normal[b]	Severe[c]	ESRD (w/o HD)
	1000 mg (n = 6)	2000 mg (n = 6)	1000 mg (n = 8)	2000 mg (n = 8)	1000 mg (n = 6)	1000 mg (n = 8)	1000 mg (n = 6)	1000 mg (n = 8)
C_{max} (mg/L)	74.4 (4.6)	156 (7.90)	68.1 (11.5)	141 (22.7)	72.9 (12.4)	81.0 (27.4)	80.1 (19.8)	93.0 (27.8)
t_{max} (h)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.20)	0.97 (0.50–1.00)	1.00 (1.0–1.0)	1.00 (1.00–1.10)	1.00 (1.00–1.00)
$AUC_{0–last}$ (mg•h/L)	167 (6.90)	389 (9.00)	171 (10.6)	337(15.6)	171 (8.40)	212 (26.7)	540 (23.6)	872 (23.9)
$AUC_{0–inf}$ (mg•h/L)	168 (7.00)	390 (9.00)	172 (10.6)	338 (15.5)	172 (8.40)	213 (26.5)	543 (23.6)	880 (24.2)
$t_{1/2,z}$ (h)	2.26 (5.80)	2.74 (10.2)	2.19 (4.30)	2.40 (13.2)	2.30 (9.50)	2.80 (16.5)	6.90 (30.6)	9.60 (33.4)
CL (L/h)	5.95 (7.00)	5.13 (9.00)	5.93 (11.0)	5.91 (15.5)	4.78 (7.6)	4.70 (26.5)	1.80 (23.6)	1.10 (24.2)
V_z (L)	–	–	–	–	15.8 (15.1)	–	–	–
V_{ss} (L)	–	–	–	–	–	13.5 (30.2)	16.4 (23.4)	14.2 (22.5)
CL_R (L/h)	–	–	–	–	–	3.2 (28.0)	–	–
fe (%)	–	–	–	–	–	68.6 (17.3)	–	–
fu (8 h)	–	–	–	–	–	0.44 (9.8)	0.44 (10.1)	0.370 (27.0)

The geometric mean (coefficient of variation) for all parameters except t_{max} for which the median (range) is shown

$AUC_{0–inf}$ area under the plasma concentration–time curve from zero to infinity, *$AUC_{0–last}$* area under the plasma concentration–time curve from zero to the time of the last quantifiable concentration, *CL* total clearance, *CLcr* creatinine clearance, *CL_R* renal clearance of the drug, *C_{max}* maximum plasma concentration, *eGFR* estimated glomerular filtration rate, *ESRD (w/o HD)* an end-stage renal disease without hemodialysis, *fe* fraction of dose excreted unchanged into urine, *fu* fraction of total drug that is unbound in plasma, *IV* intravenous, *n* number of subjects, P*K* pharmacokinetics, *$t_{1/2,z}$* terminal elimination half-life, *T_{max}* time to C_{max}, *V_z* apparent volume of distribution during the terminal elimination phase, *V_{ss}* volume of distribution at the steady-state phase

[a]PK of [^{14}C] cefiderocol in healthy subjects

[b]Normal CLcr, 90 mL/min

[c]Severe impairment, eGFR < 30 mL/[min•1.73 m^2]. Based on [17, 18, 22]

groups. In subjects with normal vs severely impaired renal function and subjects with ESRD without hemodialysis, an $AUC_{0–last}$ (geometric mean) of 212, 540, and 873 mg•h/L was attained, respectively (Table 1). Patients with mildly impaired kidney function showed only a slightly higher exposure ($AUC_{0–last}$ of 218 mg•h/L). Furthermore, the half-life of cefiderocol increased clearly with deteriorating kidney function, with a geometric mean range from 2.8 h in normal kidney function to 9.6 h in ESRD without dialysis. In patients with ESRD undergoing hemodialysis, approximately 60% of cefiderocol were removed during dialysis [23]. Differences in PK between subjects with normal and impaired kidney function were mainly attributed to differences in clearance. In contrast, C_{max} and volumes of distribution were similar among different kidney function groups. Furthermore, Katsube et al. reported that hemodialysis did not relevantly affect protein binding. In a small study in five critically ill patients, König et al. observed that cefiderocol doses could be adjusted based on the presence of acute kidney injury and continuous renal replacement therapy, concluding that therapeutic drug monitoring might be viable [24]. In summary, dosing regimens should be adjusted based on kidney function to provide an appropriate exposure to cefiderocol [6].

3.3 Pharmacokinetic Drug–Drug Interactions

Based on data from in vitro experiments and phase I trials, no clinically relevant potential for drug–drug interactions is expected for cefiderocol [6]. Initial in vitro experiments indicated a potential inhibition of organic anion transporters 1 and 3, organic cation transporters 1 and 2, multidrug and toxin extrusion protein 2K, and organic anion transporting polypeptide 1B3, but a clinical trial in healthy volunteers concomitantly receiving cefiderocol with probe substrates indicated that cefiderocol had either no or no clinically relevant impact on the PK of the probe substrates [36]. The $AUC_{0–inf}$ and C_{max} ratios ranged from 0.92 to 1.28 (Table 1 of the Electronic Supplementary Material [ESM]) [25]. Overall, the risk of cefiderocol being either a perpetrator or victim of drug–drug interactions appears to be low.

3.4 Population Pharmacokinetic Models

Katsube et al. described the population PK of cefiderocol based on phase I data in healthy volunteers [17] and patients with impaired kidney function [23], including patients receiving intermittent hemodialysis [26]. This modeling work focused on the evaluation of covariates affecting the PK of cefiderocol, and a subsequent evaluation of dosing regimens using simulations. A linear three-compartment model was found to describe the PK of cefiderocol sufficiently well (Table 2). The authors identified MDRD as an important predictor of cefiderocol clearance, while volumes of distribution were found to be related to body weight. Arguing that $CGCL_{CR}$ might be a better predictor in patients with an augmented clearance, the authors alternatively used the $CGCL_{CR}$ equation to identify patients with a creatinine clearance of at least 120 mL/min. Consequently, the authors presented a selection of final models comprising MDRD or $CGCL_{CR}$ combined with body weight. In contrast to kidney function, body weight was found to have a limited and possibly clinically irrelevant impact on the PK of cefiderocol. For example, the central volume of distribution was estimated to be 83% in patients with a body weight of 50 kg compared to 70 kg, and 115% for a body weight of 90 kg compared to 70 kg. The clearance via hemodialysis was estimated to be 7.37 L/h, with a limited inter-individual variability of 12.7%, which exceeded the typical clearance of 5.59 L/h in healthy volunteers. Overall, the inter-individual variability of pharmacokinetic parameters was limited both in healthy volunteers and patients with impaired kidney function. For example, the inter-individual variability of clearance range was from only 12% in healthy volunteers to 17% in subjects with impaired kidney function based on a model including MDRD. Based on simulations, Katsube et al. presented dosing regimens that were found to be suitable to reach a probability of target attainment (PTA) of > 90% given an fT > MIC target of 75% and an MIC of up to 4 mg/L in a simulated patient population. Starting from a prolonged 3-h infusion of 2000 mg of cefiderocol administered q8h in patients with an MDRD GFR > 90 mL/min/1.73 m^2, a shorter dosing interval was assumed in patients with augmented clearance and a decreased dose and/or an increased dosing interval was assumed in patients with impaired kidney function. In patients with augmented clearance, i.e., with a $CGCL_{CR}$ > 120 mL/min, the dosing interval was reduced to 6 hours. In patients with a moderately or severely impaired kidney function, lower doses of 1500 and 1000 mg q8h, respectively, were chosen. In patients with ESRD with and without intermittent hemodialysis, a dose of 750 mg every 12 h was used. In the case of intermittent hemodialysis, the authors furthermore simulated the administration of a supplemental dose of 750 mg as a prolonged infusion after completion of the hemodialysis. Finally, the authors concluded that the evaluated dosing regimen is expected to provide a therapeutic drug exposure across different levels of renal function.

More recently, Kawaguchi et al. published an extensive population pharmacokinetic evaluation of cefiderocol based on 3427 plasma concentrations from 516 patients and healthy volunteers [27]. The evaluated data stemmed from the phase III trial CREDIBLE-CR, which included patients with pneumonia, blood-stream infection (BSI)/sepsis and cUTI [4], the phase III trial APEKS-NP, which included patients with pneumonia [28], as well as the phase II trial APEKS-cUTI, which included patients with cUTI and

Table 2 Population pharmacokinetic parameters [22, 26, 27]

Parameter	Final model* with CrCL[a] (n = 3427)		Final model** with CrCL[a] (n = 2571)		Final model*** with CrCL[a] (n = 1624)	
	Estimate	%RSE	Estimate	%RSE	Estimate	%RSE
CL (L/h)	4.04	1.80	4.23	1.50	4.83	2.90
V1 (L)	7.78	5.20	7.93	3.10	7.58	2.70
Q2 (L/h)	6.19	5.70	5.75	5.30	5.45	4.50
V2 (L)	5.77	3.20	5.41	3.30	5.54	2.50
Q3 (L/h)	0.127	14.1	0.109	17.2	0.0969	17.0
V3 (L)	0.798	6.40	0.734	7.30	0.681	8.30
Effect of CrCL on CL (CrCL cut-off value of 150 mL/min)	0.682	4.00	0.653	3.90	–	–
Effect of body weight on V1	0.580	12.2	0.798	12.2		
Effect of pneumonia on CL	0.981	4.10	–	–	–	–
Effect of BSI/sepsis on CL	1.08	10.4	–	–	–	–
Effect of infection with cUTI in CREDIBLE-CR study on CL	0.872	6.40	–	–	–	–
Effect of infection with cUTI/AUP in APEKS-cUTI study on CL	1.27	3.10	–	–	–	–
Effect of albumin level on V1	0.617	10.9	–	–	–	–
Effect of infection on V1	1.39	6.70				
IIV for CL (CV%)	37.5	10.4	31.8	15.8	11.9	18.7
IIV for V1 (CV%)	56.9	19.8	45.8	28.2	19.3	19.7
IIV for V2 (CV%)	33.6	35.0	38.2	35.5	14.2	42.6
Proportional residual error (CV%)	20.5	5.10	15.1	12.8	12.0	14.1

This table show point estimates and %RSE of parameters reported for different population pharmacokinetic models

AUP acute uncomplicated pyelonephritis, *BSI* blood-stream infection, *CL* clearance from central compartment, *CrCL* creatinine clearance, *cUTI* complicated urinary tract infection, *CV* coefficient of variation, *IIV* inter-individual variability, *n* number of included samples, *Q2* first inter-compartmental clearance, *Q3* second inter-compartmental clearance, *RSE* relative standard error, *V1* central volume of distribution, *V2* second peripheral volume of distribution, *V3* third peripheral volume of distribution

Based on *[27], **[22], ***[26]

[a]Creatinine clearance calculated by the Cockcroft-Gault equation

acute uncomplicated pyelonephritis (AUP) [29], and from the abovementioned phase I trials in healthy volunteers [17] and subjects with impaired kidney function [23]. A total of 1861 plasma concentrations were available from healthy volunteers and 1566 from patients. Based on a linear three-compartment model (Table 2), Kawaguchi et al. found that the clearance of cefiderocol was strongly related to $CGCL_{CR}$. Differences in the PK of cefiderocol between different sites of infection (BSI/sepsis, pneumonia, or cUTI/AUP) and compared to subjects without infection were deemed clinically irrelevant despite statistical significance. This comprised a 27% higher clearance in patients with cUTI/AUP compared with subjects without infection and a 39% higher central volume of distribution in infected patients compared with subjects without infection. Additionally, a negative correlation between albumin levels and the central volume of distribution was observed. Using the established model, Kawaguchi et al. concluded that the fT > MIC based on MICs of pathogens isolated from 60 patients of the CREDIBLE-CR study and 97 patients of the APEKS-NP study was 100% in 97% of the patients. Based on simulations with the kidney function-specific dosing regimens described by Katsube et al. [26], the authors concluded that a PTA of > 95% was attained for an MIC up to 4 mg/L irrespective of the site of infection and renal function when assuming an fT > MIC target of 75%. Given an fT > MIC target of 100%, the PTA was > 90% for MICs up to 4 mg/L in all but one patient group. The only exception was the group of patients with normal renal function and BSI/sepsis, who achieved a PTA of 86%. The respective results are shown in Table 2 of the ESM. Consequently, the authors concluded that the evaluated dosing regimens provide adequate plasma exposure to cefiderocol in patients with pneumonia, BSI/sepsis, and cUTI. Kidney function was confirmed as the main predictor of cefiderocol PK, while differences between subjects

without infection and different patient groups were deemed clinically irrelevant.

4 Pharmacodynamics

Cefiderocol shows a time-dependent killing activity, with fT > MIC being the main predictor of efficacy [21, 30]. Nakamura et al. studied the pharmacodynamics of cefiderocol using neutropenic murine thigh and lung infection models, in which infections were caused by multiple Gram-negative bacteria [21]. A dose fractionation study showed that fT > MIC was superior to predict efficacy compared to the maximum free drug concentration or the AUC divided by the MIC in describing the in vivo efficacy of cefiderocol. Moreover, the authors determined the fT > MIC required for efficacy against multiple carbapenem-susceptible and carbapenem-resistant bacterial strains with cefiderocol MICs between 0.125 and 16 mg/L (Table 3). Matsumoto et al. investigated the efficacy of cefiderocol against carbapenem-resistant isolates of *K. pneumoniae* ($n = 2$), *P. aeruginosa* ($n = 2$), and *A. baumannii* ($n = 2$) in an immunocompetent-rat respiratory tract infection model (MIC range from 0.125 to 8 mg/L) [30]. Humanized exposures of 2000 mg of cefiderocol q8h administered over 3 h led to enhanced efficacy compared with infusions over 1 h, expressed by $\log_{10}$-reductions in the number of colony-forming units (CFU) per lung of 3.0–4.4 for the prolonged infusion time and 0.7–3.7 for the shorter infusion time. The authors extrapolated that 3-h infusions would achieve 100% fT > MIC for MICs up to 4 mg/L, whereas 1-h infusions would achieve 75% fT > MIC. In a neutropenic murine thigh model, Monogue et al. studied the efficacy of cefiderocol against 95 Gram-negative isolates of *Enterobacteriaceae* ($n = 39$), *P. aeruginosa* ($n = 21$), and *A. baumannii* ($n = 35$) with MICs between 0.12 and > 256 mg/L to identify a potential MIC breakpoint [31]. They used humanized dosing regimens of 2000 mg of cefiderocol given q8h as 3-h infusions. In isolates with MICs ≤ 4 mg/L ($n = 67$), bacterial stasis or a ten-fold reduction in CFU was achieved for 77%, 85%, and 88% of *Enterobacteriaceae*, *P. aeruginosa,* and *A. baumannii*, respectively. For 28 tested strains with MICs ≥ 8 mg/L, similar efficacy was observed in only two isolates. Based on humanized pharmacokinetic data, the authors predicted an fT > MIC of 96.2% in isolates with MICs ≤ 4 mg/L. Using a subset of 15 isolates, the authors compared the efficacies of cefiderocol, cefepime, and meropenem in the same model, concluding that cefiderocol provided efficacy against all cefepime-resistant or meropenem-resistant isolates with a mean bacterial reduction of 1.5 $\log_{10}$ CFU after 24 h. Humanized exposures of cefiderocol showed sustained killing activity without the development of adaptive resistance over 72 h against a group of different Gram-negative bacteria ($n = 11$) with an MIC range from 0.5 to 8 mg/L in a neutropenic murine thigh model performed by Stainton et al. [32]. In a murine urinary tract infection model, cefiderocol led to a > 3-$\log_{10}$ reduction in CFU against carbapenem-resistant *K. pneumoniae*-expressing KPC-2 and *P. aeruginosa*-expressing IMP-1 [33]. Cefiderocol was furthermore tested against eight *P. aeruginosa* isolates that showed a tendency to develop resistance to other non-catechol siderophore antibiotics in preclinical trials in another neutropenic murine thigh model [34]. Humanized exposures of cefiderocol produced a > 1 − $\log_{10}$ reduction in CFU in all eight isolates (≥ 2-log reduction in seven of the eight tested isolates), irrespective of their resistance to other non-catechol siderophore antibiotics, cefepime, or levofloxacin. In vitro experiments indicate that the antibacterial activity of cefiderocol is enhanced under iron-limited conditions [35]. Kidd et al. [36] investigated whether iron-overloaded conditions in the host affect the efficacy of cefiderocol using a murine thigh infection model. The authors observed no significant difference in efficacy against Gram-negative bacteria comparing iron-overloaded and normal hosts. In a recently published analysis based on the clinical

Table 3 Cefiderocol fT > MIC required for efficacy against multiple bacterial strains in neutropenic murine thigh and lung infection models (MICs: 0.125–16 mg/L) [6, 21]

Model	Organism (number of tested strains)	fT > MIC (mean ± SD)	
		Static	1 − $\log_{10}$ reduction
Thigh infection	*Enterobacteriaceae*[a] (10)	62.5 ± 27.4	73.3 ± 23.3
	Pseudomonas aeruginosa (3)	63.0 ± 15.5	72.2 ± 21.4
	Carbapenem-resistant strains (7)	NA	85.2 ± 12.1
	Carbapenem-susceptible strains (6)	NA	61.3 ± 25.0
Lung infection	*Enterobacteriaceae*[a] (9)	54.7 ± 24.1	64.4 ± 22.5
	Pseudomonas aeruginosa (3)	57.4 ± 10.2	70.3 ± 9.0
	Acinetobacter baumannii (3)	82.0 ± 4.6	88.1 ± 3.4
	Stenotrophomonas maltophilia (4)	45.6 ± 18.9	53.9 ± 18.1

fT > MIC fraction of time during the dosing interval where the free plasma drug concentration exceeds the minimum inhibitory concentration, *NA* not available, *SD* standard deviation

[a] *Enterobacteriaceae* included strains of *Escherichia coli* and *Klebsiella pneumoniae*. Based on [6, 21]

trials CREDIBLE-CR and APEKS-NP, Kawaguchi et al. [27] tried to relate human pharmacokinetic data to clinical efficacy measures such as clinical outcome, microbiological outcome, and vital status. The authors were unable to identify a clear pharmacokinetic/pharmacodynamic relationship for any of the efficacy measures because the fT > MIC was 100% in 97% of patients (MICs: ≤ 0.03 to 64 mg/L). This finding indicates that the dosing regimen of 2000 mg q8h, adjusted based on renal function, is likely to provide sufficient exposure for patients with pneumonia, BSI/sepsis, or cUTI. Overall, an fT > MIC of at least 90% appears to be a suitable pharmacokinetic/pharmacodynamic target in clinical practice as it provided a ≥ 1 − $\log_{10}$ reduction in CFU in vitro and in animal models. An fT > MIC of 50%, which is a typical target for other β-lactam antibiotics [37], might be insufficient in this case (Table 3).

5 Clinical Efficacy Trials

The clinical efficacy of cefiderocol has been studied in one phase II trial for the treatment of cUTI and AUP (APEKS-cUTI) and two phase III trials (CREDIBLE-CR and APEKS-NP). APEKS-cUTI, a multinational, multicenter, double-blind, non-inferiority trial, evaluated the efficacy of cefiderocol compared to imipenem/cilastatin in patients diagnosed with cUTI or AUP caused by carbapenem-susceptible Gram-negative bacteria [29]. Patients ≥ 18 years of age were randomized 2:1 to receive cefiderocol (2000 mg q8h) or imipenem/cilastatin (1000/1000 mg q8h). The treatment duration was 7–14 days and doses were adjusted based on renal function and body weight. The primary endpoint was defined as the composite of clinical response and microbiological eradication at the test of cure assessment, 7 days after the end of treatment. The primary efficacy analysis was performed in the microbiological intention-to-treat (mITT) population, which consisted of treated patients who had a Gram-negative uropathogen at baseline with > 10^5 CFU/mL in urine. The primary efficacy endpoint was achieved by 73% (183/252) in the cefiderocol group and 55% (65/119) in the imipenem/cilastatin group (adjusted treatment difference 18.6%, 95% confidence interval 8.2–28.9). Cefiderocol showed non-inferiority to imipenem/cilastatin for the primary endpoint at a − 15% non-inferiority margin.

CREDIBLE-CR investigated the efficacy of cefiderocol vs BAT for the treatment of severe carbapenem-resistant Gram-negative infections [4]. This multinational, multicenter, open-label trial was exploratory in nature and did not comprise predefined hypothesis testing. Furthermore, it was not limited to a single infection site if infections were caused by carbapenem-resistant bacteria. Forty-five percent of patients had hospital-acquired pneumonia (HAP), ventilator-acquired pneumonia (VAP), or healthcare-associated pneumonia (HCAP), 31% had BSI and/or sepsis (secondary to any source of infection), and 24% had cUTI. Patients were randomized 2:1 to receive cefiderocol (2000 mg administered q8h) or BAT. Best available therapy was determined by the investigator and could include a maximum of three antibiotic agents in combination, whereas in the cefiderocol group only one additional Gram-negative antibiotic was allowed (for cUTI, only monotherapy was permitted). In the carbapenem-resistant mITT population, 29% of patients treated with BAT received monotherapy, whereas 83% of patients in the cefiderocol group received monotherapy. Most of the treatment regimens in the BAT group included colistin (66%), while only one patient in the cefiderocol group received colistin. Treatment duration was 7–14 days (could be extended up to 21 days) in HAP/VAP/HCAP or BSI/sepsis and ≥ 5 days for cUTIs. The carbapenem-resistant mITT population consisted of treated patients with a confirmed carbapenem-resistant Gram-negative pathogen. *Acinetobacter baumannii* was the most common pathogen isolated in both treatment groups, followed by *K. pneumoniae* and *P. aeruginosa*. The primary efficacy endpoints for patients in the carbapenem-resistant mITT population were clinical cure at the test of cure assessment for patients with HAP/VAP/HCAP and BSI/sepsis and microbiological eradication for patients with cUTI (Table 4). All-cause mortality was a secondary endpoint (Table 5). In absolute numbers, there was a higher all-cause mortality in the cefiderocol group compared with the BAT group at all study timepoints. In the safety population, 6.4% (95% confidence interval − 8.6 to 19) more deaths were observed at day 28, 15% (− 0.2 to 29) more deaths were observed at the end of the study, and 13% (− 2.5 to 27) more deaths were observed at day 49 in the cefiderocol group compared with the BAT group. At the end of the study, 34% (34/101) of the patients in the cefiderocol group and 18% (9/49) in the BAT group died in the safety population. In particular, infections with *Acinetobacter* spp. were related to higher all-cause mortality at end of the study in the cefiderocol group (50%) compared with the BAT group (18%). Whether these observations reflect a true difference between the two groups needs further investigation. A comparison of post-hoc estimates of cefiderocol C_{max} and $AUC_{0–8h}$ values at steady state showed no significant relationship between cefiderocol exposure and survival in the CREDIBLE-CR trial [38].

APEKS-NP, a multinational, multicenter, double-blind, non-inferiority trial, compared cefiderocol and meropenem in the treatment of nosocomial pneumonia caused by Gram-negative bacteria [28]. Patients with nosocomial pneumonia were randomized 1:1 to receive 2000 mg of cefiderocol or 2000 mg of meropenem q8h, for a treatment duration of 7–14 days. To cover MRSA as well as Gram-positive bacteria in the cefiderocol arm, patients in both treatment groups received 600 mg of linezolid every 12 h for at least 5 days.

Table 4 Clinical efficacy results from cefiderocol phase II and III clinical trials in the mITT populations [4, 28, 29]

Trial	Description	*n*	Clinical outcome at TOC[a]		Difference (95% CI)	Microbiological eradication at TOC		Difference (95% CI)
			Cefiderocol	Comparator		Cefiderocol	Comparator	
APEKS-cUTI	Cefiderocol vs imipenem/cilastatin for the treatment of cUTI or AUP	452	90% (226/252)	87% (104/119)	2.39% (− 4.66 to 9.44)	73% (184/252)	56% (67/119)	17.25% (6.92–27.58)
CREDIBLE-CR	Cefiderocol vs best available therapy for the treatment of NP[b], BSI/sepsis, and cUTI	152	Overall					
			53% (42/80)	50% (19/38)		31% (25/80)	24% (9/38)	
			NP[b]					
			50% (20/40)	53% (10/19)		23% (9/40)	21% (4/19)	
			BSI/sepsis					
			43% (10/23)	43% (6/14)		30% (7/23)	29% (4/14)	
			cUTI					
			71% (12/17)	60% (3/5)		53% (9/17)	20% (1/5)	
APEKS-NP	Cefiderocol vs meropenem for the treatment of NP	300	65% (94/145)	67% (98/147)	− 1.8% (− 12.7 to 9.0)	41% (59/145)	42% (61/147)	− 0.8% (− 12.1 to 10.5)

BSI blood-stream infection, *CI* confidence interval, *cUTI* complicated urinary tract infection, *HAP* hospital-acquired pneumonia, *HCAP* healthcare-associated pneumonia, *mITT* microbiological intention-to-treat, *n* number of randomized patients, *NP nosocomial pneumonia*, *TOC* test of cure, *VAP* ventilator-acquired pneumonia

[a]Defined as clinical response in APEKS-cUTI and clinical cure in CREDIBLE-CR/APEKS-NP

[b]Included HAP/VAP/HCAP. APEKS-cUTI and APEKS-NP were randomized, double-blind, non-inferiority trials. CREDIBLE-CR was a randomized, open-label, descriptive trial. Based on [4, 28, 29]

Table 5 All-cause mortality in cefiderocol phase III clinical trials [4, 28]

Trial	Day 14		Day 28		End of study	
	Cefiderocol	Comparator	Cefiderocol	Comparator	Cefiderocol	Comparator
CREDIBLE-CR[a]	Overall					
	19% (19/101)	12% (6/49)	25% (25/101)	18% (9/49)	34% (34/101)	18% (9/49)
	HAP/VAP/HCAP					
	24% (11/45)	14% (3/22)	31% (14/45)	18% (4/22)	42% (19/45)	18% (4/22)
	BSI/sepsis					
	17% (5/30)	6% (1/17)	23% (7/30)	18% (3/17)	37% (11/30)	18% (3/17)
	cUTI					
	12% (3/26)	20% (2/10)	15% (4/26)	20% (2/10)	15% (4/26)	20% (2/10)
APEKS-NP[b]	12% (18/145)	12% (17/146)	21% (30/143)	21% (30/146)	27% (38/142)	23% (34/146)

Numbers in brackets represent deceased/total patients in the respective group. Based on [4, 28]

BSI blood-stream infection, *cUTI* complicated urinary tract infection, *HAP* hospital-acquired pneumonia, *HCAP* healthcare-associated pneumonia, *mITT* microbiological intention-to-treat, *VAP* ventilator-acquired pneumonia

[a]Reference safety population, comparator best available therapy

[b]Reference mITT population, comparator meropenem

All-cause mortality at day 14 was defined as the primary efficacy endpoint for the mITT population, which consisted of treated patients diagnosed with nosocomial pneumonia not only caused by Gram-positive pathogens. At day 14, all-cause mortality was 12.4% for cefiderocol and 11.6% for meropenem, with a treatment difference of 0.8% (95% confidence interval − 6.6 to 8.2). Cefiderocol showed non-inferiority to meropenem for the primary efficacy endpoint

at a − 12.5% non-inferiority margin. Clinical cure and microbiological eradication rates in the mITT population were secondary endpoints (Table 4). Patients included in the APEKS-NP study were comparable to those in the CREDIBLE-CR study diagnosed with HAP/VAP/HCAP, regarding sex distribution, age, creatinine clearance, APACHE score, and the need for ventilation (59.7% in APEKS-NP and 74.6% in CREDIBLE-CR). Notably, *A. baumannii* caused 55.2% of infections in the CREDIBLE-CR HAP/VAP/HCAP subgroup, while only 15.8% of patients in the APEKS-NP study were infected by *A. baumannii*. The proportion of patients with treatment failure before randomization was 64.2% in the CREDIBLE-CR subgroup and 32.6% in the APEKS-NP study [39].

Overall, cefiderocol showed non-inferiority to imipenem/cilastatin in the treatment of cUTI/AUP (APEKS-cUTI) and meropenem in the treatment of nosocomial pneumonia (APEKS-NP). Cefiderocol performed similarly to BAT in the treatment of severe carbapenem-resistant Gram-negative infections regarding clinical and microbiological efficacy (CREDIBLE-CR), but there was a numerically higher all-cause mortality in the cefiderocol group.

6 Safety and Tolerability

Safety data are available for subjects with renal impairment, patients with cUTI/AUP (APEKS-cUTI), patients with BSI/sepsis or pneumonia (CREDIBLE-CR), and patients with nosocomial pneumonia (APEKS-NP) [4, 17, 23, 28, 29]. In the CREDIBLE-CR study, the cure rate of cefiderocol and BAT were similar, but an increased mortality rate was reported in the cefiderocol group. Fourteen (of $n = 49$ [29%]) subjects in the BAT group and 36 (of $n = 101$ [36%]) subjects in the cefiderocol group died after the end of the study. Five deaths were considered due to the BAT and two deaths were attributed to cefiderocol by the investigators [4]. The APEKS-NP study found that in terms of mortality, cefiderocol was non-inferior to meropenem. In the APEKS-NP study, 34 ($n = 150$ [23%]) deaths were observed in the meropenem group while 39 ($n = 148$ [26%]) deaths were observed in the cefiderocol group [28]. One death ($n = 300$ [< 1%]) occurred due to cardiac arrest in the cefiderocol group of the APEKS-cUTI study, but it was considered unrelated to cefiderocol by the investigator because of the past complicated medical history of the subject [29]. In the CREDIBLE-CR study, 13 ($n = 101$ [13%]) subjects discontinued in the cefiderocol group, with three discontinuations being considered to result from adverse events (AEs) to cefiderocol. While in the BAT group, five ($n = 49$ [10%]) subjects discontinued, in which two were considered due to drug-related AEs [4]. In the APEKS-NP study, 14 ($n = 148$ [9%]) subjects in the cefiderocol group and 16 ($n = 150$ [10%]) subjects in the meropenem group discontinued the study [29]. One healthy volunteer withdrew from a phase I trial because of a raised body temperature [17], and one subject from the group with moderate renal impairment (eGFR 30 to < 60 mL/min) withdrew prematurely from the phase I study in renal impaired subjects because of an AE of urticaria [23]. Nearly half of the subjects in both the groups of the CREDIBLE-CR study had severe AEs [4]. In the APEKS-NP study, the most common AEs were urinary tract infection and hypokalemia with diarrhea, also reported in the CREDIBLE-CR study [4], and constipation. In the cefiderocol and meropenem groups, 3% of patients developed a *C. difficile* infection [28]. The safety profile observed in patients with and without renal impairment in phase II clinical trials (APELS-cUTI) is consistent in terms of AEs, with the majority of AEs being mild to moderate. No deaths or serious AEs were reported and the drug was well tolerated [23]. Adverse events that occurred in both groups (cefiderocol and imipenem-cilastatin) were gastrointestinal disorders, including abdominal pain, nausea, vomiting, constipation, and diarrhea. The most common serious AE was *C. difficile* colitis in one patient in the cefiderocol group vs two patients in the imipenem-cilastatin group [29]. Please refer to Table 6 for an overview of AEs reported in phase I–III trials. Data on the relationship between cefiderocol plasma concentrations and the risk of adverse effects are currently not available for typical patient groups.

7 Special Populations

Available data on the PK, pharmacodynamics, efficacy, and safety of cefiderocol in special patient populations are scarce. This particularly concerns pediatric patients, pregnant and breastfeeding women, geriatric patients, and patients with hepatic impairments.

The safety, tolerability, and PK of single and multiple doses of cefiderocol in pediatric patients with confirmed or suspected Gram-negative bacterial infections are currently under evaluation in a non-randomized clinical trial (NCT04335539). Results from this trial are not available yet. Katsube et al. [40] recently proposed dosing regimens for pediatric patients with an age range of < 3 months to 18 years by combining a population pharmacokinetic model in adults with allometric scaling and a maturation factor that describes kidney maturation. Based on simulations, dosing regimens that provided AUCs comparable to adults were identified. Katsube et al. [40] suggested to consider chronological age, gestational age, and body weight to choose a proper dose and infusion duration. Of note, this evaluation is not based on data obtained from pediatric patients, and it is currently only published as an abstract. Single case reports in pediatric patients are available, such as the successful combined use of cefiderocol, meropenem/vaborbactam, and bacteriophages to treat a 10-year-old female patient with

Table 6 Adverse events reported for cefiderocol [4, 17, 23, 28, 29]

Type of adverse event	Phase I (HS)		Phase I (RIS)	Phase II APEKS-cUTI		Phase III APEKS-NP		Phase III CREDIBLE-CR	
	Cefiderocol ($n = 32$)	Placebo ($n = 10$)	($n = 38$)	Cefiderocol ($n = 300$)	Imipenem-cilastatin ($n = 148$)	Cefiderocol ($n = 148$)	Meropenem ($n = 150$)	Cefiderocol ($n = 101$)	Best available therapy ($n = 49$)
Deaths	–	–	–	–	–	39	35	34	09
Withdrawal	01	–	01	05	03	14	16	13	05
Skin and subcutaneous disorders[a]	14	–	05	12	08	–	–	–	–
Gastrointestinal disorders[b]	06	–	03	38	22	20	19	32	13
Upper respiratory tract infections/cough	02	–	01	07	01	–	–	–	–
Metabolism and nutrition disorder[c]	–	–	02	05	04	16	23	–	–
Infections and infestations[d]	–	–	01	02	07	04	04	29	11
Nervous system disorders[e]	02	–	02	11	17	–	–	–	–
Cardiac failure/hypertension	–	–	–	15	11	–	–	–	–
Renal and urinary disorders[f]	–	–	01	04	05	23	16	–	–
Laboratory investigations[g]	23	06	–	–	–	–	–	30	07
Other[h]	–	–	07	–	–	–	–	27	13

HS healthy subjects, *n* number of randomized subjects, *RIS* renally impaired subjects

[a]Skin and subcutaneous disorders = rash, dermatitis, urticaria, pain on the infusion site, infusion-site erythema

[b]Gastrointestinal disorders = constipation, diarrhea, vomiting, nausea

[c]Metabolism and nutrition disorder = gout, hypoglycemia, hypokalemia

[d]Infections and infestations = *Clostridium difficile* infection, vaginal infection

[e]Nervous system disorders = headache, dizziness, insomnia, paresthesia, nausea

[f]Renal and urinary disorders = polyuria, renal cyst, renal tract infectons

[g]Laboratory investigations = elevated aminotransferase, increase in blood creatine phosphokinase, increase in white blood cell count, blood lactate dehydrogenase level, blood urea level increased

[h]Other = injury, poisoning, and procedural complications, arteriovenous fistula-site complication, postoperative wound complication, septic shock, vascular disorders, pyrexia, musculoskeletal and connective tissue disorder. Based on [4, 17, 23, 28, 29]

cystic fibrosis infected with pandrug-resistant *Achromobacter xylosoxidans* [41]. Because of the lack of relevant data, the Food and Drug Administration and European Medicines Agency labels of cefiderocol provide no recommendation on its use in pediatric patients.

Cefiderocol might be a viable treatment option in patients with cystic fibrosis, who often suffer from infections with MDR bacteria. However, only limited data are currently available for this special patient group. A study in patients with cystic fibrosis suffering from infections with MDR *A. xyloxoxidans* before or after lung transplantation reported a good tolerability and clinical efficacy of cefiderocol [16]. Consequently, cefiderocol was considered a useful option in treating *A. xyloxoxidans* bacteremia in combination with other antibiotics by the authors. However, the authors also reported a high baseline resistance to cefiderocol and a high risk of relapse, defined as the isolation of *A. xyloxoxidans* 6 months after completion of the antibiotic therapy. For example, in vitro resistance to cefiderocol at baseline was observed in three out of eight cases and microbiologic relapse occurred in 11 out of 12 cases. Consequently, further investigations on the use of cefiderocol in patients with cystic fibrosis are needed.

Data on the use of cefiderocol during pregnancy in humans are currently not available. Studies in rats and mice provided no signs of embryo-fetal toxicity or fetal malformations at a mean plasma exposure of 90% (rats) and 130% (mice) of the

average exposure attained in patients receiving cefiderocol doses of 2000 mg q8h [5]. Studies with radio-labeled cefiderocol administered to pregnant rats indicated that cefiderocol crosses the placenta, but the amount of cefiderocol found in rat fetuses was limited (< 0.5% of the administered dose) [5]. Similarly, human data on the excretion of cefiderocol into milk are currently not available. After the administration of radiolabeled cefiderocol to rats, peak cefiderocol concentrations in rat milk were approximately 6% of peak plasma concentrations in lactating rats [5]. Therefore, the Food and Drug Administration and European Medicines Agency labels suggest to carefully weigh the risks and benefits associated with breastfeeding, the exposure to cefiderocol, and the impact of the bacterial infection on the breastfeeding woman and the child [5, 6].

No dedicated evaluation of the PK, pharmacodynamics, efficacy, and safety of cefiderocol in geriatric patients is currently available. In the APEKS-cUTI trial, 158/67 out of 300 patients who received cefiderocol were aged 65/75 years or older. In this trial, no difference in efficacy and safety was observed across age ranges [42]. Furthermore, the potential effect of hepatic impairment on the treatment with cefiderocol has not been systematically evaluated in clinical trials yet. However, it appears unlikely that hepatic impairment relevantly affects cefiderocol treatments as the liver plays a negligible role in the PK of cefiderocol [5, 43].

8 Conclusions

The predominantly renal excretion, the limited inter-individual pharmacokinetic variability, the low potential for drug–drug interactions, and the limited differences between a selection of evaluated patient groups and healthy volunteers are desirable pharmacokinetic properties that suggest that cefiderocol exposure might be well predictable in a clinical setting. However, data in several relevant patient groups, such as critically ill patients, are currently lacking. The short half-life demands a frequent administration of q8h, with even shorter dosing intervals in the case of augmented clearance. Available evaluations suggest that doses and dosing intervals should be adjusted in patients with impaired kidney function. A significant removal of cefiderocol from the body is expected during hemodialysis, which might be alleviated by administering an additional dose after completion of the hemodialysis. Clinical efficacy trials indicate that cefiderocol is non-inferior to imipenem/cilastatin in the treatment of cUTI/AUP and to meropenem in the treatment of nosocomial pneumonia, while cefiderocol performed similarly to the BAT in the treatment of severe carbapenem-resistant Gram-negative infections regarding clinical and microbiological efficacy. A numerically higher all-cause mortality was observed in the cefiderocol group, which is not yet fully understood. Overall, cefiderocol shows favorable pharmacokinetic/pharmacodynamic properties and an acceptable safety profile, suggesting that cefiderocol might be a viable option to treat infections with bacteria resistant to other antibiotics in the future. Additional data from patient groups of interest are expected to further clarify the role of cefiderocol in specific clinical scenarios.

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