Cefiderocol: A Review in Serious Gram-Negative Bacterial Infections

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Abstract
Intravenous cefiderocol (Fetroja®; Fetcroja®) is the first siderophore cephalosporin approved for the treatment of adults with serious Gram-negative bacterial infections. Cefiderocol is stable against all four Ambler classes of β-lactamases (including metallo-β-lactamases) and exhibits excellent in vitro activity against many clinically relevant Gram-negative pathogens, including multidrug resistant strains. In randomized, double-blind clinical trials, cefiderocol was noninferior to imipenem/cilastatin for the treatment of complicated urinary tract infections (cUTI) and to meropenem for nosocomial pneumonia. Furthermore, in a pathogen-focused clinical trial in patients with carbapenem-resistant (CR) infections, cefiderocol showed comparable efficacy to best available therapy (BAT), albeit all-cause mortality rate was higher in the cefiderocol arm, the cause of which has not been established. Cefiderocol had a good tolerability and safety profile in clinical trials. Thus cefiderocol is a novel, emerging, useful addition to the current treatment options for adults with susceptible Gram-negative bacterial infections (including cUTI and nosocomial pneumonia) for whom there are limited treatment options.

Plain Language Summary
Infections caused by carbapenem-resistant (CR) Enterobacterales and nonfermenters (such as Pseudomonas, Acinetobacter, Stenotrophomonas, Burkholderia) are a major global health threat. Cefiderocol, a cephalosporin with activity against CR Enterobacterales and nonfermenters, uses the bacteria’s own iron uptake system to gain cell entry, like a Trojan horse. Once inside, the drug disrupts the formation of the bacterial cell wall, killing the bacteria. Cefiderocol is approved for the treatment of serious Gram-negative bacterial infections. In clinical trials, cefiderocol was effective versus carbapenems or best available therapy for complicated urinary tract infections, nosocomial pneumonia and bloodstream infections/sepsis, including those caused by CR bacteria. The drug had a good tolerability and safety profile. Thus, cefiderocol is a useful addition to the current treatment options for adults with cefiderocol-susceptible Gram-negative bacterial infections for whom there are limited treatment options.

1 Introduction
Multidrug-resistant (MDR) Gram-negative pathogens are causing an increasing number of infections, including complicated urinary tract infections (cUTI) [1], nosocomial pneumonia [2] and bloodstream infections (BSI)/sepsis [3]. The WHO has designated carbapenem-resistant (CR) strains of Enterobacterales, Pseudomonas aeruginosa and Acinetobacter baumannii, and third-generation cephalosporin-resistant Enterobacterales, as ‘priority 1: critical’ pathogens for which new treatments are urgently needed [4]. The US CDC have identified CR Enterobacterales and A. baumannii as urgent threats and MDR P. aeruginosa as a serious threat [5]. Stenotrophomonas maltophilia is also an emerging MDR opportunistic pathogen.
Cefiderocol: clinical considerations

First siderophore cephalosporin.

Excellent in vitro activity; stable vs all Ambler classes of β-lactamases (including metallo-β-lactamases).

Noninferior efficacy to carbapenems for cUTI and nosocomial infections; comparable efficacy to BAT in serious CR infections.

Good tolerability and safety profile.

that confers intrinsic resistance to multiple antibacterial classes, including β-lactams [6].

Carbapenem resistance mechanisms include β-lactamases, efflux pumps, and porin loss or mutation [7]. Novel β-lactam/β-lactamase-inhibitor combinations (ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, imipenem/cilastatin–relebactam) and non-β-lactam antibacterials (e.g. plazomicin) overcome some of these resistance mechanisms [8]. However, none of the new β-lactam/β-lactamase inhibitor combinations are stable against metallo-β-lactamases and ceftolozane–tazobactam is not stable against KPC [8, 9]. Thus, additional antibacterials against CR pathogens remains an unmet medical need [10].

Cefiderocol (Fetroja®, Fetcroja®), an intravenously infused siderophore cephalosporin with a unique mechanism of bacterial cell entry, is approved in the EU and the USA for the treatment of adults with Gram-negative bacterial infections (Sect. 6). This article reviews the efficacy and tolerability of cefiderocol in the approved indications and overviews its pharmacological properties.

2 Pharmacodynamic Properties

Cefiderocol is actively transported into the periplasmic space of Gram-negative bacteria through the bacterial siderophore iron uptake system, as well as through passive diffusion via outer membrane porin channels [11–13]. Iron transporters PiuA in P. aeruginosa, and CirA and Fiu in Escherichia coli have been shown to contribute to the transport of cefiderocol across the outer membrane [14]. Once inside, cefiderocol binds to penicillin binding proteins (PBPs), primarily PBP3, and inhibits peptidoglycan cell wall synthesis, causing cell death [11–13]. Cefiderocol is structurally related to ceftazidime and cepefepme. While all three compounds have an aminothiazole ring at C7, which confers stability against β-lactamases, cefiderocol has a catechol side chain at C3 that acts as an iron-binding siderophore. Thus, it mimics bacterial siderophore and gains cell entry, like a ‘Trojan horse’ [11–13]. The unique structure of cefiderocol, along with low catalytic efficiencies of carbapenemases against this drug, confers stability against all four Ambler classes of β-lactamases [15, 16]. Truncation or loss of porin channels and upregulation of efflux pumps had no marked effect on the activity of cefiderocol [14, 17, 18]. Cefiderocol has no clinically relevant activity against Gram-positive or anaerobic bacteria [10].

2.1 Antibacterial Activity

Due to its iron transporter-based mechanism of cell entry, in vitro susceptibility testing of cefiderocol is performed using iron-depleted cation-adjusted Mueller–Hinton broth, recommended by the CLSI and the EUCAST. CLSI-approved cefiderocol minimum inhibitory concentration (MIC) breakpoints are ≤ 4, 8 and ≥ 16 mg/L (susceptible, intermediate and resistant, respectively) for Enterobacteriales, P. aeruginosa and A. baumannii, and ≤ 1 and > 1 mg/L (susceptible and nonsusceptible) for S. maltophilia (based on limited clinical data) [19]. Cefiderocol breakpoints approved by CLSI, US FDA and EUCAST differ markedly, which could impact susceptibility or resistance reporting [20, 21], particularly for NDM-producing carbapenem–nonsusceptible Enterobacteriales and IMP-producing P. aeruginosa [21]. Disk diffusion method could also be a convenient alternative to the broth microdilution method for cefiderocol susceptibility testing [20]. Cefiderocol susceptibility rates reported in this article are based on the CLSI breakpoints, using the broth microdilution method.

The in vitro activity of cefiderocol and relevant comparators against Gram-negative clinical isolates was evaluated in two multinational surveillance programmes, SIDERO-WT [18, 22–26] and SIDERO-CR [27], as part of its preclinical development. In SIDERO-WT, > 30,000 isolates were collected from North American and European hospitals in three consecutive studies during 2014–2015, 2015–2016 and 2016–2017. In SIDERO-CR, 1873 carbapenem–nonsusceptible isolates, including Enterobacteriales, MDR A. baumannii, MDR P. aeruginosa, and S. maltophilia were collected globally between 2014 and 2016. In vitro data are also available from other studies assessing cefiderocol against a wide range of clinically important isolates collected globally [14, 28–30] and from Canada [31], Germany [32], Greece [33], Japan [34, 35], Spain [36], Taiwan [37], the UK [38] and the USA [17, 39–42].

In a pooled analysis of SIDERO-WT studies, MIC required to inhibit 90% of isolates (MIC90) ranged from 0.12 to 2 mg/L for Enterobacteriales (E. coli, Klebsiella pneumonia, Klebsiella oxytoca, Citrobacter freundii, Citrobacter koseri, Enterobacter cloacae, Enterobacter aerogenes, Serratia marcescens), Nonfermenters (P. aeruginosa, A.
Cefiderocol: A Review

Cefiderocol had potent activity against Gram-negative bacteria producing all four Ambler classes of β-lactamases, including extended spectrum β-lactamases (ESBL) and carbapenemases [14, 17, 18, 29, 32, 35, 36, 38, 41, 42, 44–48]. In meropenem-resistant or -intermediate isolates in SIDERO-WT (n = 1272) [18] and SIDERO-CR (n = 1651) [45], 97–98% of β-lactamase-producing Enterobacteriales, *P. aeruginosa* and *A. baumannii* isolates were susceptible to cefiderocol. Cefiderocol MIC90 values were ≤ 4 mg/L for isolates positive for KPC, GES, IMP, VIM, OXA-23 and OXA-58, and 8 mg/L for those positive for NDM or OXA-24/40 [18, 45]. In vitro activity of cefiderocol and comparator agents against individual β-lactamase genotypes is summarized in Table 2. Cefiderocol was the only agent active against all genotypes, while ceftazidime–avibactam and colistin were active against KPC and OXA genotypes (Table 2).

In other studies, cefiderocol susceptibility rates were 94–100% for ESBL-producing Enterobacteriales [31, 32, 40], 100% for *S. maltophilia* producing L1 and L2 β-lactamases [41], ≈ 72% for NDM-producing Enterobacteriales and *P. aeruginosa* [38] and 73% for PER-producing *P. aeruginosa* [38]. Cefiderocol was stable against chromosomal AmpC β-lactamases of *P. aeruginosa* and *E. cloacae*, and had a low propensity to induce AmpC β-lactamases in these isolates [47]. In Enterobacteriales harbouring ESBL or AmpC β-lactamases and porin loss, cefiderocol susceptibility was 88–100% [38].

### 2.1.1 In Vivo Activity

The in vitro activity of cefiderocol correlated well with its bactericidal effects in murine models of thigh or lung infection [49–56], respiratory tract infection [57] and ventilator-associated pneumonia (VAP) [58], caused by Enterobacteriales, *P. aeruginosa* and *A. baumannii* or *S. maltophilia*, including CR strains [56–58]. Data from representative animal studies are discussed in Sect. 2.2.

### 2.1.2 Resistance Mechanisms

Cefiderocol may have a low potential for resistance development. In SIDERO-WT [59] and SIDERO-CR [60], 0.56% and 3.8% of isolates (n = 28,629 and 1837) were nonsusceptible to cefiderocol (i.e. MIC ≥ 4 mg/L); the most common nonsusceptible isolates were PER-producing *A. baumannii* and NDM-producing Enterobacteriales. While PER or NDM could contribute to cefiderocol resistance, they alone may not be sufficient to cause the resistance [60–62]. Other possible mechanisms of resistance to cefiderocol include siderophore receptor gene truncation, PBP3 modification and AmpC β-lactamase mutations [59, 61, 63]. In *E. coli* strains, PBP3 modification by YRIN insertion was associated with

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a twofold increase in cefiderocol MIC (from 0.06 to 0.125 ng/L), compared with an eightfold increase for ceftazidime, ceftazidime-avibactam, and a fourfold increase for ceftazidime/avibactam [64]. *pvdS* gene mutation in *P. aeruginosa* was also associated with increased cefiderocol MICs, mainly due to reduced expression of iron transporters [65].

### 2.2 Pharmacological Considerations

The fraction of dosing interval during which the free drug concentration in plasma exceeds the MIC (%T > MIC) is considered a reliable pharmacodynamic index for cefiderocol. In a murine thigh infection model with *P. aeruginosa* (cefiderocol MIC 0.063–0.5 mg/L), bacterial stasis and 1 log₁₀ and 2 log₁₀ reductions in colony forming unit (CFU) at 24 h were observed at cefiderocol mean %T > MIC values of 76.3%, 81.9% and 88.2%, respectively [54]. In the same model, a human-simulated cefiderocol regimen (2 g
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every 8 h, 3-h infusion) produced bacterial stasis or 2 log₁₀ reduction in CFU at 24 h in 88% of *A. baumannii* (*n* = 16), 85% of *P. aeruginosa* (*n* = 20) and 77% of Enterobacterales (*n* = 31) isolates, with a cefiderocol MIC of ≤ 4 mg/L [55]. This regimen is predicted to have a % $T > MIC$ of 96% and 80% for a MIC of 4 and 8 mg/L [55]. In a murine lung infection model, the mean % $T > MIC$ required for a 1 log₁₀ reduction in CFU was 64.4% for Enterobacterales, 70.3% for *P. aeruginosa*, 88.1% for *A. baumannii* and 53.9% for *S. maltophilia* [51]. With the humanized regimen, increasing the infusion period from 1 to 3 h increased % $T > MIC$ for MICs of 4 mg/L (from 75% to 100%) and 8 mg/L (from 50% to 100%) in immunocompetent rat models [57]. Results from an in vitro chemostat model were consistent with those from animal studies [34].

A population pharmacokinetic model showed that the recommended cefiderocol dosage regimen of 2 g every 8 h (3-h infusion), adjusted for kidney function, would provide adequate drug exposure in patients with serious infections (pneumonia, cUTI or BSI/sepsis) [66]. The probability of target attainment for 100% $T > MIC$ against MICs ≤ 4 mg/L was > 90% for different infections sites and kidney function groups, with the exception of BSI/sepsis and normal kidney function (86%) [66].

### 3 Pharmacokinetic Properties of Cefiderocol

Cefiderocol showed linear pharmacokinetics within a 100–4000 mg dose range [67, 68]. Following multiple 3-h infusions of 2 g every 8 h (or kidney function-adjusted dosage), the mean maximum plasma concentration of cefiderocol was 115 mg/L in patients with cUTI and 111 mg/L in those with bacterial hospital-acquired pneumonia (HAP) or VAP; area under the plasma concentration–time curve (AUC) from time zero to 24 (AUC₂₄) was 1944 and 1773 mg • h/L [67]. In healthy volunteers, the geometric mean volume of distribution of cefiderocol was 18.0 L; 40–60% of cefiderocol is bound to plasma proteins, mainly albumin [67, 68]. Cefiderocol is minimally metabolized and is excreted mainly by the kidneys. Following a single [¹⁴C]-labelled cefiderocol dose of 1 g infused over 1 h, cefiderocol accounted for 92.3% of the plasma AUC for total radioactivity, and 98.6% of total radioactivity was excreted in urine. The estimated geometric mean clearance of cefiderocol is 5.18 L/h and the terminal elimination half-life is 2–3 h [67, 68].

Cefiderocol showed good epithelial lining fluid (ELF) penetration in mechanically-ventilated patients with bacterial pneumonia receiving standard-of-care antibacterials [69]. At steady state after multiple 3-h infusions of 2 g (or kidney function-adjusted dose), geometric mean cefiderocol ELF concentration was 7.63 mg/L at the end of infusion and 10.4 mg/L at 2 h post infusion [69]. In these patients, the ELF to free plasma concentration ratio was 0.212 at the end of infusion and 0.547 at 2 h post infusion, compared with the ELF to free plasma AUC ratio of 0.239 in healthy subjects, suggesting delayed distribution and sustained exposure of cefiderocol in the ELF in pneumonia patients [69, 70].

Kidney function has an impact on cefiderocol pharmacokinetics [71, 72]. Cefiderocol dosage should be reduced in patients with moderate (creatinine clearance [CL₉₀] ≥ 30 to

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**Table 2** In vitro activity of cefiderocol against selected clinical isolates by β-lactamase genotype in SIDERO-WT and SIDERO-CR

| Pathogen/β-lactamase genotypes (no. of isolates) | MIC₉₀ (mg/L) [% susceptible] |
|---|---|
| | FDC | FEP | CZA | C/T | CIP | CST | MEM |
| **Enterobacterales** | | | | | | | |
| KPC (644) [18, 45] | 2–4 [98.1] | > 64 [0] | 4 [96] | > 64 [0] | > 8 [5.3] | > 8 | > 64 [0] |
| NDM (162) [44, 45] | 8 [84–87.2] | > 64 | > 64 | > 64 | > 8 | 1 to > 8 | > 64 |
| VIM (174) [44, 45] | 4 [98.0] | > 64 | > 64 | > 64 | > 8 | 2 to > 8 | ≥ 64 |
| OXA-48 (168) [18, 45] | 4 [100] | > 64 [12.5] | 4 to > 64 [90.6] | > 64 [3.1] | > 8 [3.1] | > 8 [78.1] | ≥ 64 [0] |
| VIM (174) [44, 45] | 4 [98.0] | > 64 | > 64 | > 64 | > 8 | 2 to > 8 | ≥ 64 |
| **P. aeruginosa** | | | | | | | |
| VIM (256) [44, 45] | 0.5–1 [100] | > 64 | > 64 | > 64 | > 8 to > 64 | 1–2 | > 8 to > 64 |
| IMP (16) [44] | 1 | > 64 | > 64 | > 64 | > 64 | 2 | > 8 |
| **A. baumannii** | | | | | | | |
| OXA-23 (775) [18, 45] | 1–2 [92.2] | > 64.7 [1.7] | > 64 | > 64 | > 8 [0] | 1 to > 8 [79.6] | > 64 [0] |
| OXA-24 (237) [18, 45] | 1–8 [89.4] | > 64.7 [1.3] | > 64 | > 64 | > 8 [0] | 1 [96.8] | > 64 [0] |
| OXA-58 (14) [18] | 1 | > 64 [0] | > 64 | > 64 | > 8 [0] | 1 [92.9] | 16 [0] |

C/T: ceftolozane-tazobactam, CIP: ciprofloxacin, CST: colistin, CZA: ceftazidime-avibactam, FDC: cefiderocol, FEP: cefepime, MEM: meropenem, MIC₉₀: minimum inhibitory concentration required to inhibit 90% of isolates

*Reported only where available*
< 60 mL/min [68] or 30–59 mL/min [67]) or severe (CLCR ≥ 15 to < 30 mL/min [68] or 15–29 mL/min [67]) kidney impairment, or kidney failure (CLCR < 15 mL/min), and in those receiving haemodialysis. It should be increased in patients with augmented kidney function (CLCR ≥ 120 mL/min) [67, 68]. Hepatic impairment is unlikely to affect the pharmacokinetics of cefiderocol [68]. No clinically relevant drug-drug interactions are expected when cefiderocol is coadministered with substrates or inhibitors of CYP enzymes or substrates of drug transporters [67, 68, 73].

4 Therapeutic Efficacy of Cefiderocol

The efficacy of cefiderocol was assessed in two noninferiority trials in patients with cUTI (APEKS-cUTI) [74] or nosocomial pneumonia (APEKS-NP) [75] and in a pathogen-focused trial in patients with serious infections (CREDIBLE-CR) [76]. Design details of these trials are summarized in Table 3. APEKS-cUTI and APEKS-NP excluded patients with known CR bacterial infections, whereas eligible patients in CREDIBLE-CR had to have CR pathogens. Nonetheless, in APEKS-cUTI and APEKS-NP, carbapenem resistance was identified post randomization in several patients. APEKS-NP and CREDIBLE-CR enrolled a high-risk, critically ill patient population. Within each trial, demographic and baseline characteristics were generally similar between the treatment groups and the majority of patients had moderate or severe disease [74–76].

4.1 In Patients with cUTI

In the microbiological intent-to-treat (ITT) population (n = 371) in APEKS-cUTI, 73% of patients had cUTI with or without pyelonephritis and 27% had acute uncomplicated pyelonephritis [74]. Most patients (96%) had one uropathogen > 1 x 10^5 CFU/mL at baseline, most commonly E. coli (≈ 63%) and K. pneumoniae (20%); resistance to cefepime or levofloxacin was common among these pathogens [74]. The microbiological ITT population of cUTI in CREDIBLE-CR included 22 patients; the most prevalent CR pathogens in this population were K. pneumoniae (63%) and P. aeruginosa (27%) [76]. The median treatment duration in the cefiderocol and comparator groups were 9 days each in APEKS-cUTI [74], and 10.5 and 6.5 days in CREDIBLE-CR [76].

In APEKS-cUTI, cefiderocol was noninferior to high-dose imipenem/cilastatin for the composite of clinical and microbiological outcomes at test of cure in the microbiological ITT population (Table 4; primary endpoint) [74]. While clinical cure rates were similar between the groups, microbiological eradication rates were significantly higher with cefiderocol (Table 4). Composite outcome results for prespecified subgroups based on age (< 65 or ≥ 65 years), sex (men or women) or clinical diagnosis (cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis) and in subgroups with E. coli and K. pneumoniae at baseline were consistent with that of the microbiological ITT population.

In CREDIBLE-CR, cefiderocol was associated with favourable microbiological (primary endpoint) and clinical outcomes versus best available therapy (BAT; i.e. a combination of up to three Gram-negative antibiotics) in the microbiological ITT population of cUTI (Table 4) [76].

4.2 In Patients with Nosocomial Pneumonia

In the modified ITT population (n = 292) in APEKS-NP, 42%, 41% and 17% of patients had VAP, HAP and healthcare-associated Gram-negative pneumonia (HCAP), respectively [75]. HCAP, which is no longer a separate clinical entity, was included as a subset clinical diagnosis to enrich the study population. The cefiderocol and meropenem groups were well balanced with respect to ventilation status for VAP (98% vs 98%) and HAP (37% vs 35%)

| Table 3 Design of randomized, multinational cefiderocol trials in hospitalized adults with aerobic Gram-negative bacterial infections |
|---------------------------------------------------------------|
| **APEKS-cUTI [74]**                                   | **APEKS-NP [75]**                                   | **CREDIBLE-CR [76]**                                 |
| **Design**              | Double-blind, noninferiority, phase 2, US FDA-approved design | Double-blind, noninferiority, phase 3, US FDA-approved design | Open-label, pathogen-focused, descriptive, phase 3, EMA-approved design |
| **Treatments**          | Cefiderocol 2 g q8h 1-h infusion or imipenem/cilastatin 1 g q8h infusion | Cefiderocol 2 g q8h 3-h infusion or meropenem 2 g q8h 3-h infusion | Cefiderocol 2 g q8h 3-h infusion or best available therapy |

BSI bloodstream infection, cUTI complicated urinary tract infection, HAP hospital-acquired pneumonia, HCAP healthcare-associated pneumonia, pts patients, q8h every 8 h, VAP ventilator-associated pneumonia

*Administered for 7–14 days (could be extended up to 21 days in APEKS-NP and CREDIBLE-CR). Dosages adjusted for kidney function; ²Both groups received open-label intravenous linezolid for Gram-positive bacteria and/or mexiticillin-resistant Staphylococcus aureus coverage; ³One adjunctive agent (excluding polymyxins, cephalosporins and carbapenems) was permitted in pts with pneumonia or BSI/sepsis; ⁴A maximum of three prespecified antibacterials, dosed as per the country’s label

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subgroups, empirical treatment failure (33% vs 32%), presence in an ICU at randomization (70% vs 66%). Among HCAP patients, more cefiderocol than meropenem recipients required mechanical ventilation at baseline (33% vs 9%). The two groups were also similar with respect to kidney function, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Clinical Pulmonary Infection Score (CPIS) and Sequential Organ Failure Assessment (SOFA) score. A qualifying Gram-negative pathogen was identified in 251 (86%) patients, with *K. pneumoniae* (32%), *P. aeruginosa* (16%), *A. baumannii* (16%) and *E. coli* (14%) the most prevalent. The mean duration of study treatment was 10.4 and 10.1 days.

In APEKS-NP, cefiderocol was noninferior to high-dose, extended-infusion meropenem for all-cause mortality at day 14 in the modified ITT population (Table 4; primary endpoint) [75]. No clinically relevant between-group differences were seen for this outcome in prespecified subgroups based on clinical diagnosis, sex, race, geographical region, APACHE II score, CPIS, concomitant bacteraemia, kidney function, empirical treatment failure, ICU or ventilation status at randomization, or baseline pathogens. All-cause mortality at day 28 was also similar between cefiderocol and meropenem groups in the modified ITT population (21.0% vs 20.5%) and in subgroups based on higher risk scores (e.g. APACHE II score ≥ 20; SOFA score ≥ 7), previous empirical treatment failure or ICU status at randomization [75].

Clinical and microbiological outcomes were also similar between cefiderocol and meropenem groups in the modified ITT population in APEKS-NP (Table 4) and in subgroups based on the five most prevalent baseline pathogens [75]. In patients with HCAP, clinical cure rates were 82% and 91%.

Clinical outcome data are generally supported by change from baseline in CPIS and SOFA score [75]. During treatment in APEKS-NP, six patients in the cefiderocol group and five patients in the meropenem group had a ≥ 4-fold increase in the MIC values for respective agents; none of these patients died by day 14 [75]. The isolates with increased MIC values were: *K. pneumoniae* (3 patients), *E. aerogenes* (2) and *E. cloacae* and *S. marcescens* (1) in the

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**Table 4: Efficacy of cefiderocol in patients with Gram-negative bacterial infections in clinical studies**

| Treatment (no. of pts)* | ACM at day 14 (% pts) [95% CI] | Clinical cure at TOCb (% pts) [95% CI] | Microbiological eradication at TOCb (% pts) [95% CI] |
|-------------------------|--------------------------------|--------------------------------------|-----------------------------------------------|
| **In pts with complicated urinary tract infection** | | | |
| APEKS-cUTI [74] | | | |
| Cefiderocol (252)c | ND | 90 | 73 |
| Imipenem/cilastatin (119) | ND | 87 | 56 |
| Treatment difference | ND | 2.39 [−4.66 to 9.44] | 17.25 [6.92–27.58] |
| CREDIBLE-CR [76] | | | |
| Cefiderocol (17) | 12 [1.5–36.4] | 71 [44.0–89.7] | 53d [27.8–77.0] |
| Best available therapy (5) | 40 [5.3–85.3] | 60 [14.7–94.7] | 20d [0.5–71.6] |
| **In pts with nosocomial pneumonia** | | | |
| APEKS-NP [75] | | | |
| Cefiderocol (145) | 12.4 | 65 | 41 |
| Meropenem (147) | 11.6 | 67 | 42 |
| Treatment difference | 0.8* [−6.6 to 8.2]d | −1.8 [−12.7 to 9.0] | −0.8 [−12.1 to 10.5] |
| CREDIBLE-CR [76] | | | |
| Cefiderocol (40) | 25 [12.7–41.2] | 50d [33.8–66.2] | 23 [10.8–38.5] |
| Best available therapy (19) | 11 [1.3–43.7] | 53d [28.9–75.6] | 21 [6.1–45.6] |
| **In pts with bloodstream infection or sepsis (CREDIBLE-CR) [76]** | | | |
| Cefiderocol (23) | 22 [7.5–43.7] | 43d [23.2–65.5] | 30 [13.2–52.9] |
| Best available therapy (14) | 7 [0.2–33.9] | 43d [17.7–71.1] | 29 [8.4–58.1] |
| **In overall population with CR infections (CREDIBLE-CR) [76]** | | | |
| Cefiderocol (80) | 21 [12.9–31.8] | 53 [41.0–63.8] | 31 [21.3–42.6] |
| Best available therapy (38) | 13 [4.4–28.1] | 50 [33.4–66.6] | 24 [11.4–40.2] |

ACM all-cause mortality, ITT intent-to-treat, ND not determined, pts patients, TOC test of cure

*p = 0.002 for noninferiority (at 12.5% margin) hypothesis

Primary efficacy populations: microbiological ITT in APEKS-cUTI and CREDIBLE-CR, and modified ITT in APEKS-NP; b7 ± 2 days after the end of treatment; cCefiderocol was noninferior (at 15% margin) to the comparator for the primary endpoint of composite of clinical and microbiological outcomes at TOC (73% vs 55%; treatment difference 18.58%; 95% CI 8.23–28.92; p = 0.0004); dPrimary endpoint
increase, cefiderocol MIC values remained at ≤ 1 mg/L for
and K. pneumoniae (1), P. aeruginosa (3) cefiderocol group;
1566 Y. Y. Syed (44% vs 50%) and K. pneumoniae population were
A. baumannii (44% vs 29%), another pathogen (76). Conversely, in patients with infec-
tions due to nonfermenters other than Acinetobacter spp. with or without co-infection with
another pathogen (76). Consistently, in patients with infections due to nonfermenters other than Acinetobacter spp.,
mortality was not higher with cefiderocol versus BAT (68). The cause of the increased mortality in the cefiderocol group
has not been established (68), although, among Acinetobacter-infected patients, baseline mortality risk (septic shock
and ICU status) was higher in the cefiderocol group than in the BAT group (76).

After randomization in APEKS-NP, 30 patients in the cefiderocol and 26 in the meropenem group were found to have pathogens with a meropenem MIC of > 8 µg/mL at baseline (75). Clinical and microbiological outcomes in this subgroup were less favourable compared with those with MIC < 8 µg/mL. In the MIC > 8 µg/mL subgroup, all-cause mortality rates in the cefiderocol and meropenem groups were 20% and 19% at day 14 (27% and 31% at day 28); at test of cure, clinical cure rates were 57% and 58%, and microbiological eradication rates were 40% and 31% (75).

5 Safety and Tolerability of Cefiderocol
Cefiderocol was generally well tolerated in patients with cUTI in APEKS-cUTI (74) and had an acceptable tolerability profile in patients with nosocomial pneumonia in APEKS-NP (75) and those with CR serious infections in CREDIBLE-CR (76). Apart from the unexplained imbalance in all-cause mortality in CREDIBLE-CR (Sect. 4.4), the safety profile of cefiderocol was consistent with that expected for a cephalosporin, with no new safety signals seen in these clinical trials (74–76). The adverse event (AE) profile of cefiderocol was generally similar to that of comparators (74–77).

The most common adverse reactions with cefiderocol were diarrhoea, infusion site reactions, constipation, rash, candidiasis, cough, elevations in liver tests, headache, hypokalaemia, nausea and vomiting in patients with cUTI, and elevations in liver function tests, hypokalaemia, diarrhoea, hypomagnesaemia and atrial fibrillation in patients with nosocomial pneumonia (67).

Treatment-emergent AEs, severe AEs and serious AEs occurred in similar proportions of patients in each treatment arm in APEKS-cUTI (74), APEKS-NP (75) and CREDIBLE-CR (76). Across these trials, treatment-related AEs (TRAEs) occurred in 10.2% of 549 cefiderocol recipients, < 1% had serious TRAEs and 1.5% discontinued treatment because of TRAEs (77). The most common TRAEs with cefiderocol were elevations in liver function tests and diarrhoea (77). In CREDIBLE-CR, treatment-emergent AEs led to more deaths in the cefiderocol arm than in the BAT arm (33.7% vs 18.4%), particularly infections and infestations (20.8% vs 6.1%) and septic shock (10.9% vs 6.1%) (10).

Consistent with the known class effects of cephalosporins, AEs of special interest with cefiderocol include Clostridium difficile-related AEs, liver-related AEs, seizures and hypersensitivity reactions (77). Across all trials, C. difficile-related AEs (mostly mild or moderate) occurred in eight cefiderocol recipients, including one serious TRAE

4.3 In Patients with BSI/sepsis
In CREDIBLE-CR, cefiderocol was comparable to BAT with regards to clinical cure (primary endpoint) and microbiological eradication rates in the CR microbiological ITT population of nosocomial pneumonia (n = 118) were comparable between cefiderocol and BAT groups (Table 4) (76). The most prevalent CR pathogens in the cefiderocol and BAT groups in this population were K. pneumoniae (44% vs 29%), A. baumannii (44% vs 50%) and P. aeruginosa (9% vs 21%) (76).

4.4 In Patients with CR Bacterial Infections
In the overall CREDIBLE-CR population, cefiderocol showed comparable clinical and microbiological efficacy to BAT (Table 4), with numerical between-group differences favouring cefiderocol in patients with infections caused by Enterobacterales (clinical cure 66% vs 45%; microbiological eradication 48% vs 18%) or metallo-β-lactamase producers (75% vs 29%; 44% vs 14%) (76). A similar proportion of patients in the respective treatment groups achieved the composite endpoint of survival without the need to change antibacterial(s) due to toxicity or absence of efficacy (63% vs 61%; treatment difference 1.1%; 95% CI –17.7 to 20.0) (76).

In CREDIBLE-CR, the all-cause mortality rate in the CR microbiological ITT population was higher in the cefiderocol than the BAT group at day 14 (Table 4). Similar result was seen in the safety population at day 14 (19% vs 12%), day 28 (25% vs 18%) and at study end (34% vs 18%); the between-group difference was particularly evident in patients with nosocomial pneumonia or BSI/sepsis, caused by Acinetobacter spp. with or without co-infection with another pathogen (76). Conversely, in patients with infections due to nonfermenters other than Acinetobacter spp., mortality was not higher with cefiderocol versus BAT (68). After randomization in APEKS-NP, 30 patients in the cefiderocol and 26 in the meropenem group were found to have pathogens with a meropenem MIC of > 8 µg/mL at baseline (75). Clinical and microbiological outcomes in this subgroup were less favourable compared with those with MIC < 8 µg/mL. In the MIC > 8 µg/mL subgroup, all-cause mortality rates in the cefiderocol and meropenem groups were 20% and 19% at day 14 (27% and 31% at day 28); at test of cure, clinical cure rates were 57% and 58%, and microbiological eradication rates were 40% and 31% (75).
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of colitis. The incidence of liver-related AEs was similar between treatment groups in APEKS-cUTI (0.7% with cefiderocol vs 0.7% with imipenem/cilastatin) and APEKS-NP (25% with cefiderocol vs 24% with meropenem), but was higher with cefiderocol in CREDIBLE-CR (29.7% vs 14.3% with BAT). The majority of liver-related AEs in CREDIBLE-CR had an alternate aetiology (underlying medical history or concomitant medication) and none met the criteria for Hy’s law or drug-induced liver injury. Four cefiderocol recipients had seizures and none were treatment-related. The incidence of rash or hypersensitivity reactions was similar between cefiderocol and comparator groups and none were serious; cefiderocol-related rash occurred in one patient each in APEKS-NP and CREDIBLE-CR [77].

As cefiderocol is a siderophore antibacterial, its effect on host iron homeostasis is of interest. In APEKS-cUTI, APEKS-NP and CREDIBLE-CR, it did not increase the risk of iron homeostasis-related AEs compared with nonsiderophore antibacterials [77].

6 Dosage and Administration of Cefiderocol

Cefiderocol is approved for the treatment of adults with cUTIs (including pyelonephritis), HAP or VAP, caused by designated susceptible Gram-negative bacteria, in the USA [67] and for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options in the EU [68]. The recommended dosage of cefiderocol in patients with normal kidney function is 2 g every 8 h (3-h infusion) for 5–14 days [67, 68]. As cefiderocol is predominantly excreted by the kidneys (Sect. 3), dosage adjustment is recommended for patients with impaired or augmented kidney function and in those with kidney failure or who require dialysis [67, 68]. Consult local prescribing information for detailed information, including dosage and administration details, specific dosage adjustments for kidney function, contraindications, potential drug interactions, use in special patient populations, and warnings and precautions.

7 Place of Cefiderocol in Managing Serious Gram-Negative Bacterial Infections

β-Lactams are the mainstay of treatment for Gram-negative bacterial infections; against β-lactam-resistant pathogens, conventional options are colistin, fosfomycin and tigecycline, all of which have efficacy and/or toxicity limitations [10]. Cefiderocol is the first siderophore cephalexosporin against Gram-negative bacteria to be approved in the USA [67] and the EU [68]. The approved indications vary between the USA and the EU (Sect. 6). Other approved new agents for cUTI, HAP or VAP include ceftriaxone–avibactam, ceftazidime–tazobactam, ceftazidime–cilastatin–relebactam, meropenem–voorbactam and plazomicin. In the USA, cefiderocol, ceftazidime–tazobactam, ceftazidime–avibactam and imipenem/cilastatin–relebactam are approved for cUTI as well as for HAP and VAP in adults; ceftazidime–avibactam is also approved for cUTI in children.

Cefiderocol has a unique mechanism of bacterial cell entry and a wide spectra of Gram-negative antibacterial activity (Sect. 2); of the available new agents, only cefiderocol is stable against all classes of β-lactamases, including metallo-β-lactamases [8, 9]. A differentiating feature of cefiderocol is its activity against MDR P. aeruginosa, MDR A. baumannii, S. maltophilia and B. cepacia [12].

The choice of antibacterial for cUTI depends on a number of factors, including disease severity and local resistance patterns [78]. The initial empirical therapy should be followed by definitive antibacterial therapy based on the uropathogen identified [78]. Cefiderocol is approved for cUTI (including pyelonephritis) caused by E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa and E. cloacae complex [67]. The approval was based on results from the APEKS-cUTI trial in which cefiderocol was noninferior to imipenem/cilastatin for the treatment of cUTI (Sect. 4.1). Furthermore, a network meta-analysis (5 studies, 2349 patients), subject to its limitations such as inclusion of studies with different designs, found that cefiderocol was superior to imipenem/cilastatin for microbiological eradication and was similar to ceftazidime–avibactam, ceftozolane–tazobactam, doripenem and levofloxacin for clinical or microbiological outcomes [79].

According to IDSA, cefiderocol is one of the preferred treatment options for cUTI and pyelonephritis caused by CR Enterobacteriales (resistant to both ertapenem and meropenem) or by difficult-to-treat resistant P. aeruginosa [80]. Cefiderocol also has a place in the management of infections outside of the urinary tract caused by CR Enterobacteriales [preferred option against NDM and other metallo-β-lactamase-producing strains, and an alternative option when carbapenemase (including KPC) testing results are either not available or negative]. The increased mortality seen with cefiderocol versus BAT in CREDIBLE-CR does not appear to extend to patients with UTIs [80].

The choice of empiric antibacterial therapy for HAP and VAP is guided by the risk for MDR pathogens and mortality, and in high-risk patients by the presence or absence of septic shock [81, 82]. The choice of agent(s) for definitive therapy is based on antimicrobial susceptibility testing results and patient-specific factors (e.g. allergy, comorbidities) [81, 82]. Cefiderocol is approved for HAP and VAP caused by A. baumannii complex, E. coli, E. cloacae

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complex, *K. pneumoniae*, *P. aeruginosa* and *S. marcescens* [67]. In the registrational APEKS-NP trial, cefiderocol was noninferior to meropenem for 14-day all-cause mortality in critically ill patients with nosocomial pneumonia caused by Gram-negative bacteria, including those at high risk of MDR pathogens (Sect. 4.2). Of note, APEKS-NP is the first study to include extended infusion of high-dose meropenem (2 g every 8 h) as a comparator. The definitive therapy options recommended by the current 2016 IDSA and the American Thoracic Society guidelines include carbapenem, ampicillin/sulbactam and polymyxins against *Acinetobacter* spp. and polymyxins against CR pathogens [82]. The approval of cefiderocol is too recent for the drug to have been included in these guidelines.

Carbapenem resistance is a good indicator of multidrug resistance and is associated with limited treatment options [83]. In the pathogen-focused CREDIBLE-CR trial, cefiderocol had similar clinical and microbiological outcomes to BAT (up to three drugs) in a heterogeneous patient population with CR infections (Sect. 4.4). The increased mortality in the cefiderocol arm in this trial remains unexplained. While CREDIBLE-CR represents a real-world setting, it was a small open-label study and included only a few patients with complicated intra-abdominal infections [76]. Based on the CREDIBLE-CR data, cefiderocol was approved in the EU for the treatment of Gram-negative infections in adults who have limited treatment options [68]. The only other drug approved for this indication is imipenem/cilastatin–relebactam, which has no in vitro activity against class B (e.g. NDM, VIM) and D (e.g. OXA-48) carbapenemases [84]. According to NICE, cefiderocol may be an option for treating Gram-negative infections in adults who have limited treatment options, particularly when other antimicrobials have failed [83].

Cefiderocol was well tolerated in patients with cUTI and had an acceptable tolerability profile in critically ill patients with HAP, VAP or life-threatening CR infections (Sect. 5). The AE and safety profile of cefiderocol was broadly similar to those of other β-lactam agents. The increased mortality seen with cefiderocol in patients with CR infections was not due to cefiderocol-related toxicity.

Limited real-world data suggest that cefiderocol mono-therapy or in combination with other antibacterials may be useful as rescue treatment for severe, CR or extensively-resistant, Gram-negative infections in critically ill or immunocompromised patients [85, 86]. According to a systematic review (24 case series/reports; 60 patients), cefiderocol was effective and well tolerated in managing difficult-to-treat CR infections in the real-world setting (clinical cure rate 80%, microbiological eradication rate 41.7%, all-cause mortality 20%, AE incidence 13.3%) [87].

In conclusion, cefiderocol is a siderophore cephalosporin with activity against CR and MDR Gram-negative bacteria; it is stable against all four Ambler classes of β-lactamases. The drug was effective and had a good tolerability and safety profile in patients with cUTI, HAP, VAP or CR serious infections due to aerobic Gram-negative bacteria. Further data on real-world experience, resistance development and cost-effectiveness of cefiderocol would be of interest. More data are also required to clarify the increased mortality seen with cefiderocol in CREDIBLE-CR. Current evidence indicates that cefiderocol is a novel, emerging, definitive therapy option that is a useful addition to the current treatment options for adults with susceptible Gram-negative bacterial infections (including cUTI, HAP or VAP) for whom there are limited treatment options.

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