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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (KC CLAEYS AND J SMITH, SECTION EDITORS)

Clinical Appraisal of Cefiderocol in the Treatment of Non-fermenting Gram-Negative Bacilli

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Abstract

Purpose of Review Cefiderocol has a potential role in the treatment of infections caused by increasingly resistant non-fermenting Gram-negative organisms.

Recent Findings Non-fermenting Gram-negative organisms pose a unique threat to public health given their arsenal of inherent resistance mechanisms. High rates of intrinsic resistance to a wide array of agents, inducible adaptive resistance, and the ability to acquire resistance through horizontal transfer of resistance genes limit the utility of conventional antimicrobial treatment options against non-fermenting Gram-negative infections. Beta-lactams, one of the most reliable classes of antimicrobials, are often rendered inactive by the acquisition of beta-lactamases, with activity potentially restored by beta-lactamase inhibitors. Alteration of intrinsic mechanisms of resistance, porin channels, and efflux pumps reduce the ability of beta-lactamase inhibitors to protect the activity of beta-lactams. This multifactorial nature of resistance exhibited by non-fermenting Gram-negative organisms is difficult to overcome and novel agents are needed to combat this growing threat.

Summary Cefiderocol is a novel siderophore cephalosporin that utilizes the active transport of ferric iron to gain access to the periplasmic space of Gram-negative organisms. Cefiderocol also has additional modifications that confer some stability in the presence of beta-lactamases, which can be particularly beneficial for infections caused by non-fermenters. Herein, we discuss the potential role of cefiderocol therapy in the management of infections caused by non-fermenting Gram-negative bacilli, with an intentional focus on carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Pseudomonas aeruginosa*, and *Stenotrophomonas* spp.

Keywords Cefiderocol · Bacilli · Gram-negative organism

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Introduction

The rising prevalence of antimicrobial resistance presents a significant challenge to public health. According to the CDC, in 2019 alone, 2.8 million cases of antimicrobial-resistant infections occurred in the USA, resulting in an estimated 35,000 annual deaths [1]. Non-fermenting Gram-negative organisms, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia* spp., pose a serious threat and are notable for their ability to acquire multiple mechanisms of resistance, including enzymatic resistance mechanisms like beta-lactamases [2, 3]. While the addition of beta-lactamase inhibitors can be effective against many bacteria that develop resistance due to beta-lactamases alone, non-fermenting Gram-negative organisms are also known for their ability to exhibit resistance through regulation of porin channels and efflux pumps [2].

Currently, no pharmacologic agents are available to restore reduced susceptibility conferred by these mechanisms. While optimizing pharmacokinetic and pharmacodynamics parameters may overcome permeability- or efflux-mediated resistance in some situations, the acquisition of multiple resistance mechanisms can lead to higher levels of resistance that are unlikely to respond to dose optimization alone. In cases where multiple resistance mechanisms are present, treatment with an antimicrobial agent with a novel mechanism of action may be beneficial.

Cefiderocol (CFDC) is a siderophore cephalosporin that gains access to the periplasmic space of Gram-negative organisms by active transport of ferric iron [4]. In addition to its siderophore mechanism, CFDC also has additional modifications that allow it to resist hydrolysis by various beta-lactamases, including those commonly found in Gram-negative non-fermenting organisms (OXA-23, OXA-24, and OXA-48) [5]. Due to its purported stability in the presence of beta-lactamases and its unique mechanism of entry into the periplasmic space, CFDC is uniquely suited to overcome the multifactorial resistance often displayed by non-fermenting Gram-negative organisms.

This review article will provide an overview of the pharmacology, in vitro activity, and clinical studies of CFDC with a focus on its role for the treatment of Gram-negative non-fermenting organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Burkholderia* spp.

Literature Search

A PubMed search was performed using key terms "S-649266" and "cefiderocol" to identify relevant articles published between January 1, 2013, and September 30, 2022. The search strategy included in vitro studies, clinical trials, observational studies, case studies and case series, review articles, and systematic reviews. The search was limited to articles available in the English language.

Chemistry

Notably, CFDC has a pharmacophore that is structurally similar to ceftazidime and cefepime. Cefiderocol shares a common C-7 (shown in Fig. 1) carboxypropanoxyimino side chain with ceftazidime, which enhances its penetration across the outer membrane of Gram-negative pathogens, but decreases its activity against Gram-positive pathogens [6, 7]. Similar to cefepime, CFDC also contains C-3 side chain modifications to include a positively charged pyrrolidinium moiety, providing additional stability in the presence of beta-lactamases (shown in Fig. 1) [6, 7]. This pyrrolidinium moiety is further modified to include a conjugated catechol moiety, which provides the defining siderophore mechanism of CFDC [6, 7]. The catechol addition to the C-3 side chain allows CFDC to chelate soluble ferric iron, providing the ability to undergo active transport across the outer membrane of Gram-negative organisms via siderophore receptors [4]. The combination of modifications, which provide enhanced stability against beta-lactamases, increased passive transport across the outer membrane, and allow for active transport across the outer membrane, contributes to the potential of CFDC as a treatment option for non-fermenting Gram-negative organisms in our antibiotic armamentarium.

Cefiderocol Microbiological Activity Against Non-fermenting Gram-Negative Organisms

Overall, CFDC has demonstrated high affinity for the penicillin-binding protein 3 (PBP3) of many non-fermenting Gram-negative organisms. Cefiderocol has also been shown to retain activity

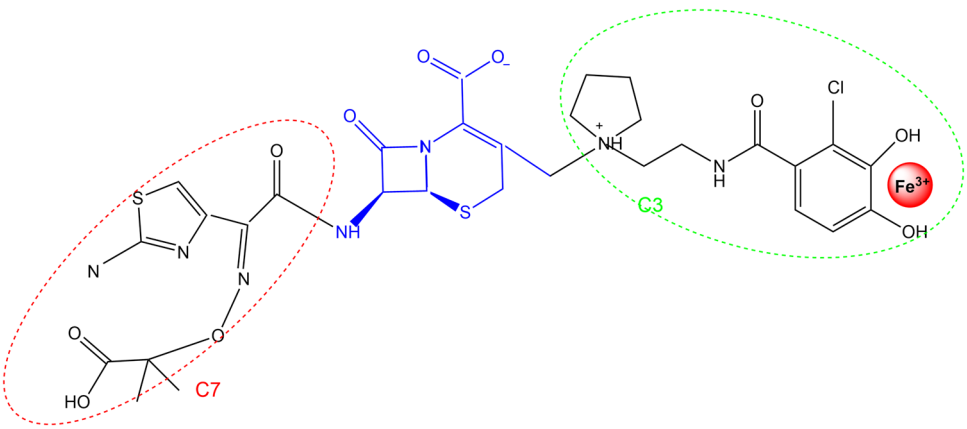

Fig. 1 Cefiderocol pharmacophore. Structure of cefiderocol, central cephalosporin nucleus with a C-7 carboxypropanoxyimino side chain and C-3 side chain containing a positively charged pyrrolidinium moiety. Also shown at C-3 is the conjugated catechol moiety and chelated ferric iron

in the presence of both serine- and zinc-based carbapenemase enzymes. A 2016 study examined the kinetics of various beta-lactamases against CFDC [5]. The results showed that among metallo-beta-lactamases, IMP-1, VIM-2, and L1, CFDC was hydrolyzed at a rate 260-fold lower than that of meropenem [5]. The study was unable to calculate the specificity for NDM-1, but the relative velocity of CFDC hydrolysis was 3–10 times lower than other agents [5]. Additionally, the kinetic parameters for KPC-3 and OXA-23 suggest that CFDC is relatively stable compared to meropenem, providing additional stability against organisms like OXA-producing *Acinetobacter baumannii* [5]. The following sections provide in-depth details regarding the activity of CFDC against various non-fermenting Gram-negative organisms.

Pseudomonas aeruginosa

Of note, CFDC demonstrates in vitro activity against *Pseudomonas aeruginosa* with MIC_{90} typically ranging from 0.5 to 1 µg/mL, meeting the FDA-established breakpoint of 1 µg/mL and falling below the CLSI M100-established breakpoint of 4 µg/mL [8–11]. There was no significant difference in affinity between CFDC and ceftazidime for PBP3 of *Pseudomonas aeruginosa* (0.06 µg/mL vs. 0.09 µg/mL) [12]. CFDC also has increased affinity for PBP 1a of *Pseudomonas aeruginosa* compared to ceftazidime (0.85 µg/mL vs. 3.62 µg/mL), but not against other organisms tested [12]. In a 2016 study, which included 103 *P. aeruginosa* isolates, CFDC MIC values ranged from ≤ 0.063 to 4 µg/mL and MIC_{90} was low at 1 µg/mL [10]. The subset of beta-lactamase-producing *P. aeruginosa* isolates ($n = 33$) included were found to have MIC values ranging from 0.03 to 8 µg/mL and MIC_{90} was 4 µg/mL [10]. Subsequently, a 2018 study of CFDC activity against carbapenem-nonsusceptible and multidrug-resistant pathogens included 262 *P. aeruginosa* isolates and found that CFDC retained activity against most with MIC values ranging from ≤ 0.002 to 32 µg/mL and MIC_{90} was 1 µg/mL despite the high prevalence of resistance to meropenem (92%) and ceftazidime-avibactam (63.7%) [9]. Similarly, a 2020 study of CFDC activity against multidrug-resistant isolates collected in the UK from 2008 to 2018, which included 111 carbapenemase-producing *P. aeruginosa* isolates, found that 86.5% of *P. aeruginosa* isolates remained susceptible to CFDC based on CLSI breakpoints [13]. Results from the five multinational SIDERO-WT surveillance studies included 7700 *P. aeruginosa* isolates, with CFDC MIC values ranging from ≤ 0.002 to 8 µg/mL and the MIC_{90} was 0.5 µg/mL, even among meropenem and ceftazidime-avibactam-nonsusceptible isolates [14] [14]. Overall, these studies indicate substantial in vitro activity of CFDC against *P. aeruginosa* isolates.

Acinetobacter baumannii

Additionally, CFDC demonstrates strong in vitro activity against *Acinetobacter baumannii*, including carbapenem-resistant strains, with most isolates retaining susceptibility based upon the CLSI-established breakpoint of 4 µg/mL [11]. A study comparing the affinity of CFDC and ceftazidime for PBP3, determined by 50% inhibitory concentrations, found that CFDC is more potent against *Acinetobacter baumannii* (0.67 µg/mL vs. 1.78 µg/mL) than ceftazidime [12]. The aforementioned 2016 in vitro study also included a 203 *A. baumannii* isolates; 99 isolates were collected from 2000 to 2009 and 104 isolates were randomly collected from 2009 to 2011. Overall, CFDC MIC values ranged from ≤ 0.063 to 4 µg/mL with MIC_{90} of 2 µg/mL [10]. Among the 29 beta-lactamase-producing *A. baumannii* isolates studied, MIC values ranged from 0.03 to > 32 µg/mL and MIC_{90} was 8 µg/mL [10]. Similarly, in vitro results reported in a 2017 study examining CFDC activity among clinical isolates collected between 2014 and 2015 from the USA and Europe included 309 *A. baumannii* isolates from 50 centers in the USA and 839 isolates from 49 centers in Europe [8]. Among these isolates, CFDC MIC values ranged from ≤ 0.002 to 8 µg/mL with a MIC_{90} of 1 µg/mL [8]. Cefiderocol retained activity among the 173 American and 595 European meropenem-nonsusceptible isolates with MIC_{90} remaining 1 µg/mL for both American and European isolates [8]. The activity of CFDC against carbapenem-nonsusceptible and multidrug-resistant pathogens was further corroborated in a 2018 in vitro study that included 368 *A. baumannii* isolates. Cefiderocol retained activity against most *A. baumannii* isolates in this study with MIC values ranging from 0.015 to > 256 µg/mL with MIC_{50} of 0.25 µg/mL and MIC_{90} of 8 µg/mL despite the high prevalence of resistance to meropenem (MIC_{50} 64µ/mL) [9]. A 2020 study also determined the potential activity of CFDC against carbapenemase enzymes, including NDM, OXA-23, OXA-51, OXA-58, and OXA-24/40. This study, which examined the activity of CFDC against multidrug-resistant isolates collected in the UK from 2008 to 2018, included 99 carbapenemase-producing *A. baumannii* isolates; 88.9% of *A. baumannii* isolates remained susceptible to CFDC according to CLSI-established breakpoint [13]. Data from in vitro susceptibility studies support the use of CFDC to treat *A. baumannii* infections; however, subsequent clinical data has warranted caution against its use as a first-line agent.

Stenotrophomonas maltophilia

Cefiderocol also demonstrates in vitro activity against *Stenotrophomonas maltophilia*, with most tested clinical isolates remaining susceptible according to the CLSI-established breakpoint of 1 µg/mL [11]. A 2016 study that included 108 *S. maltophilia* isolates, both randomly collected clinical

isolate from 2009 to 2011 and beta-lactam-resistant isolates collected from 2000 to 2009, found that CFDC MIC values ranged from ≤ 0.063 to 4 µg/mL with MIC_{90} of 0.5 µg/mL [10]. A 2017 study of clinical isolates collected between 2014 and 2015 from the USA and Europe found that among the 152 *S. maltophilia* isolates from the USA, CFDC MIC values ranged from ≤ 0.002 to 4 µg/mL with MIC_{90} of 0.5 µg/mL, and among 276 isolates in Europe, MIC values ranged from 0.004 to 2 µg/mL with MIC_{90} of 0.25 µg/mL [8]. In a 2018 study that included 217 *S. maltophilia* isolates, CFDC retained activity against most *S. maltophilia* isolates with MIC values ranging from 0.004 to 2 µg/mL with MIC_{50} of 0.06 µg/mL and MIC_{90} of 0.25 µg/mL despite the high prevalence of resistance to ceftazidime-avibactam (MIC_{50} 8 µg/mL, MIC_{90} 64 µg/mL) [9].

Other Non-fermenting Gram-Negative Bacteria

There is limited data that supports the use of CFDC against other non-fermenting Gram-negative organisms; nonetheless, several studies have shown promising results. A 2017 study was conducted examining CFDC activity among clinical isolates collected between 2014 and 2015 from the USA and Europe. This study included six *Burkholderia cepacia* isolates from 50 centers in the USA and six isolates from 49 centers in Europe [8]. The MIC values for *B. cepacia* isolates ranged from 0.008 to 16 µg/mL, with all but one isolate having a value of ≤ 1 µg/mL [8]. A 2018 study of CFDC activity against carbapenem-nonsusceptible and multidrug-resistant pathogens included four *B. cepacia* isolates, with MIC values of 0.004, 0.008, 0.015, and 8 µg/mL [9]. A 2021 study examined the activity of CFDC against *Burkholderia pseudomallei* clinical isolates from Queensland, Australia, and included 246 isolates. Among all isolates tested, MIC values ranged from ≤ 0.03 to 16 µg/mL with MIC_{90} of 0.125 µg/mL, and only four isolates had MIC values of > 1 µg/mL. These in vitro data may suggest the potential activity of CFDC against *Burkholderia* species and other non-fermenting Gram-negative organisms, but further studies are needed to confirm the widespread susceptibility of CFDC.

Resistance

While CFDC does retain in vitro activity against many non-fermenting isolates, resistance to CFDC has been observed. Studies have identified multiple mechanisms of resistance involved in CFDC resistance, including beta-lactamase activity, alterations in siderophore receptor genes, and PBP3 mutations. Cefiderocol may have increased stability in the presence of beta-lactamases, but the production of multiple enzymes may overwhelm this stability. Resistance to CFDC has been most thoroughly described in carbapenem-resistant *A. baumannii*. In a study of eight cefiderocol-resistant *Acinetobacter baumannii*, all resistant isolates harbored OXA-23 beta-lactamases. Also, all isolates also harbored PER-type beta-lactamases; however, the presence of these enzymes alone did not lead to resistance. This suggests that beta-lactamases may contribute to CFDC resistance, but a fully resistant phenotype may also require the presence of other mechanisms [15].

An additional study of 12 *Acinetobacter baumannii* isolates identified multiple possible mechanisms, not involving beta-lactamase activity, involved in CFDC resistance [16]. In this study, three isolates identified as international clone strain type ST2, and lacking the expression of siderophore receptor gene *pirA* also exhibited CFDC resistance [16]. In addition to *pirA*, these three isolates also lacked expression of *piuA*; however, another isolate lacked *piuA* (a siderophore receptor gene) expression but remained susceptible to CFDC [16]. Collectively, this data may indicate that *piuA* contributes to diminished CFDC susceptibility, but overt resistance likely involves additional factors [16]. Four isolates from other international clone strain types also had unsuccessful amplification of *pirA* and *piuA* products, suggesting that mutations in these genes play a role in reduced CFDC susceptibility [16]. Furthermore, one ST2 isolate exhibiting CFDC resistance also had PBP3 mutations that may have contributed to resistance [16]. Taken together, alterations in siderophore receptor genes *pirA* and *piuA* likely contribute to diminished CFDC susceptibility, but resistance is likely multifactorial.

In addition to frank resistance, treatment with CFDC may also be complicated by the presence of heteroresistance and the presence of resistant sub-populations within a larger population that appears in vitro susceptible to the antibiotic. A 2021 study examined CFDC resistance in carbapenem-resistant Gram-negative pathogens. Among non-fermenting organisms included, resistance was detected in 8% of 108 *Acinetobacter* spp., 0% of 69 *Pseudomonas* spp., and 0% of *Stenotrophomonas* spp. isolates [17•]. Despite relatively low rates of CFDC resistance, population analysis profiling identified CFDC heteroresistance in 59% of *Acinetobacter* spp., 9% of *Pseudomonas* spp., and 48% of *Stenotrophomonas* spp. isolates [17•]. These findings highlight potential challenges in using CFDC for the treatment of these organisms.

Pharmacokinetics and Pharmacodynamics of Cefiderocol Against Non-fermenting Gram-Negative Organisms

Pharmacokinetic parameters of CFDC have been studied in both healthy and infected populations, with population pharmacokinetic models being derived from patients with varying degrees of renal function. In a phase I study, 40

healthy adults received a single dose ranging from 100 to 2000 mg of CFDC over 60 min, and 30 healthy adults received multiple doses of 1000 mg or 2000 mg of CFDC every 8 h as a 60-min infusion for 10 days [18]. The results of this study found that maximal concentration and area under the concentration–time curve increased proportionally with increasing doses of CFDC. The plasma half-life of CFDC ranged from 1.98 to 2.74 h and minimal accumulation was observed in multiple dosing concentration or area under the curve, with similar pharmacokinetics between single and multiple dosing. The pharmacokinetics of CFDC was found to be linear pharmacokinetics at doses of 2000 mg or less [18]. Cefiderocol was primarily excreted in the urine as an unchanged drug (60–70%) with 10% excretion in the urine as metabolites [18]. An additional pharmacokinetic study examining radioactivity equivalent of ^{14}C-cefiderocol in six healthy adults determined that 98.7% of CFDC was excreted in the urine, primarily as an unchanged drug (90.6%), up to 120 h after administration [19].

The effects of renal impairment on the pharmacokinetics of CFDC were evaluated in a phase I study involving in 30 patients with varying degrees of renal dysfunction and 8 matched patients with normal renal function. Mild renal dysfunction had a minimal effect on the pharmacokinetics of CFDC; however, moderate and severe renal dysfunction increased the half-life and area under the curve 1.5-fold and two-fold respectively [20]. Hemodialysis was found to effectively clear CFDC with 60% removal by a 3- to 4-h hemodialysis session [20].

Cefiderocol distributes into tissues well and has been shown to distribute into the epithelial lining fluid of healthy adults with concentrations parallel to plasma concentrations [21]. When administered as a 2000-mg dose over 60 min, CFDC pulmonary epithelial lining fluid concentrations fell below the upper limit of CLSI-established breakpoints of 4 µg/mL at 4 h (2.78 µg/mL) and 6 h (1.38 µg/mL) after administration [21]. In a rat model, CFDC penetrated into the cerebrospinal fluid (CSF) at comparable CSF:plasma ratios to other beta-lactams, and penetration was enhanced threefold by meningeal inflammation [22]. The currently approved dosing regimen is 2000 mg every 8 h as a prolonged 3-h infusion, which should help optimize the pharmacodynamic and pharmacokinetic profile of CFDC, particularly when utilized against highly resistant non-fermenting Gram-negative organisms.

Given the critical state of many patients with highly resistant Gram-negative infections, which is often the case when infected with non-fermenters, the probability of target attainment at relevant minimal inhibitory concentrations comparing 1-h and 3-h infusions was determined using existing data from phase I studies. For patients with normal renal function, the probability of target attainment for free concentration above the MIC for 75% of the dosing interval was > 90% for MIC values of ≤ 4 µg/mL following a dose of 2000 mg every 8 h, given over a 3-h infusion [23]. In patients with augmented renal function defined as creatinine clearance > 120 mL/min, the dosing interval would need to be increased to every 6 h [23]. Targeting longer time of the dosing interval at which CFDC concentrations exceed the pathogen MIC is especially important for non-fermenting Gram-negative organisms, as some organisms require increased exposure for adequate antimicrobial activity as shown in a study of CFDC pharmacodynamic profile in murine thigh and lung models. Cefiderocol concentrations exceeding the MIC of *P. aeruginosa* for 63.0% and 72.2% of the dosing interval were required for bacteriostatic and bactericidal activity, respectively, in a murine thigh model [24]. For bactericidal activity against *A. baumannii*, CFDC concentrations exceeding the MIC for 88.1% of the dosing interval were required in a murine lung model [24]. Furthermore, carbapenem-resistant organisms required greater exposure than carbapenem-susceptible organisms for adequate antimicrobial activity [24].

Cefiderocol Clinical Trials and the Inclusion of Non-fermenting Organisms

Cefiderocol was studied in three clinical trials, summarized in Table 1, prior to receiving FDA approval for the treatment of complicated urinary tract infections or pyelonephritis and hospital- or ventilator-acquired pneumonia. The following sections will focus on reviewing the clinical evidence for CFDC in the management of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia.*

Clinical Activity of CFDC Against Non-fermenting Gram-Negative Organisms

Pseudomonas aeruginosa

In addition to its in vitro activity, clinical studies have reported promising results with CFDC in the management of difficult-to-treat *P. aeruginosa* infections. *P. aeruginosa* was the only non-fermenting organism represented in each of the three major clinical trials evaluating CFDC. In the APEKS-cUTI, less than 10% of included study patients had *P. aeruginosa* isolated. Cefiderocol-treated patients achieved microbiological eradication in 44.4% and clinical cure in 73.3% of patients with genitourinary tract infections caused by *P. aeruginosa* compared to microbiological eradication in 60.0% and clinical cure in 75.0% of patients receiving imipenem [25]. The APEKS-NP trial included *P. aeruginosa* infections, representing approximately 16.4% of all collected isolates. Clinical cure was similar between both groups,

Table 1 A summary of cefiderocol studied in three clinical trials

Study	Aim(s)	Microbiology	Results	Conclusion
APEKS-cUTI [25] (NCT02321800)	Compared the efficacy of cefiderocol to imipenem-cilastatin for genitourinary infections Primary outcome: composite of clinical and microbiological response	• A total of 371 Gram-negative pathogens isolated • 23 *Pseudomonas aeruginosa* • 1 *Acinetobacter calcoaceticus-baumannii* complex	Cefiderocol was non-inferior to imipenem-cilastatin with similar clinical response (90% vs 87%) and increased microbiological eradication (73% vs 56%) at test of cure	Supports the use of cefiderocol for genitourinary infections; few patients with non-fermenting pathogens were included
APEKS-NP [26] (NCT03032380)	Efficacy of cefiderocol compared to high-dose, extended-infusion meropenem for nosocomial pneumonia Primary outcome: all-cause mortality	• A total of 251 Gram-negative pathogens identified • 48 *Pseudomonas aeruginosa* • 47 *Acinetobacter baumannii* isolates were included	All-cause mortality was similar for cefiderocol and meropenem at 14 days (12.4% vs 11.6%); however, there was a numeric increase in 14-day all-cause mortality for patients with HCAP who received cefiderocol (15% vs 4%)	Supports the use of cefiderocol for nosocomial pneumonia caused by carbapenem-susceptible organism
CREDIBLE-CR [27•] (NCT02714595)	Role of cefiderocol compared to best available therapy (BAT) in the treatment of genitourinary infections, nosocomial pneumonia, or bloodstream infections caused by carbapenem-resistant organisms Primary outcome: clinical cure (pneumonia, bloodstream infection or sepsis) or microbiological eradication (UTI)	• A total of 118 Gram-negative pathogen identified • 54 *Acinetobacter baumannii* • 22 *Pseudomonas aeruginosa* • 5 *Stenotrophomonas maltophilia* • 2 *Acinetobacter nosocomialis*	Compared to BAT at test of cure, cefiderocol had similar rates of clinical cure (53% vs 50%) and microbiological eradication (31% vs 24%), although cefiderocol was associated with increased all-cause mortality for patients with nosocomial pneumonia and bloodstream infections	The cause of excess mortality in the cefiderocol arm is not entirely clear; however, there were some between-group differences and a lower utilization of combination therapy in the cefiderocol arm

reported in 67% of patients treated with CFDC and 71% of patients treated with meropenem [26]. All-cause mortality was numerically lower for patients treated with CFDC at 8% compared to 26% of patients treated with meropenem. *P. aeruginosa* was similarly represented in the CREDIBLE-CR trial, accounting for 18.6% of all isolates. The rate of overall all-cause mortality was higher among patients who received CFDC at 35% of patients compared to 17% of patients who received comparator. However, for patients with *P. aeruginosa* as the only pathogen isolated, mortality was 18% for both CFDC and comparator [27•]. Outside of clinical trials, CFDC use has also been reported in a small number of case reports and case series with success (see Table 2). Caution should be taken when applying these results as they represent subgroups with small numbers; however taken together, CFDC appears to be an appropriate option for the treatment of infections caused by *P. aeruginosa* with limited treatment options when susceptibility to CFDC is retained. Recent guidance from the Infectious Diseases Society of America (IDSA) recommends the use of CFDC for infections caused by difficult-to-treat *P. aeruginosa* cystitis or pyelonephritis, and as an alternative treatment for extra-urinary pseudomonal infections [28].

Acinetobacter baumannii

A. baumannii was not isolated in an adequate number of cases in the APEKS-cUTI trial to draw meaningful conclusions; however, data is available regarding clinical outcomes from the APEKS-NP and CREDIBLE-CR trials. *A. baumannii* was isolated from 16.1% of patients in the APEKS-NP trial, a similar proportion to *P. aeruginosa*. Clinical cure was similar between the two groups, achieved in 52% of patients receiving CFDC and 58% of patients receiving meropenem [26]. All-cause mortality was also similar, with 39% mortality among patients receiving CFDC and 33% mortality among patients receiving meropenem [26]. While *A. baumannii* represented a smaller proportion of pathogens in the APEKS-NP trial, it was the most predominant pathogen in the CREDIBLE-CR trial, isolated from 45.7% of patients. In the CREDIBLE-CR trial, all-cause mortality was strikingly different between the 42 patients who received CFDC and 17 patients who received comparator for *Acinetobacter* species, with CFDC associated with 50% mortality and comparator with 18% mortality [27•]. While the exact cause of increased mortality in the CFDC group is unclear, more patients were in the intensive care unit at randomization (56% vs 43%) or in septic shock (19% vs 12%) and combination therapy was used less frequently in the CFDC arm (18% vs 71%) [27•].

A recent observational, retrospective cohort study compared the outcomes of 141 patients who received CFDC-based or colistin-based regimens for the treatment of carbapenem-resistant *A. baumannii* (CRAB) infections. Cefiderocol was used in the treatment of 47 patients, including 32 patients who received combination therapy, and colistin was used in the treatment of 77 patients, 64 of whom received combination therapy [29•]. Cefiderocol was most commonly used in combination with tigecycline (21 patients) or fosfomycin (8 patients), while meropenem-vaborbactam, ampicillin-sulbactam, and ertapenem combinations were each employed for a single patient. The population in this study was critically ill at baseline with 89% of patients in the intensive care unit and 56% of patients mechanically ventilated. The most common infections were bloodstream infection (62%) or ventilator-associated pneumonia (28%) [29•]. In contrast to the CREDIBLE-CR trial, CFDC-based therapy was associated with decreased 30-day mortality (34% vs 55.8%), with the largest difference among bloodstream infections (25.9% vs 57.5%) and no significant difference for ventilator-associated pneumonia (58.3% vs 56.5%) [29•]. Of note, monotherapy with either CFDC or colistin was associated with increased microbiological failure (42.9% vs 6.3%, respectively), and CFDC monotherapy was associated with increased mortality (40% vs 6.3%) [29•]. The evaluation of CFDC used largely as combination therapy while compared to monotherapy could explain the difference in mortality seen in the CREDIBLE-CR trial; however, further investigation is needed. Cefiderocol use has also been reported in case reports and case series with some reported success (see Table 2). Based on clinical data, CFDC may be appropriate, as a monotherapy, for the treatment of CRAB when options are limited due to resistance or intolerance; however, it is likely best used as part of a combination regimen. IDSA guidance recommends CFDC as combination therapy for only refractory infections or situations in which tolerance limits the use of other agents [30].

Stenotrophomonas maltophilia

Clinical data regarding the use of CFDC for *S. maltophilia* are sparse. No *S. maltophilia* isolates were reported in APEKS-cUTI and only four isolates from APEKS-NP with no specific outcomes data available. In the CREDIBLE-CR trial, five *S. maltophilia* isolates were isolated, all of which were treated with CFDC. While no comparison can be made to alternative treatment, four of five patients with *S. maltophilia* died during the trial, including two of three patients with *S. maltophilia* but without *A. baumannii* [27•]. Two case reports of *S. maltophilia* treatment with CFDC have been identified. In the first case from a case series of 10 patients, a 79-year-old female was successfully treated for ventilator-associated pneumonia with both *S. maltophilia* and NDM-producing *Klebsiella pneumoniae* after failing initial treatment with ceftazidime-avibactam, aztreonam, and fosfomycin, although specific CFDC duration and concomitant agents are not available [31]. In the second case, a

Table 2 Case studies and case series of cefiderocol use for non-fermenting Gram-negative infections [34, 36–48]

Source	Sex	Indication	Organisms isolated	Prior antibiotics	Cefiderocol duration	Concomitant agents	Clinical success	Patient survival	Other comments
Alamarat et al. [46]	Male	Chronic osteomyelitis	**Extensively drug-resistant *Pseudomonas aeruginosa*** ESBL *Klebsiella pneumoniae*	Vancomycin Cefepime Metronidazole Aztreonam Polymyxin B Tigecycline	14 weeks	Aztreonam	Yes	Yes	Pediatric patient Aztreonam overlap 14 days Required bone graft, antibiotic nail exchange, and antibiotic cement nail placement
Bavaro et al. [44]	Male	Bloodstream infection	**CRAB**	Colistin Tigecycline Fosfomycin	5 days	Fosfomycin Tigecycline	Yes	No	Patients with central venous catheter-associated bacteremia and catheter removal
	Female	Bloodstream infection	**CRAB**	Meropenem Colistin	13 days	Colistin Meropenem	Yes	Yes	
	Male	Bloodstream infection	**CRAB**	Meropenem Colistin	10 days	Colistin	Yes	Yes	
	Male	Bloodstream infection	**CRAB**	Meropenem Colistin Tigecycline	8 days	Tigecycline	Yes	Yes	
	Female	Bloodstream infection	**CRAB**	Meropenem Colistin Fosfomycin	5 days	Fosfomycin	Yes	Yes	
	Male	Ventilator-associated pneumonia	**CRAB**	Colistin Fosfomycin Tigecycline	9 days	Fosfomycin Tigecycline	yes	Yes	
	Male	Bloodstream infection	**CRAB**	Meropenem Colistin Fosfomycin Ampicillin/sulbactam	8 days	Colistin Fosfomycin	Yes	Yes	
	Male	Neurosurgical wound infection	**Extensively drug-resistant *Pseudomonas aeruginosa***	Colistin Fosfomycin	10 days	Fosfomycin	Yes	Yes	
	Male	Perihepatic abscess	**CRAB** Multidrug-resistant *Enterobacter cloacae* *Morganella morganii* *Enterococcus faecium*	Meropenem Tigecycline Daptomycin Fosfomycin	21 days	Tigecycline Daptomycin Fosfomycin	Yes	yes	

Table 2 (continued)

Source	Sex	Indication	Organisms isolated	Prior antibiotics	Cefiderocol duration	Concomitant agents	Clinical success	Patient survival	Other comments
	Male	Ventilator-associated pneumonia Bloodstream infection	**CRAB**	Colistin Meropenem Daptomycin Tigecycline	12 days	Tigecycline Colistin Fosfomycin	Yes	No	Immunocompromised patients
	Male	Bloodstream infection	**CRAB**	Meropenem Colistin	3 days	Colistin	Yes	No	
	Male	Pneumonia	**Extensively drug-resistant *Pseudomonas aeruginosa***	Colistin Meropenem Fosfomycin	10 days	Fosfomycin	Yes	Yes	
Bleibtreu et al. [34]	Not reported	Respiratory tract infection	**VIM-4 *Pseudomonas aeruginosa***	Not reported	Not reported	None reported	Yes	Yes	
	Not reported	Vascular infection	**OXA-23 *Acinetobacter baumannii***	Not reported	Not reported	None reported	Yes	Yes	
	Not reported	Respiratory tract infection Intra-abdominal infection	**OXA-23 *Acinetobacter baumannii***	Not reported	Not reported	Colistin Tigecycline	Yes	Yes	
	Not reported	Respiratory tract infection	***Pseudomonas aeruginosa***	Not reported	Not reported	None reported	Yes	Yes	
	Not reported	Respiratory tract infection	**VIM-2 *Pseudomonas aeruginosa***	Not reported	Not reported	None reported	Yes	Yes	
	Not reported	Respiratory tract infection	OXA-48 *Klebsiella pneumoniae* **NDM-1 *Pseudomonas aeruginosa***	Not reported	Not reported	Colistin	No	Yes	
	Not reported	Respiratory tract infection Intra-abdominal infection	**VIM-2 *Pseudomonas aeruginosa***	Not reported	Not reported	Colistin	No	No	Cefiderocol MIC = 8
	Not reported	Respiratory tract infection	**OXA-836 *Pseudomonas aeruginosa***	Not reported	Not reported	Colistin Doxycycline	No	No	Cefiderocol MIC = 16

Table 2 (continued)

Source	Sex	Indication	Organisms isolated	Prior antibiotics	Cefiderocol duration	Concomitant agents	Clinical success	Patient survival	Other comments
	Not reported	Respiratory tract infection Urinary tract infection	***Pseudomonas aeruginosa***	Not reported	Not reported	Colistin	No	Yes	Cefiderocol MIC = 16
	Not reported	Bone/joint infection Skin/soft tissue infection	**VIM-2** ***Pseudomonas aeruginosa***	Not reported	Not reported	Colistin	No	Yes	Cefiderocol MIC > 32
	Not reported	Respiratory tract infection	***Pseudomonas aeruginosa***	Not reported	Not reported	Colistin	No	Yes	Cefiderocol MIC = 16
Bodro et al. [40]	Male	Left ventricular assist device infection	***Achromobacter xylosoxidans***	Piperacillin/tazobactam Tigecycline Colistin	14 days	Piperacillin/tazobactam Tigecycline	Yes	Yes	Piperacillin/tazobactam and tigecycline continued for 28 days after cefiderocol discontinuation
	Male	Bacteremia Portal shunt infection	**Extensively drug-resistant** ***Pseudomonas aeruginosa***	Meropenem Colistin	6 weeks	Colistin	Yes	Yes	
Borghesi et al. [48]	Male	Pleural empyema	**Extensively drug-resistant** ***Pseudomonas aeruginosa***	Ceftolozane-tazobactam	21 days	Colistin Fosfomycin	Yes	Yes	Chronic pleural empyema with increasing resistance
Cipko et al. [42]	Female	Retained spinal hardware infection	**OXA-23** ***Acinetobacter baumannii***	Vancomycin Ceftriaxone Flucloxacillin Piperacillin/tazobactam Colistin Tigecycline	24 days	None reported	Yes	Yes	Cefiderocol induced acute interstitial nephritis
Edgeworth et al. [38]	Female	Native aortic valve endocarditis	**Extensively drug-resistant** ***Pseudomonas aeruginosa***	Colistin Gentamicin Meropenem	23 days	Colistin Meropenem	Yes	Yes	Aortic valve replacement 2 days after cefiderocol initiation Neutropenia likely due to cefiderocol or colistin
Grande Perez et al. [41]	Male	Pancreatic fluid collection	**Extensively drug-resistant** ***Pseudomonas aeruginosa***	Meropenem Colistin	6 weeks	Metronidazole	Yes	Yes	Multiple cefiderocol-resistant organisms isolated after treatment

Table 2 (continued)

Source	Sex	Indication	Organisms isolated	Prior antibiotics	Cefiderocol duration	Concomitant agents	Clinical success	Patient survival	Other comments
König et al. [43]	Male	Community acquired pneumonia	**Multidrug-resistant *Pseudomonas aeruginosa***	Not reported	7 days	None reported	Yes	Yes	Patients received cefiderocol therapeutic drug monitoring guided-dose adjustments
	Female	Hospital acquired pneumonia	**ESBL *Pseudomonas aeruginosa*** **Multidrug-resistant *Pseudomonas aeruginosa***	Not reported	14 days	None reported	Yes	No	
	Male	Hospital acquired pneumonia Primary sepsis	**Multidrug-resistant *Acinetobacter baumannii***	Not reported	9 days	None reported	Yes	no	
	Male	Primary sepsis	**VIM *Pseudomonas aeruginosa***	Not reported	8 days	None reported	No	No	
	Male	Hospital acquired pneumonia	**CRAB**	Not reported	6 days	None reported	No	No	
Kufel et al. [37]	Female	Empyema	**Extensively drug-resistant *Pseudomonas aeruginosa***	Meropenem Vancomycin Micafungin Ceftazidime-avibactam Fluconazole Amikacin Polymyxin B	21 days	Fluconazole	Yes	Yes	Isolation of 2 cefiderocol-nonsusceptible *Pseudomonas* isolates after treatment
Rose et al. [47]	Male	Osteomyelitis	**CRAB *Pseudomonas aeruginosa*** *Proteus mirabilis* MRSA	Daptomycin Eravacycline Polymyxin Cefepime	6 weeks	Daptomycin	Yes	Yes	Subsequent isolation of *Candida albicans* from infection site
Stevens et al. [36]	Male	Intra-abdominal Infection	**Multidrug-resistant *Pseudomonas aeruginosa*** *Escherichia coli* *Bacteroides fragilis*	Ceftazidime-avibactam Polymyxin B Metronidazole	27 days	Metronidazole	Yes	Yes	Cefiderocol continued for 7 days following removal of drainage catheter

Table 2 (continued)

Source	Sex	Indication	Organisms isolated	Prior antibiotics	Cefiderocol duration	Concomitant agents	Clinical success	Patient survival	Other comments
Trecarichi et al. [45]	Male	Ventilator-associated pneumonia	**Extensively drug-resistant *Acinetobacter baumannii*** KPC *Klebsiella pneumoniae*	Piperacillin/tazobactam Clarithromycin Linezolid Meropenem Vancomycin Colistin Daptomycin Fosfomycin Tigecycline Ampicillin/sulbactam Ceftazidime-avibactam Rifampin	14 days	Linezolid	Yes	Yes	Patient on 35 days of various alternative therapies before cefiderocol
Zingg et al. [39]	Male	Acute osteomyelitis	**VIM *Pseudomonas aeruginosa* OXA-23 *Acinetobacter baumannii*** KPC *Enterobacter cloacae*	Not reported	14 days	Ceftazidime-avibactam Colistin	Yes	Yes	Cefiderocol started after removal of foreign implants
	Male	Implant-associated surgical site infection	**OXA-40, NDM *Acinetobacter baumannii***	Not reported	54 days	Ceftazidime-avibactam Colistin	Yes	Yes	Antimicrobials started after surgical revision Acute kidney injury due to colistin
	Male	Pleural empyema	**OXA-23, OXA-58 *Acinetobacter baumannii***	Not reported	42 days	Colistin	Yes	Yes	Acute kidney injury due to colistin

Non-fermenting Gram-negative organisms are bolded

58-year-old male was treated with CFDC and tigecycline for *S. maltophilia* pneumonia and ESBL-producing *Escherichia coli* bacteremia. During treatment, the patient was receiving continuous venovenous hemodiafiltration and patient-specific monitoring of CFDC levels confirmed adequate exposure for both isolates. Tigecycline was utilized for 10 days and CFDC for 14 days with clearance of blood cultures and clinical cure of infection; however, patient ultimately expired due to end-organ damage [32].

In an in vitro study of the activity of CFDC alone or in combination with other agents, CFDC was active against 9 of 9 *S. maltophilia* isolates studied [33]. Synergy was observed with levofloxacin (4 of 9 isolates), minocycline (6 of 9 isolates), polymyxin B (5 of 9 isolates), and trimethoprim/sulfamethoxazole (6 of 9 isolates) [33]. Given the lack of available clinical data regarding the use of CFDC for *S. maltophilia*, it should be reserved for clinical scenarios with no viable alternatives due to resistance, concomitant infections, or intolerance to other agents. IDSA guidance recommends CFDC as monotherapy for mild infections and as part of a combination regimen for moderate to severe infections caused by *S. maltophilia* [30].

Clinical Considerations for Cefiderocol Use in the Management of Non-fermenting Gram-Negative Infections

In the treatment of non-fermenting Gram-negative infections, various factors must be considered in clinical practice. After an infectious diagnosis is established, cultures and susceptibility results should be reviewed to identify available in vitro active agents. For extensively drug-resistant non-fermenting Gram-negative organisms, additional antimicrobial susceptibility testing may be required. Cefiderocol susceptibility testing can be performed by either the standard disk-diffusion method or Thermo Scientific Sensititre AST plates. Alternatively, cultures can be sent to a reference lab for susceptibility results. Obtaining MIC values quickly is crucial, as clinical outcomes are expectedly lower for isolates with MIC values greater than established breakpoints [34]. With that, if CFDC is used as initial therapy prior to the receipt of MIC values, then therapy should be escalated and/or de-escalated based on finalized isolate-specific cultures and sensitivities.

Irrespective of the retained widespread susceptibility of CFDC against MDR non-fermenting organisms, a lack of real-world clinical data relegates CFDC to be considered solely as a component in salvage therapy regimens. Monotherapy may be a viable option for resistant *Pseudomonas* isolates, as it has been used in clinical trials and has lower rates of reported heteroresistance (9%) [17]. In contrast, for infections caused by *A. baumannii*, combination therapy is likely to be the preferred option due to increased mortality associated with CFDC use in patients with infections caused by *Acinetobacter* spp., included in the CREDIBLE-CR trial. Nevertheless, the excess mortality in the CREDIBLE-CR trial may be related to its use as a monotherapy as outcomes with CFDC were favorable when used in combination with other agents compared to colistin-based combination regimens [29•]. Additionally, the higher rates of reported CFDC heteroresistance among surveillance isolates (59%) further attest to CFDC-based combination therapy being the most reliable option for *Acinetobacter* spp. infections [17•].

Notably, case reports of CFDC often describe its use in combination with other agents, most frequently with colistin. Nonetheless, the selection of agents for use in combination regimens with CFDC can be challenging; thus, preference should be given to agents with reported in vitro activity when possible. In vitro data suggest the potential for synergy when CFDC is combined with amikacin, ampicillin/sulbactam, or meropenem against *A. baumannii*, presenting attractive options for combination regimens with CFDC [35]. Cefiderocol combinations may also be a carbapenem-sparing option for some CRAB isolates, as the addition of beta-lactamase inhibitors in vitro has been shown to restore CFDC activity against otherwise resistant isolates [35].

Clinical data regarding CFDC for the treatment of infections caused by *Stenotrophomonas maltophilia* and other non-fermenting organisms are sparse; however, its use should be reserved when options are limited either due to resistance or concomitant infections. Heteroresistance in *S. maltophilia* has been reported in a study of surveillance isolates (48%) [17•] and mortality was high in the CREDIBLE-CR trial; however, only five isolates were reported in this trial and *Acinetobacter* spp. were also isolated as a pathogen in two patients [27•]. An in vitro study examined the potential for synergy against *S. maltophilia* for CFDC combined with levofloxacin, minocycline, polymyxin B, or trimethoprim-sulfamethoxazole. The most reliably synergistic combinations were found to be CFDC with trimethoprim-sulfamethoxazole or minocycline, with each agent exhibiting synergy in six of nine isolates tested [33], suggesting that CFDC may be useful as an add-on agent for patients failing to respond to initial therapy.

Conclusion

Antimicrobial resistance in non-fermenting Gram-negative organisms is a serious global health threat given the limited in vitro active agents readily available. Thus, novel agents are essential, and identifying their placement in our current antibiotic armamentarium is critical. The pharmacophore of CFDC and the substantial antimicrobial activity positions it as a viable option in the treatment of infections caused by

non-fermenting pathogens. Cefiderocol monotherapy may be an appropriate option as monotherapy for infections caused by *P. aeruginosa* or mild infections caused *S. maltophilia* when susceptibility has been confirmed. However, cefiderocol should be used as part of a combination regimen for infections caused by carbapenem-resistant *A. baumannii* or for moderate to severe infections caused by *S. maltophilia* whenever possible. Synergistic combinations that have been shown to be effective include CFDC in combination with meropenem or amikacin when treating *A. baumannii*, and CFDC in combination with minocycline or trimethoprim-sulfamethoxazole when treating *S. maltophilia*. Data regarding the use of CFDC for other non-fermenting Gram-negative organisms are scarce, and CFDC use should be reserved for situations with no alternative. Ultimately, CFDC is an important novel therapy and has an integral role in the management of infections caused by non-fermenting Gram-negative organisms.

Compliance with Ethical Standards

Conflict of Interest JAM has participated on advisory board for Shionogi and Entasis Therapeutics. All other authors have no conflicts to report.

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