Antimicrobial Stewardship News
Volume 8, Number 1
January 2020

Cefiderocol: A first-in-class siderophore cephalosporin designed to combat resistance

Introduction

Cefiderocol (Fetroja®) is a first-in-class siderophore cephalosporin that received FDA-approval for treatment of complicated urinary tract infections (cUTI) on November 14th, 2019.[1] In the era of increasing antimicrobial resistance among Gram-negative bacteria, cefiderocol may be useful for treating infections when few or no alternative treatment options exist. This newsletter reviews key points about cefiderocol including its unique mechanism of action, antimicrobial spectrum, clinical efficacy, safety, and potential niche in therapy.

Mechanism of Action

The chemical structure of cefiderocol consists of a cephalosporin antibiotic linked to a catechol moiety that can bind to a single iron atom in the extracellular space (Figure 1).[1-2] This "iron binding" feature is important because iron is an essential nutrient for bacterial survival, and bacteria are normally starved of iron during acute infections due to the host's immune response. As a result, bacteria trigger iron transport systems to increase intracellular iron by releasing "siderophores". Cefiderocol, which is bound to a single iron atom, is actively transported into the periplasmic space of the bacteria. Once inside the cell, cefiderocol acts as a beta-lactam by binding to penicillin-binding proteins and inhibiting cell wall synthesis (Figure 2).[1-3] In addition, cefiderocol is not removed by efflux pumps or degraded by beta-lactamases (including carbapenemases). Ultimately, these unique characteristics allow it to maintain activity against nearly all Gram-negative pathogens.

Figure 1. Chemical structure of cefiderocol

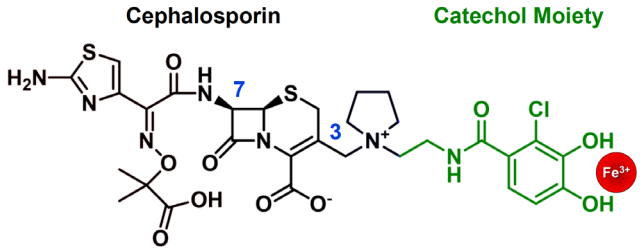
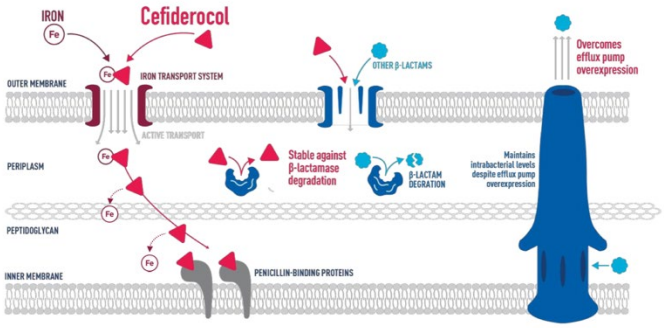


Figure 2: Cefiderocol mechanism of action[2]



Spectrum of Activity

Cefiderocol has excellent activity against most Gram-negatives, including Enterobacteriaceae, *Acinetobacter spp*., *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*.[3] It is also active against bacteria that produce enzymes that confer resistance to many other beta-lactam antibiotics, such as ESBLs, AmpC, carbapenemases (KPC), and metallo-beta-lactamases. Cefiderocol has limited activity against Gram-positive and anaerobic organisms.[2]

Summary of Clinical Trials

APEKS-cUTI Study: The safety and efficacy of cefiderocol in treating cUTI was evaluated in this phase II study that included 452 patients.[4] This study compared cefiderocol vs imipenem-cilastatin for 7 to 14 days. The primary endpoint was a composite of clinical and microbiologic outcomes at the test of cure (TOC) visit 7 days after

completion of therapy. Overall, cefiderocol was non-inferior to imipenem-cilastatin with 73% and 55% of patients achieving the composing primary endpoint at the TOC visit, respectively. Notably, most patients (> 70%) in this study did not have infections caused by multidrug-resistant organisms (MDROs). Overall, the study drug was well-tolerated with adverse events reported in 41% of patients receiving cefiderocol compared to 51% receiving imipenem-cilastatin. This study ultimately led to the approval of cefiderocol in cUTI, demonstrating that it can safely treat these infections.[4]

CREDIBLE-CR: This phase III study evaluated cefiderocol vs best available treatment (BAT) for a variety of types of infections caused by carbapenem-resistant Gram-negatives.[2] This study included 118 patients and demonstrated similar clinical cure rates (53% vs 50%) and microbiologic eradication (31% vs 24%) at the TOC visit when comparing cefiderocol to BAT. However, an important finding from this study was an increase in all-cause mortality in the cefiderocol group vs BAT group (34% vs 18%). A large portion of these cases included pneumonia and bloodstream infection/sepsis groups as opposed to the cUTI group.[2]

APEKS-NP: This phase III study evaluated the safety and efficacy of cefiderocol plus linezolid vs meropenem plus linezolid for patients with nosocomial pneumonia. The primary outcome was all-cause mortality 14 days after treatment initiation. This study found cefiderocol to be non-inferior to meropenem in the treatment of nosocomial pneumonia with an all-cause mortality of 12.4% vs. 11.6%, respectively.[2] This finding led to a safety warning for the drug.

Safety

Adverse effects associated with cefiderocol are similar to those of other cephalosporins.[1-2] The most common effects seen in the APEKS-cUTI trial are shown in Table 1.[4] Warnings associated with the drug include: seizure, hypersensitivity reactions, *Clostridioides difficile*-associated Diarrhea (CDAD), and a warning for increase in all-cause mortality in patients with infections caused by carbapenem-resistant Gram-negatives.[3]

The warning for increase in all-cause mortality in critically ill patients with carbapenem-resistant Gam-negative bacterial infections remains one of the greatest concerns surrounding the future use of cefiderocol. While this difference in mortality was not seen in the APEKS-cUTI or APEKS-NP studies, an increase from 18% to 34% in the study of resistant infections has drawn warranted concern.[2] Trial investigators and Shionogi, the drug's manufacturer, have analyzed each death in the trial and concluded that the deaths were not due to an adverse effect from the drug or treatment with cefiderocol.[2] Given that cefiderocol will primarily be used in similarly resistant infections, more data are needed to determine it efficacy in this patient population.

Table 1: Adverse reactions occurring in more than 1% of patients in the APEKS-cUTI study[4]

Adverse Reaction	Cefiderocol (N = 300)	Imipenem/Cilastatin (N = 148)
Diarrhea	4%	6%
Infusion site reactions	4%	5%
Constipation	3%	4%
Rash	3%	<1%
Candidiasis	2%	3%
Cough	2%	<1%
Elevations in liver tests	2%	<1%
Headache	2%	5%
Hypokalemia	2%	3%
Nausea	2%	4%
Vomiting	2%	1%

Dosing and Administration

Cefiderocol is administered as a 2g intravenous injection given every 8 hours to patients with normal renal function.[3] This drug requires renal dosage adjustments, which are shown in Table 2. Cefiderocol should not be given to pediatric patients, as safety and efficacy has not been established in this population.[3]

Cefiderocol is only available as an intravenous injection. Vials must be reconstituted and are only stable for 1 hour at room temperature upon reconstituation.[3] Once reconstituted, vials of cefiderocol can be mixed into infusion bags where they are stable for 4 hours. The drug

then needs to be administered over 3 hours, allowing only a tight window for this drug's preparation and administration.[3]

Table 2: Cefiderocol dosing recommendations[3]

Estimated Creatinine Clearance (CrCl)	Dose	Frequency
≥ 120 mL/min	2 g	**Every 6 hours**
119 – 60 mL/min	2 g	Every 8 hours
30 – 59 mL/min	1.5 g	Every 8 hours
15 – 29 mL/min	1 g	Every 8 hours
< 15 mL/min with or without intermittent HD	0.75 g	Every 12 hours

What is the Role of Cefiderocol in Therapy?

Cefiderocol is a novel cephalosporin with excellent activity against MDR Gram-negative bacteria. It is approved for treatment of cUTIs, but there are safer alternatives (e.g., ceftazidime/avibactam) that are highly potent against most MDROs implicated in cUTI that should be used first-line. The most attractive feature of cefiderocol is its activity against extensively drug-resistant (XDR) bacteria, such as bacteria producing metallo-beta-lactamases (e.g., NDM-1). Fortunately, these pathogens are relatively uncommon in the US, but the incidence is on the rise. Unfortunately, the majority of patients with infections caused by XDR bacteria are medically complex. While cefiderocol, in theory, appears to be the most attractive agent to treat infections caused by these organisms, the increase in all-cause mortality observed among critically-ill patients receiving cefiderocol for infections caused by CRE is alarming. Ultimately, we believe this agent should be reserved for compassionate use in critically-ill patients with infections caused by XDR bacteria when no alternatives exist. In addition to these concerns, we expect the anticipated high cost and lack of commercially-available susceptibility tests to be barriers to use.

Take Home Points:

1. Cefiderocol (Fetroja®) is a first-in-class siderophore cephalosporin approved for complicated urinary tract infections (cUTI) in adults.
2. Cefiderocol's novel mechanism of entry into the cell and stability against efflux pumps and beta-lactamases make it highly active against most Gram-negative pathogens, including CRE.
3. An increase in all-cause mortality in critically-ill patients with infections caused by CRE was observed in patients receiving cefiderocol; therefore, this agent should be reserved as a last-line option when no alternative agents exist.
4. Barriers to cefiderocol use include cost and lack of commercially-available susceptibility testing.

References

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