Cefiderocol: A siderophore cephalosporin

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Disclosure Statement

I have no actual or potential conflict of interest in relation to this presentation
Objectives

Pharmacist
1. Describe the mechanism of action for cefiderocol
2. Identify the spectrum of activity for cefiderocol
3. Outline a dosing regimen for cefiderocol based on specific patient populations

Technician
1. Identify the dosage form and strength cefiderocol is supplied as
2. Recognize common side effects of cefiderocol
3. Review storage and handling of cefiderocol
# Cefiderocol (Fetroja®)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Shinogi</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approval Date</td>
<td>November 14, 2019</td>
</tr>
<tr>
<td>Class</td>
<td>Cephalosporin</td>
</tr>
<tr>
<td>FDA Approved Indications</td>
<td>Complicated urinary tract infections, including pyelonephritis, hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia</td>
</tr>
<tr>
<td>Cost</td>
<td>1 g solution: $227.70</td>
</tr>
</tbody>
</table>
## Cefiderocol (Fetroja®)

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Reconstituted solution, intravenous (preservative free) 1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing and Administration</td>
<td>IV: 2 g every 8 hours</td>
</tr>
<tr>
<td>How Supplied/Preparation</td>
<td>White to off-white sterile lyophilized powder for reconstitution in single-dose. Reconstitute with 10 mL of 0.9% NaCl or 5% dextrose injection. Each vial is supplied in cartons containing 10 single-dose vials.</td>
</tr>
<tr>
<td>Storage and Stability</td>
<td>Should be refrigerated at 2°C to 8°C. Protect from light. Store in carton until time of use. Store reconstituted solutions of Fetroja® at room temperature for up to 4 hours.</td>
</tr>
</tbody>
</table>
Mechanism of Action

- Siderophore that binds to extracellular free ferric iron
- Passive diffusion via porin channels
- Transported across outer cell membrane of bacteria into periplasmic space using siderophore iron uptake mechanism
- Bactericidal – inhibits cell wall biosynthesis through binding to penicillin-binding proteins (PBPs)
Fetroja® (cefiderocol): How Fetroja works.

Active transport allows for an additional method of entry into bacterial cells.

Overcomes porin channel changes by entering through the iron transport system.

Stable against all classes of ß-lactamases (A, B, C, and D).

In vitro activity does not necessarily correlate with clinical efficacy.

Adapted from Zhiang et al.
Indications

Complicated urinary tract infections (cUTI)
• Including pyelonephritis

Hospital acquired bacterial pneumonia (HABP)

Ventilator associated bacterial pneumonia (VABP)
Complicated Urinary Tract Infection

**Definition**

Urinary tract infection with high risk factors such as:

- Diabetes, pregnancy, hospital acquired infection, renal failure, urinary tract obstruction, presence of indwelling urethral catheter, nephrostomy tube, functional or anatomic abnormality of the urinary tract, immunosuppression, male sex

**Common pathogens:**

- E. coli
- Klebsiella spp.
- Serratia spp.
- Citrobacter spp.
- Enterobacter spp.
Bacterial Pneumonia

HABP Definition
Pneumonia not incubating at the time of hospital admission and occurring ≥48 hours after admission, not associated with mechanical ventilation

VABP Definition
Pneumonia occurring >48 hours after endotracheal intubation

Common pathogens:
- Pseudomonas aeruginosa
- Escherichia coli
- Klebsiella pneumoniae
- Enterobacter spp
- Acinetobacter spp
- Staphylococcus aureus (including methicillin-resistant. S. aureus)
- Streptococcus spp
Pharmacokinetics

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Protein binding: 40-60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Minimal metabolism (less than 10%)</td>
</tr>
</tbody>
</table>
| Excretion     | Half-life: 2-3 hours  
               | Renal excretion: 98.6%  
               | Dialyzable: Yes (HD), 60% removed |
Pharmacodynamics

Compared to a 1-hour infusion, a 3-hour infusion increased the percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the MIC
Spectrum of Activity

**cUTI including pyelonephritis**
- Escherichia coli
- Enterobacter cloacae complex
- Klebsiella pneumoniae
- Proteus mirabilis
- Pseudomonas aeruginosa

**HABP/VABP**
- Acinetobacter baumannii complex
- Escherichia coli
- Enterobacter cloacae complex
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Serratia marcescens
Spectrum of Activity

cUTI including pyelonephritis
- Escherichia coli
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- Proteus mirabilis
- Pseudomonas aeruginosa

HABP/VABP
- Acinetobacter baumannii complex
- Escherichia coli
- Enterobacter cloacae complex
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Serratia marcescens
Resistance Rates

- Cefiderocol does not cause induction of AmpC beta-lactamase in P. aeruginosa and E. cloacaee
- Resistance gram-negative bacteria including carbapenemase at 10x MIC: $10^{-6}$ to $<10^{-8}$
- Cross resistance with other classes has not been identified
<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>SIDERO-WT-2014</th>
<th></th>
<th>SIDERO-WT-2015</th>
<th></th>
<th>SIDERO-WT-2016</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Test Strains</td>
<td>MIC_{90} µg/mL</td>
<td>No. of Test Strains</td>
<td>MIC_{90} µg/mL</td>
<td>No. of Test Strains</td>
<td>MIC_{90} µg/mL</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>6087</td>
<td>0.5</td>
<td>6013</td>
<td>1</td>
<td>7019</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1529</td>
<td>0.5</td>
<td>1830</td>
<td>1</td>
<td>1780</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1526</td>
<td>1</td>
<td>1528</td>
<td>1</td>
<td>1573</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>505</td>
<td>0.25</td>
<td>389</td>
<td>0.5</td>
<td>540</td>
<td>0.25</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>303</td>
<td>0.5</td>
<td>252</td>
<td>1</td>
<td>273</td>
<td>0.5</td>
</tr>
<tr>
<td>Citrobacter koseri</td>
<td>172</td>
<td>0.5</td>
<td>169</td>
<td>0.5</td>
<td>176</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>514</td>
<td>1</td>
<td>594</td>
<td>1</td>
<td>692</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>442</td>
<td>0.5</td>
<td>244</td>
<td>0.5</td>
<td>331</td>
<td>0.5</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>927</td>
<td>0.25</td>
<td>776</td>
<td>0.5</td>
<td>679</td>
<td>0.5</td>
</tr>
<tr>
<td>Serratia spp</td>
<td>996</td>
<td>0.25</td>
<td>794</td>
<td>0.5</td>
<td>718</td>
<td>0.5</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>195</td>
<td>0.25</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>40</td>
<td>0.12</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>329</td>
<td>0.25</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1530</td>
<td>0.5</td>
<td>1540</td>
<td>0.5</td>
<td>1872</td>
<td>0.5</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>1148</td>
<td>1</td>
<td>837</td>
<td>2</td>
<td>911</td>
<td>4</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>12</td>
<td>1</td>
<td>45</td>
<td>0.12</td>
<td>37</td>
<td>0.03</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>428</td>
<td>0.25</td>
<td>340</td>
<td>0.5</td>
<td>405</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Table 2. Susceptibility Ratio to Cefiderocol and Comparators of Carbapenem-resistant Isolates From the SIDEROCR-2014/2016 Study

<table>
<thead>
<tr>
<th>Species (No. of Strains)</th>
<th>Ratio of Susceptible Strains(^a), (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefiderocol</td>
</tr>
<tr>
<td>Carbapenem-nonsusceptible strains(^b)</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (1022)</td>
<td>97.0</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> (262)</td>
<td>99.2</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em> (368)</td>
<td>90.9</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em> (217)</td>
<td>100(^a)</td>
</tr>
</tbody>
</table>

Source: Adapted from [23].

Abbreviation: NA, susceptibility breakpoints not available.

\(^a\)Ratio of susceptible strains (%) was calculated using the following minimum inhibitory concentration (MIC) criteria: cefiderocol MIC ≤ 4 µg/mL; ceftazidime-avibactam MIC ≤ 8 µg/mL; ceftolozane-tazobactam MIC ≤ 2 µg/mL for Enterobacteriaceae, ≤ 4 µg/mL for nonfermenters; ciprofloxacin MIC ≤ 1 µg/mL; colistin MIC ≤ 2 µg/mL.

\(^b\)Carbapenem-nonsusceptible strain was defined as meropenem MIC > 2 µg/mL for Enterobacteriaceae, > 4 µg/mL for nonfermenters.

\(^c\)Includes 39 *Serratia* species that are intrinsically resistant to colistin.
Resistance Rates

• Enterobacterales and P. aeruginosa resistant to:
  • Meropenem, ciprofloxacin, amikacin, cefepime, ceftazidime-avibactam and ceftolozane/tazobactam

• A. baumanii complex resistant to:
  • Meropenem, ciprofloxacin and amikacin

• Colistin-resistant E. coli isolates containing mcr-1

• K. pneumoniae porin channel deletions

• P. aeruginosa porin channel deletions and efflux pump up-regulation
Dosing Considerations

Renal
• Requires renal dose adjustment

Hepatic
• None
# Dosing Considerations: Renal

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;120</td>
<td>2 g IV q6h, infusion over 3 hours</td>
</tr>
<tr>
<td>60-119</td>
<td>2 g IV q8h, infusion over 2 hours</td>
</tr>
<tr>
<td>&lt;60</td>
<td>30-59: 1.5 g IV q8h, infusion over 3 hours</td>
</tr>
<tr>
<td></td>
<td>15-29: 1 g IV q8h, infusion over 3 hours</td>
</tr>
<tr>
<td></td>
<td>&lt;15: 750 mg IV q12h, infusion over 3 hours</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Dialyzable</td>
</tr>
<tr>
<td></td>
<td>750 mg q12h</td>
</tr>
<tr>
<td></td>
<td>Given after HD on dialysis days</td>
</tr>
</tbody>
</table>

Warnings and Precautions

• Increase in all-cause mortality in patients with carbapenem-resistant gram-negative bacterial infections
• Hypersensitivity reactions
  • *Cross-hypersensitivity may occur with history of penicillin allergy*
• Clostridioides difficile-associated diarrhea
• Seizures and other central nervous system adverse reactions
Contraindications

Known history of severe hypersensitivity to cefiderocol and other beta-lactam antibacterial drugs or other components of Fetroja
Adverse Reactions

1% to 10%:

- 2% - atrial fibrillation, bradycardia, seizure, insomnia, hypokalemia, hypervolemia, nausea, vomiting, abdominal pain, cholecystitis, Clostridioides difficile associated diarrhea, increased INR, thrombocytopenia, increased liver enzymes, drug-induced hypersensitivity reaction, cough, dyspnea, candidiasis, fever, xerostomia

- 4% - Diarrhea, infusion site reaction
Drug Interactions

- **Aminoglycosides:** antibiotics may enhance nephrotoxic effect
- **BCG vaccine:** antibiotics may diminish therapeutic effect of BCG
- **Immune checkpoint inhibitors:** antibiotics may diminish the therapeutic effect of immune checkpoint inhibitors
- **Probenecid:** may increase serum concentration of cephalosporins
- **Vitamin K antagonists:** cephalosporins may enhance the anticoagulant effect of vitamin K antagonists
Monitoring Parameters

• Monitor renal function

• Observe for signs and symptoms of anaphylaxis during first dose
Special Populations: Pregnancy

Pregnancy

- No available data for use in pregnant women
- Animal studies show no evidence of embryo-fetal toxicity and drug-induced fetal malformations at doses higher than average maximum recommended daily dose

Lactation

- Cefiderocol-derived radioactivity was detected in milk following intravenous administration to lactating rats (6% at peak plasma level)
Special Populations: Pediatrics

Safety and effectiveness in pediatric patients younger than 18 years of age have not been established
Special Populations: Geriatrics

**cUTI**
- 300 patients, 52.7% were 65 years of age and older, 22.3% were 75 years of age and older
- No overall differences in safety or efficacy were observed between these patients and younger patients

**HABP/VABP**
- 148 patients, 56.1% were 65 years of age and older, 27% were 75 years of age and older
- Incidence of adverse reactions was similar in patients under 65 years of age as compared to older patients
Cefiderocol vs. Imipenem/Cilastatin

- Portsmouth S et al, 2018
- Phase 2 randomized, active-controlled, double-blind, parallel-group, multicenter non-inferiority trial
- 448 hospitalized patients with cUTI
- Randomized in 2:1 ratio receiving either cefiderocol 2 g IV q8h (1 hour infusion) or imipenem/cilastatin 1 g IV q8h (1 hour infusion) for 7-14 days
Cefiderocol vs. Imipenem/Cilastatin

• Efficacy was assessed as a composite of microbiological eradication and clinical cure at test of cure visit

<table>
<thead>
<tr>
<th>Study Endpoint</th>
<th>FETROJA n/N (%)</th>
<th>Imipenem/Cilastatin n/N (%)</th>
<th>Treatment Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite response at TOC</td>
<td>183/252 (72.6%)</td>
<td>65/119 (54.6%)</td>
<td>18.6 (8.2, 28.9)</td>
</tr>
<tr>
<td>Microbiologic response TOC</td>
<td>184/252 (73.0%)</td>
<td>67/119 (56.3%)</td>
<td>17.3 (6.9, 27.6)</td>
</tr>
<tr>
<td>Clinical response TOC</td>
<td>226/252 (89.7%)</td>
<td>104/119 (87.4%)</td>
<td>2.4 (-4.7, 9.4)</td>
</tr>
</tbody>
</table>

CI = confidence interval; Micro-ITT = microbiological intent-to-treat; TOC = Test of Cure.
* The treatment difference and 95% CI were based on the Cochran-Mantel-Haenszel method.
Cefiderocol vs. Imipenem/Cilastatin

- In the cefiderocol treatment group, 24.2% bacterial isolates were ESBL producers compared with 26.9% in the imipenem/cilastatin group
Cefiderocol vs. Meropenem

• Wunderink et al, 2020
• Randomized, double-blind trial
• 298 hospitalized patients with HABP/VABP
• Compared cefiderocol 2 g IV q8h (3 hr infusion) or meropenem 2 g IV q8h (3 hr infusion) and both received linezolid 600 mg q12h for at least 5 days
• Measured all-cause mortality
Cefiderocol vs. Meropenem

- Efficacy was assessed as a composite of microbiological eradication and clinical cure at test of cure visit
Cefiderocol vs. Meropenem

- In the cefiderocol treatment group, 31% of patients had ESBL-producing bacterial isolates compared with 28.6%.

![Table 12: Clinical Cure Rates by Baseline Pathogen Susceptible to Meropenem* at the TOC Visit in HABP/VABP (mITT Population) in Trial 2](image-url)
Which of the following is the correct mechanism of action for cefiderocol?

A. Inhibits DNA-gyrase in susceptible organisms, inhibits relaxation of supercoiled DNA and promotes breakage of double-stranded DNA

B. Forms chelated complexes with ferric iron allowing use of iron transport systems to deliver drug across outer membrane of gram-negative bacilli and binds to penicillin-binding proteins inhibiting cell wall biosynthesis

C. Interferes with bacterial folic acid synthesis and growth via inhibition of dihydrofolic acid formation from para-aminobenzoic acid resulting in sequential inhibition of enzymes of the folic acid pathway

D. Inhibits bacterial RNA synthesis by binding to the beta subunit of DNA-dependent RNA polymerase, blocking RNA transcription
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D. Inhibits bacterial RNA synthesis by binding to the beta subunit of DNA-dependent RNA polymerase, blocking RNA transcription
True or False: Cefiderocol is indicated in Staphylococcus aureus infections
A. True
B. False
Post-Test

True or False: Cefiderocol is indicated in Staphylococcus aureus infections

A. True

B. False
Which of the following statements is true regarding cefiderocol use in special populations?

A. Cefiderocol is not indicated in pediatric patients younger than 18 years of age
B. Cefiderocol has been added to the Beer’s List and should be avoided in the geriatric population
C. There is sufficient data to suggest safe administration in lactation and pregnancy
D. Dose adjustments are necessary in patients with impaired hepatic function
Which of the following statements is true regarding cefiderocol use in special populations?

A. **Cefiderocol is not indicated in pediatric patients younger than 18 years of age**

B. Cefiderocol has been added to the Beer’s List and should be avoided in the geriatric population

C. There is sufficient data to suggest safe administration in lactation and pregnancy

D. Dose adjustments are necessary in patients with impaired hepatic function
Post-Test

What is typical dosing strength and frequency for cefiderocol?

A. 1 g IV q12h
B. 500 mg IV q8h
C. 1 g PO q12h
D. 2 g IV q8h
Post-Test

What is typical dosing strength and frequency for cefiderocol?

A. 1 g IV q12h
B. 500 mg IV q8h
C. 1 g PO q12h
D. 2 g IV q8h
Post-Test

Which of the following side effects may occur with cefiderocol?

A. QTc prolongation
B. Hemolytic anemia
C. Clostridioides difficile-associated diarrhea
D. Hepatotoxicity
Post-Test

Which of the following side effects may occur with cefiderocol?

A. QTc prolongation
B. Hemolytic anemia
C. *Clostridioides difficile*-associated diarrhea
D. Hepatotoxicity
Post-Test

True or False: Cefiderocol must be protected from light

A. True
B. False
Post-Test

True or False: Cefiderocol must be protected from light

A. True

B. False
References

- Fetroja® [package insert]. Osaka, Japan. Shionogi % Co., Ltd.; 2020
- Yamano Y. In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria. Clin Infect Dis. 2019
Thank you!

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