CEFIDEROCOL:
A NOVEL SIDEROPHORE CEPHALOSPORIN
FOR MULTIDRUG RESISTANT INFECTIONS

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Disclosures

◦ The presenter for this activity has been required to disclose all relationships with any proprietary entity producing health care goods or services, with the exemption of non-profit or government organizations and non-health care related companies.

◦ No significant financial relationships with commercial entities were disclosed by the speaker.
Objectives

- Describe cefiderocol’s unique mechanism of action and antimicrobial activity

- Discuss evidence supporting cefiderocol’s use in complicated urinary tract infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia

- Review safety considerations for the use of cefiderocol, including concern for all-cause mortality, and its place in therapy
In 2010, at a time when drug resistance was on the rise and antibacterial agents being investigated were dwindling, the Infectious Diseases Society of America (IDSA) announced the “10 x ‘20 initiative.”

This initiative supported the development of ten new systemic antibacterial agents by the year 2020 through the discovery of new drug classes and new drugs within existing classes to combat the threat of antimicrobial resistance.
Bacteria & Iron

- Bacteria depend on free iron for survival and proliferation
- Lactoferrin is released as part of the host's immune response to sequester iron, making it less easily available to bacteria
- To obtain iron from the host, bacteria release **siderophores**
  - These are small molecules that chelate with iron
  - They also have a higher affinity for iron and can take it from lactoferrin
- Bacteria then transport iron-bound siderophores into their cells

Cefiderocol & Iron

- Cefiderocol exploits this need for iron to infiltrate bacterial cells!

- Its unique chemical structure includes both a cephalosporin as well as an attached catechol side-chain

- This allows cefiderocol to use a "Trojan Horse" type strategy by binding iron to enter bacterial cells through active transport

Fetroja (cefiderocol) [package insert].
Figure adapted from: https://www.fetroja.com/overcoming-carbapenem-resistance
Mechanisms of Resistance

- Bacteria employ a variety of resistance mechanisms to evade antibiotics

- Cefiderocol overcomes these resistance mechanisms to remain active, making it a viable treatment option for organisms that are often treatment-resistant

Enter bacteria via iron transport system

Stable against all classes of B-lactamases

Active against bacteria resistance due to efflux pump up-regulation

Fetroja (cefiderocol) [package insert].
# Antimicrobial Activity

<table>
<thead>
<tr>
<th>Activity both in vitro and in clinical infections</th>
<th>In vitro activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated Urinary Tract Infections</td>
<td>Achromobacter spp</td>
</tr>
<tr>
<td></td>
<td>Burkholderia cepacia complex</td>
</tr>
<tr>
<td></td>
<td>Citrobacter freundii complex</td>
</tr>
<tr>
<td></td>
<td>Citrobacter koseri</td>
</tr>
<tr>
<td></td>
<td>Klebsiella aerogenes</td>
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<tr>
<td>Hospital &amp; Ventilator Acquired Bacterial Pneumonia</td>
<td></td>
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<tr>
<td></td>
<td>Acinetobacter baumannii complex</td>
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<tr>
<td></td>
<td>Escherichia coli</td>
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<tr>
<td></td>
<td>Enterobacter cloacae complex</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td></td>
<td>Serratia marcescens</td>
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</tbody>
</table>
Cefiderocol for cUTI

- November 2019 - cefiderocol received approval for the treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-negative bacteria in adults with limited to no alternative treatment options

APEKS-cUTI

- **Study Design:** Multicenter, double-blind, non-inferiority trial
- **Comparator:** Imipenem-cilastatin
- **Primary Endpoint:** Composite of clinical response and microbiological eradication at test of cure 7 days post therapy
  - Clinical response: resolution or improvement of the symptoms of cUTI at study entry and no new symptoms
  - Microbiological eradication: reduction of the baseline bacterial pathogen to $<10^4$ CFUs/mL
Cefiderocol for cUTI

- **Patient Population:** 452 patients randomized, 448 received treatment (300 cefiderocol, 148 imipenem-cilastatin)

- Noninferiority of cefiderocol **was demonstrated**, with 73% of those in the cefiderocol group and 55% of those in the imipenem-cilastin group reaching the primary endpoint
  - Treatment difference 18.6% (95% CI 8.2 - 28.9, p=0.0004)

- However, **clinical response rates were similar** between these two groups, with the microbiologic portion driving the difference in the primary endpoint
  - A greater portion of those in the cefiderocol group had suppressed pathogen growth

Cefiderocol for HABP/VABP

- September 2020 – cefiderocol received approval for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia

APEKS-NP

- **Objective:** Compare the efficacy and safety of cefiderocol versus high-dose, extended-infusion meropenem in patients with HAP, VAP, or HCAP caused by Gram-negative bacteria
- **Study Design:** Phase III, double-blind, non-inferiority trial
- **Comparator:** Meropenem
- **Primary Endpoint:** All-cause mortality at day 14

Cefiderocol for HABP/VABP

- **Population:** 300 participants randomized, 148 received cefiderocol and 152 received meropenem

- Cefiderocol was shown to be non-inferior to extended-infusion, high-dose meropenem
  - 12.4% for the cefiderocol group and 11.6% for the meropenem group
  - Adjusted treatment difference 0.8 (95% CI –6.6 to 8.2, p=0.002)

- The proportions of patients with clinical cure at test of cure (65% cefiderocol, 67% meropenem) and microbiological eradication at test of cure (48% cefiderocol, 48% meropenem) were similar among both groups

Safety Considerations

- **Warnings**
  - Increase in all-cause mortality in patients with carbapenem-resistant gram-negative bacterial infections
  - Hypersensitivity reactions
  - *Clostridioides difficile*-associated diarrhea
  - Seizures and other CNS adverse reactions
  - Development of drug-resistant bacteria

- **Adverse Reactions:** Diarrhea (4%), infusion site reactions (4%), constipation (3%), rash (3%), candidiasis (2%), cough (2%), elevations in liver tests (2%), headache (2%), hypokalemia (2%), nausea (2%), vomiting (2%), atrial fibrillation (<2%)
**All-Cause Mortality Concern**

**CREDIBLE-CR**

- **Objective:** Assess the efficacy and safety of cefiderocol or best available therapy for the treatment of patients admitted to the hospital with various serious carbapenem-resistant Gram-negative infections who required intravenous antibiotic therapy

- **Study Design:** Phase III, randomized, open-label study

- **Comparator:** Best available therapy

- **Primary Endpoint:**
  - In patients with nosocomial pneumonia, bloodstream infection or sepsis: the proportion achieving a clinical cure at TOC
  - In patients with cUTIs: the proportion achieving microbiological eradication at TOC

- **Population:**
  - Patients hospitalized with nosocomial pneumonia, bloodstream infections/sepsis, or cUTI, and evidence of a carbapenem-resistant Gram-negative pathogen
  - 101 randomized to cefiderocol, 51 to best available therapy

Fetroja (cefiderocol) [package insert].
All-Cause Mortality Concern

<table>
<thead>
<tr>
<th></th>
<th>HAP/VAP/HCAP</th>
<th>BSI/Seepsis</th>
<th>cUTI</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefiderocol (N=45)</td>
<td>BAT (N=22)</td>
<td>Cefiderocol (N=30)</td>
<td>BAT (N=17)</td>
</tr>
<tr>
<td>Day 14</td>
<td>11 (24%)</td>
<td>3 (14%)</td>
<td>5 (17%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Day 28</td>
<td>13 (31%)</td>
<td>4 (18%)</td>
<td>7 (23%)</td>
<td>3 (18%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cefiderocol (N=101)</th>
<th>BAT (N=49)</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28</td>
<td>25 (25%)</td>
<td>9 (18%)</td>
<td>6.4% (-8.6 to 19.2)</td>
</tr>
<tr>
<td>End of Study</td>
<td>34 (34%)</td>
<td>9 (18%)</td>
<td>15.3% (-0.2 to 28.6)</td>
</tr>
<tr>
<td>Day 49</td>
<td>34 (34%)</td>
<td>10 (20%)</td>
<td>13.3% (-2.5 to 26.9)</td>
</tr>
</tbody>
</table>

- All-cause mortality differences were largely driven by infections caused by *Acinetobacter species*
Cefiderocol is available as a sterile, lyophilized powder for reconstitution to be diluted with either 0.9% sodium chloride injection, USP or 5% dextrose injection, USP. Vials should be protected from light and refrigerated while being stored. Once reconstituted, it can be stored at room temperature for up to 1 hour. The diluted infusion solution is stable for up to 6 hours at room temperature and up to 24 hours when refrigerated.

<table>
<thead>
<tr>
<th>Estimated CrCl</th>
<th>Dose</th>
<th>Frequency</th>
<th>Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 – 119 mL/min</td>
<td>2 grams</td>
<td>Every 8 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>30 – 59 mL/min</td>
<td>1.5 grams</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 – 29 mL/min</td>
<td>1 gram</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 15 mL/min</td>
<td>0.75 gram</td>
<td>Every 12 hours</td>
<td></td>
</tr>
<tr>
<td>&gt; 120 mL/min</td>
<td>2 grams</td>
<td>Every 6 hours</td>
<td></td>
</tr>
</tbody>
</table>

Fetroja (cefiderocol) [package insert].
Place in Therapy

- Additional research is needed to understand differences in all-cause mortality and to determine whether resistance emerges to cefiderocol.
- Until then, cefiderocol is best used as a salvage regimen for patients with multidrug resistant gram-negative infections for which options are limited.
QUESTIONS?

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References


