We’re ready for MAD-ID! Are you?

The MAD-ID scientific committee and speakers are working hard to plan another fun and engaging conference. We can’t wait to share all of the new data and innovative practices in infectious diseases therapy and stewardship and to hear from our attendees about the work you’ve done this year.

You can look forward to plenary sessions on new guidelines, difficult to treat infections, and clinical controversies in a wide range of topics. And based on your feedback, we’ve included a special pre-meeting workshop highlighting challenging cases from our community of members in “Tales from the Trenches.” This session, facilitated by Susan Davis, will feature three long-time MAD-ID attendees, Lynne Krop, David Lourwood, and Nick Zaksek discussing cases from their own practice and sharing stewardship strategies from diverse settings.

Check out the full conference agenda and the list of pre-meeting workshops at our website https://mad-id.org/2020-mad-id-annual-meeting/agenda-2/
MAD-ID Annual Meeting Updates

Registration Deadlines

Registration is open for the 23rd annual MAD-ID meeting to be held in ChampionsGate/Orlando, Florida, May 27-30, 2020. [https://www.omnihotels.com/hotels/orlando-championsgate](https://www.omnihotels.com/hotels/orlando-championsgate)

The deadline to receive early registration discount is April 27th, so don’t wait too long. This year, the pre-meeting workshop classrooms are not included in the basic registration fee. To attend the workshops you’ll need to register separately or enroll in the Advanced Antimicrobial Stewardship Program (AASP).

You can register here: [https://mad-id.org/2020-mad-id-annual-meeting/registration-2/](https://mad-id.org/2020-mad-id-annual-meeting/registration-2/)

Call for Abstracts

You are invited by the MAD-ID Scientific Advisory Committee to submit your abstract for consideration for presentation in poster format at the 2020 Annual Meeting. The submission deadline is **Friday, April 24, 2020.** Abstracts describing all aspects of Antimicrobial Stewardship and Infectious Diseases Prevention and Treatment are welcome!

Posters will be on display throughout the meeting and highlighted during the poster exhibition on Thursday, May 28th. Students, residents, and fellows submitting original research abstracts may be eligible for a travel grant to support their attendance. See the website for full details!

BCIDP Recertification Credit in Partnership with SIDP

We are very excited to offer recertification credit for Board Certified Infectious Diseases Pharmacists (BCIDP) at this year’s annual meeting, provided through a partnership with the Society of Infectious Diseases Pharmacists (SIDP).

Sessions offering BCIDP credit this year are:

- The Public Health Crisis of Vaccines (presented by Jeff Goad and Daniel Solomon)
- Disease State Guideline Updates (presented by Emily Spivak and Tom File)
- Emerging and Difficult to Treat Infections (presented by Wendy Bullington and Jeff Rybak)

Registration for BCIDP recertification can be completed at the time of general meeting registration.

Thank you to SIDP for providing this great new opportunity at the MAD-ID Annual Meeting!
CME Accredited Provider
For several years, the MAD-ID annual meeting has been working with external partners to provide continuing education credit for nurses and physicians. This year we are pleased to tell our members and attendees that MAD-ID is now officially approved by Accreditation Council for Continuing Medical Education as a CME provider. This will allow a more efficient process for CME processing for our physicians.

Congratulations to our continuing education director, Jean Nappi, on this important accomplishment!

First Ever Trainee Focus Session
Before the full meeting starts, MAD-ID is hosting a special session for trainees only on Wednesday, May 27 from 1:30 – 3:00. Attendance at this session is suggested for all trainees for introductions and networking and will be required for all travel grant recipients.

Give Me the Good News First:
Transitioning into Infectious Diseases Practice

1:30: Panel Discussion: Career choices and challenges
Featuring:
Erin McCreary, PharmD, BCPS, BCIDP
Antimicrobial Stewardship/Infectious Diseases Pharmacist
University of Pittsburgh Medical Center
Jordan Smith, PharmD
Assistant Professor
High Point University

2:30: Networking Speed Dating

Urgent Antibiotic Resistance Threats
Nearly 3 million people in the US have an antibiotic resistant infection every year, and over 35,000 of those patients die as a result of their infections. Can you name all of the urgent health threats in the newly-updated Threat Report from the Centers for Disease Control and Prevention? Find the must-read document here: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf We’ll be talking about many of the urgent, serious and concerning threats at this year’s MAD-ID meeting.
MAD-ID Research Network: Call for Proposals

The MAD-ID Research Network is soliciting applications for proposals designed to advance the practice of and/or demonstrate the value of antimicrobial stewardship. Proposals to be considered include a variety of experimental, observational or quasi-experimental designs. The successful proposal will be an innovative application that advances the science and practice of antimicrobial stewardship. Up to two awards of a maximum $30,000 will be funded.

Applications to this request for proposals should address one or more of the following topics and be aligned with the mission of MAD-ID.

- Reducing antimicrobial resistance
- Improving patient safety
- Improving patient outcome(s)
- Applying antimicrobial stewardship in novel settings

Letters of intent will be accepted until March 15th. Full applications are due May 1st. See our website for the full request for proposals.

News from around MAD-ID

- Did you know, MAD-ID works with several strategic media partners to help spread new information about infectious diseases and stewardship? Please check out the ID current events and headlines provided at Infectious Diseases Special Edition, https://www.idse.net/ and Pharmacy Practice News https://www.pharmacypracticenews.com/


- And after you read Rolf’s article, if you feel called to action to support antibiotic development, consider contacting your legislator to support the DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms) Act. The Infectious Diseases Society of America has a handy form! http://cqrcengage.com/idsociety/app/write-a-letter?0&engagementId=500554

Live from [Your City], It’s MAD-ID?

In 2019-2020, MAD-ID speakers were able to travel to 10 cities across the United States to facilitate networking and discussion about antimicrobial resistance and stewardship. We had a GREAT time, met some new people, and shared lots of tips and information. This program was supported by a partnership with Allergan plc. If you think your city would be a good place to host a MAD-ID event like this in the future, contact Emily Milliot emilliot@agcomm.com to let us know.
Disclosures: Doctors Smith and Stone have no conflicts of interest to disclose relevant to this learning activity.

Learning Objectives:
At the end of this article, learners will be able to:
1. Introduce and discuss cefiderocol, the first siderophore cephalosporin antibiotic available for clinical use, and its FDA indications for use
2. Describe the importance of siderophores to cellular function and how those siderophores have been used to develop cefiderocol
3. Describe relevant susceptibility and pharmacokinetic data pertinent to cefiderocol
4. Summarize the available clinical data regarding efficacy and safety of cefiderocol
5. Given a specific patient case scenario, select an appropriate antibiotic regimen

Introduction
Cefiderocol (Fetroja, Shionogi) is a recently approved, cephalosporin antibiotic with a novel mechanism of action involving iron transporters called siderophores.¹ The name “Fetroja” appears to be derived from a combination of “Fe,” the chemical abbreviation for iron, and “troja,” a shortening of Trojan horse. It is indicated for the treatment of complicated urinary tract infections (cUTI) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex.¹ In this educational activity, we will describe the role of siderophores and discuss the susceptibility, pharmacokinetic, clinical, and safety data of cefiderocol.

Siderophores
Iron plays a central role in human biological functions from DNA synthesis to oxygen transport. In humans, iron is obtained from the environment, almost exclusively through diet, and circulating iron is present primarily in the ferric (Fe³⁺) form. Ferric iron is transported throughout the body by proteins such as transferrin and lactoferrin, although the majority circulating is found within hemoglobin.² Bacteria, too, require iron for basic cellular processes and must cope with the relatively sparse amounts of iron available to them. In the setting of infection, there is a continuous tug-of-war between host and bacteria over circulating iron stores. Bacteria, in an effort to sequester iron, produce molecules called siderophores. A siderophore, derived from the Greek term for “iron carrier,” chelates ferric iron and transports it into the bacterial cell.³ Siderophores are quite adept at their jobs, able to chelate not only freely circulating iron but also to strip iron off of host lactoferrin and transferrin.⁴ Iron is then transported across the cellular membrane through active transport, entering the periplasmic space of gram-negative bacteria before ultimately being transported into the cytoplasm. These functions allow bacteria to survive and thrive in the host, even with little environmental iron available. Among bacterial species, several forms of siderophores are produced, with different
species possessing molecules that have specific differences in their iron binding pockets. Although there are subtle differences, the important matter is that Staphylococci, *P. aeruginosa*, *E. coli*, *K. pneumoniae*, among others, all produce some form of siderophore. The ubiquitous nature of siderophores within bacteria and their importance to cellular function has led to consideration of these molecules as a potential antibiotic target, and several agents have been developed. Cefiderocol is the first of those to be approved for clinical use.

**Structure and Mechanism of Action**

Cefiderocol is a derivative of ceftazidime that possesses a catechol siderophore moiety. It is the only catechol siderophore + β-lactam with data available, as the two other siderophore + β-lactam antibiotics currently in development, MC-1 and BAL30072, possess dihydroxypridone siderophore moieties. Mechanistically, the siderophore moiety binds ferric iron and allows transport of cefiderocol across bacterial membranes and bypasses several important resistance mechanisms (Figure 1). Once bound to ferric iron, cefiderocol is transported across the cellular membrane in a similar fashion to endogenous siderophore molecules. The benefits of this transport are two-fold. Not only is the molecule able to bypass several important resistance mechanisms, including altered porins, such as OprD, and increased efflux pumps, but it is actively transported across the outer membrane as opposed to the passive transport of standard β-lactam antibiotics. Data with MC-1 and BAL30072 suggest that specific siderophore receptors are integral to antibiotic activity, although these specific receptors have yet to be elucidated for cefiderocol. Once present within the periplasmic space, cefiderocol exerts its antimicrobial activity in a similar fashion to other β-lactam antibiotics, binding to penicillin-binding-protein (PBP) and disrupting cell wall synthesis. Similar to ceftazidime, cefiderocol acts primarily through PBP3.

![Chemical structure of cefiderocol in the absence (top) and presence (bottom) of ferric iron.](image)

Figure 1. Chemical structure of cefiderocol in the absence (top) and presence (bottom) of ferric iron.
In Vitro Susceptibility

Cefiderocol has demonstrated potent *in vitro* activity against a wide variety of gram-negative bacteria. Among a sample of 617 *Enterobacteriaceae*, cefiderocol demonstrated an MIC$_{90}$ of 0.5 μg/ml, with only 8 isolates possessing MIC values >8 μg/ml.$^{10}$ Among these 617 isolates were strains that possessed variants of KPC, NDM-1, ESBL and AmpC β-lactamases. In general, cefiderocol demonstrated excellent efficacy against these resistant isolates, although 5 of the 8 isolates with cefiderocol MIC values >8 μg/ml were NDM-1 producing *Escherichia coli*. The other 3 isolates with elevated MIC values were VIM, IMP, and KPC types. When tested against 104 *Acinetobacter baumannii*, 104 *Pseudomonas aeruginosa*, and 108 *Stenotrophomonas maltophilia*, MIC$_{90}$ values were 2 μg/ml, 1 μg/ml, and 0.5 μg/ml, respectively, and no isolates possessed MIC values >4 μg/ml.$^{11}$ A collection of 8,954 Gram-negative bacilli from sites across Europe and North America has been evaluated for susceptibility to cefiderocol.$^{12}$ 99.9% of *Enterobacteriaceae*, 99.9% of *P. aeruginosa*, 96.4% of *A. spp.*, 99.4% of *S. maltophilia*, and 94.4% of *Burkholderia cepacia* demonstrated cefiderocol MIC values ≤4 μg/mL. Of note, cefiderocol MIC values were ≤4 μg/mL against 56/57 (98.2%) of *Enterobacteriaceae* nonsusceptible to ceftazidime/avibactam and 590/597 (98.8%) of *Enterobacteriaceae* nonsusceptible to ceftolozane/tazobactam. Cefiderocol demonstrated MIC values ≤4 μg/mL in 1137/1145 (99.3%) imipenem-nonsusceptible *P. aeruginosa*. Cefiderocol demonstrated MIC values ≤4 μg/mL against all ceftolozane/tazobactam and ceftazidime/avibactam-nonsusceptible *P. aeruginosa* isolates. Cefiderocol MIC values were ≤4 μg/mL in 540/562 (96.8%) of *A. baumannii* isolates nonsusceptible to meropenem.

During cefiderocol’s development, the Clinical Laboratory Standards Institute (CLSI) defined provisional MIC breakpoints for cefiderocol of ≤4 μg/mL considered susceptible, 8 μg/mL considered intermediate, and >16 μg/mL considered resistant. *Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* were all evaluated under those same breakpoints. These breakpoints were based *in vitro* and *in vivo* data demonstrating that cefiderocol is able to achieve pertinent pharmacodynamic parameters against bacterial isolates with MIC values ≤4 μg/mL.$^{13}$ However, as of cefiderocol’s approval by the FDA in November 2019, the FDA criteria for *Enterobacteriaceae*, including *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *E. cloacae*, are <2 μg/mL susceptible, 4 μg/mL intermediate, and >8 μg/mL resistant. For *P. aeruginosa*, those values are ≤1 μg/mL, 2 μg/mL, and >4 μg/mL, respectively. Worth noting is that, owing to its iron-dependent mechanism, cefiderocol requires iron-depleted media for accurate MIC testing. In standard media, MIC values are up to 4-fold greater than in iron-depleted media.$^7$ Iron depletion in broth is achieved via chelation with cation binding resins or supplementation with human apo-transferrin.$^7,^{10,11}$ Clinical microbiology laboratories must bear this in mind, as this practice is not routinely performed and requires labor-intensive, specific testing conditions for siderophore antibiotics.

Resistance

Little resistance to cefiderocol has thus far been demonstrated, and the exact mechanism of elevated cefiderocol MIC values has not been elucidated. One possible explanation is that bacterial resistance may occur due to enhanced expression of other siderophores present within the bacteria.$^{11}$ This effect has been observed within *P. aeruginosa* against MB-1, another siderophore/β-lactam agent. In an experiment performed by Tomaras and colleagues, MB-1 exposure led to several *P. aeruginosa* isolates developing elevated MB-1 MIC values due to overexpression of pyoverdine, a competing siderophore.$^{14}$ In mice, cefiderocol was unable to achieve bactericidal activity against these strains. The same group of authors repeated a similar experiment, instead using cefiderocol, against the same strains of *P. aeruginosa*. In this study, however, there was no evidence of overexpression of pyoverdine or elevated cefiderocol MIC values. Although these data represent only a handful of isolates, it stands to reason that cefiderocol is not
vulnerable to overexpression of the same alternative siderophores that cause resistance within other siderophore + β-lactam antibiotics.

β-lactamases could be another potential mechanism for bacterial resistance to cefiderocol. To date, however, β-lactamases have not demonstrated reliable hydrolysis of cefiderocol. In fact, cefiderocol has retained reliable activity against most β-lactamase producing bacterial isolates, including those of type NDM-1, VIM, IMP, and KPC. Ito-Horiyama and colleagues demonstrated that cefiderocol is much less easily hydrolyzed by β-lactamases, including IMP-1, VIM-2, NDM-1, KPC-3, and OXA-23, than comparators meropenem, ceftazidime, cefepime, and nitrocefin. Although the data are impressive, the mechanism of stability in the presence of various β-lactamases has yet to be elucidated, as cefiderocol is structurally very similar to ceftazidime. The stability of cefiderocol in the presence of β-lactamases warrants further investigation.

Pharmacodynamics and Pharmacokinetics

Cefiderocol has been evaluated both in vitro and in animal models to determine the most efficacious dosing strategy against gram-negative pathogens. Similar to other β-lactam antibiotics, the pharmacodynamic property most associated with activity is time above bacterial MIC. In animal models, free antibiotic time above MIC (T\textsubscript{f>MIC}) between dosing intervals of 40-70% and 55-80% demonstrate bacteriostatic and bactericidal activity, respectively, against Enterobacteriaceae, P. aeruginosa, and A. baumannii. In patients with normal renal function, the standard, 2,000 mg IV dose administered over 1 hour achieves 75% T\textsubscript{f>MIC} in 90% of bacterial isolates with cefiderocol MIC values up to 4 μg/ml.

Phase 1 data describe the pharmacokinetic parameters of cefiderocol, and it has been studied in both healthy subjects and patients with renal impairment. In healthy subjects, dose-ranging studies were performed that included 100 mg, 250 mg, 500 mg, 1,000 mg, and 2,000 mg administered intravenously over 1 hour. These doses were administered once on day 1 and every 8 hours on days 2 through 9. The 2,000-mg dose was well tolerated, with no subjects reporting relevant adverse effects, and it achieved the most favorable pharmacokinetic profile for efficacy. Among the 8 subjects that received the 2,000-mg dose, after 1 dose, cefiderocol achieved an average C\textsubscript{max} of 156 μg/ml, an average AUC\textsubscript{0-last} of 389.7 μg*hr/ml, an average t\textsubscript{1/2} of 2.74 hours, an average clearance of 5.13 L/hr, and demonstrated 61.5% unchanged excretion in urine. After 10 days of 2,000 mg every 8 hours dosing, average C\textsubscript{max} was 153 μg/ml, average AUC was 366.5 μg*hr/ml, average t\textsubscript{1/2} was 2.72 hours, average clearance was 5.46 L/hr, and 71.4% was excreted unchanged in urine. (Table 1)

### Cefiderocol PK Parameters\textsuperscript{16-18}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{max} (2,000 mg dose, 3-hour infusion)</td>
<td>89.7 (20.5) μg/mL</td>
</tr>
<tr>
<td>AUC\textsubscript{0-last} (2,000 mg, 3-hour)</td>
<td>384.8 (17.3) μg*hr/mL</td>
</tr>
<tr>
<td>t\textsubscript{1/2}</td>
<td>2.41 hr</td>
</tr>
<tr>
<td>CL</td>
<td>5.18 L/hr</td>
</tr>
<tr>
<td>f\textsubscript{e}</td>
<td>61.5%</td>
</tr>
<tr>
<td>f\textsubscript{u}</td>
<td>42%</td>
</tr>
<tr>
<td>% Removed by 3-4 hour HD</td>
<td>62.3%</td>
</tr>
</tbody>
</table>

Table 1. Average cefiderocol pharmacokinetic parameters with the 2,000 mg IV infusion over 1-hour dose at steady state from 3 studies. C\textsubscript{max} = maximum serum concentration after administration; AUC = area under the curve over dosing interval; t\textsubscript{1/2} = half-life; CL = clearance; f\textsubscript{e} = fraction excreted in urine; f\textsubscript{u} = fraction of unbound drug; HD = hemodialysis
Another phase 1 study evaluated cefiderocol pharmacokinetics, as well the potential for QTc prolongation, when the drug was administered in doses of 2,000 mg or 4,000 mg.\textsuperscript{18} 43 healthy subjects aged 18-50 were included in the study, and cefiderocol was administered via a 3-hour infusion every 8 hours. After administration of the 2,000 mg dose over 3 hours, $C_{\text{max}}$ was 89.7 μg/mL, AUC$_{0$-$\text{last}$} was 384.8 μg*hr/mL, and $t_{1/2}$ was 2.41 hours. (Table 1) The 3-hour infusion was demonstrated to provide superior $T_{\text{f}}>\text{MIC}$ compared to the 1-hour infusion and has been used in clinical studies against resistant pathogens. The authors found no evidence of cefiderocol-induced QTc prolongation in doses up to 4,000 mg, double the clinical dose.

To observe the effects of renal impairment on cefiderocol pharmacokinetics, 38 subjects with varying degrees of renal function received 1,000 mg over 1 hour.\textsuperscript{19} Subjects were classified as normal renal function (eGFR by MDRD of $\geq$90 ml/min$\cdot$1.73 m$^2$, $n = 8$), mild impairment (60-89 ml/min$\cdot$1.73 m$^2$, $n = 8$), moderate impairment (30-59 ml/min$\cdot$1.73 m$^2$, $n = 8$), severe impairment ($<30$ ml/min$\cdot$1.73 m$^2$, $n = 6$), and end-stage renal disease on hemodialysis ($n = 8$). Mild renal impairment had negligible effects on cefiderocol pharmacokinetics. In subjects with moderate renal impairment, AUC and $t_{1/2}$ were increased by a factor of 1.5 on average, and clearance was roughly 40% of normal. In subjects with severe renal impairment, AUC and $t_{1/2}$ were increased by a factor of 2.5 on average, and clearance was roughly 25% of normal. A 3 to 4-hour session of hemodialysis removed 62.3% of drug. The authors also reported that the unbound fraction of cefiderocol ranged from 0.35 to 0.47 times total drug. No serious adverse effects were experienced, even among patients who were exposed to the most amount of drug due to renal failure.

These renal data prompted the same group of authors to develop a model of cefiderocol pharmacokinetics at simulated renal functions from ESRD to augmented clearance of 150 to 200 ml/min.\textsuperscript{13} Within their model, the authors developed dosing strategies for cefiderocol based on renal function in which patients with normal and mildly impaired renal function receive 2,000 mg every 8 hours, patients with moderate renal impairment receive 1,500 mg every 8 hours, patients with severe renal impairment receive 1,000 mg every 8 hours, and patients with ESRD receive 750 mg every 12 hours.\textsuperscript{13} In patients with augmented renal clearance $\geq$120 ml/min, the authors recommend 2,000 mg every 6 hours. Of note, given the time-dependent nature of antimicrobial activity of cefiderocol, the authors recommend infusing the dose over 3 hours rather than the standard 1-hour infusion, and this dosing strategy has been employed in the currently active clinical trials and is the dose recommended in the FDA prescribing information. A table describing dosing of cefiderocol in various levels of renal impairment is included at the end of this article.

\textit{Clinical Data}

Cefiderocol gained FDA approval in November 2019 for the treatment of cUTI, including pyelonephritis, in patients who have limited or no treatment alternatives, are at least 18 years of age, and have infections caused by susceptible Gram-negative organisms requiring intravenous antimicrobial therapy. The approval came after the completion of a phase 2, randomized, double-blind, non-inferiority trial conducted at 67 hospitals in 15 countries that evaluated the safety and efficacy of cefiderocol versus imipenem-cilastatin in the treatment of cUTIs.\textsuperscript{20}

Patients were randomized 2:1 to receive cefiderocol (2 g) or imipenem/cilastatin (1 g/1 g) via 1-hour intravenous (IV) infusion every 8 hours for 7-14 days. Dose adjustments were allowed to account for renal dysfunction and/or low body weight. Notably, immunocompromised patients, such as renal transplant patients, were not excluded in effort to enroll those at risk of having resistant organisms. Additionally, the proportion of patients with acute uncomplicated pyelonephritis was capped at 30%. Patients with polymicrobial, fungal, or carbapenem-resistant urinary tract infections were excluded as were those with creatinine clearance $<20$ ml/min. At no point during treatment was transition to oral therapy permitted.
Assessments of microbiological and clinical response were completed as follows: early assessment (day 4 ± 1 day), end of treatment (last day of study drug), test of cure (7 ± 2 days after end of treatment), and follow up (2 weeks after end of treatment).

The primary endpoint of the study was a composite of clinical response and microbiological response at the test of cure assessment for those who received ≥ 1 dose of study drug and had a qualifying pathogen, the modified intention-to-treat population (MITT). Clinical response was defined as improvement or resolution of initial cUTI symptoms and without onset of new symptoms. Microbiological response was defined as quantitative urine culture with 1x10⁴ CFU/mL or less.

Four-hundred fifty-two patients were randomized to receive either cefiderocol or imipenem/cilastatin with 371 (252 in the cefiderocol group and 119 in the imipenem/cilastatin group) in the MITT population. Baseline characteristics were similar between the groups. Slightly more than half of the study population had pyelonephritis and about half of these had cUTI with pyelonephritis. Twenty percent and 17% of patients in the cefiderocol and imipenem/cilastatin groups, respectively, were considered by investigators to have severe disease. Approximately 10% of patients in either group had received antibiotic therapy in the 2 weeks before randomization. Seven percent and 5% of patients in the cefiderocol and imipenem/cilastatin groups, respectively, had pathogens that were resistant to at least three broad-spectrum antibiotics (imipenem, cefepime, piperacillin-tazobactam, and levofloxacin).

The primary composite outcome at test of cure (TOC) occurred in 183 of 252 (73%) patients in the cefiderocol group and 65 of 119 (55%) patients in the imipenem/cilastatin group (95% CI 8.23-28.92; \( p=0.0004 \)), meeting the predefined two-sided 95% confidence interval margins for non-inferiority. While clinical response rates for cefiderocol and imipenem/cilastatin at TOC were similar (90% vs 87%), microbiological response was higher with cefiderocol (73% vs 55%). Secondary endpoints included safety outcomes in addition to clinical and microbiological response per-patient and per-pathogen at various points of treatment. When comparing primary outcome per pathology, cefiderocol performed similar to imipenem/cilastatin against \( P. \text{ aerugi}nosa \) (47% vs 50%) and performed better against \( E. \text{ coli} \) (74% vs 58%) and \( K. \text{ pneumoniae} \) (74% vs 48%). Overall, adverse events were described in 41% of patients receiving cefiderocol compared to 51% receiving imipenem/cilastatin. The most common adverse events consisted of gastrointestinal syndromes, such as diarrhea and constipation. Serious adverse events occurred in 5% of patients receiving cefiderocol and 8% receiving imipenem/cilastatin. \( C. \text{ difficile} \) infection was the most common serious adverse event in both treatment groups (0.03% in cefiderocol group vs. 1% in imipenem/cilastatin group).

In this study, cefiderocol established non-inferiority to imipenem/cilastatin for the treatment of complicated urinary tract infections. Post-hoc analysis of the composite primary endpoint in all clinical diagnostic groups and analyzed populations revealed an absolute difference of 18.58%, favoring cefiderocol. The difference appeared to have been driven primarily by the higher rate of microbiological response at TOC in the cefiderocol group. The safety profile observed in the phase-2 trial was similar to the results of two previous phase-1 trials. Common adverse events, such as gastrointestinal complications and dermatitis, were generally mild and rarely lead to discontinuation of therapy.\(^{16, 17, 20}\) The adverse effect profile seems to align with other \( \beta \)-lactam antibiotics, specifically other cephalosporins. The most notable limitation was exclusion of infections caused by carbapenem-resistant organisms.\(^{20}\) Additional phase-3 studies evaluating cefiderocol compared to best available therapy in the treatment of serious infections caused by carbapenem-resistant Gram-negative infections and cefiderocol plus linezolid versus meropenem plus linezolid for the treatment of nosocomial pneumonia caused by Gram-negative pathogens are completed with results pending.\(^{21, 22}\) Of note, preliminary data from the study evaluating cefiderocol versus best available therapy (BAT) for treatment of multidrug-resistant Gram-negative pathogens are available.\(^{21}\) The CREDIBLE-CR study enrolled 150 patients
(101 cefiderocol, 49 BAT) with hospital-acquired pneumonia, bloodstream infection, or cUTI. The trial was available for analysis of descriptive statistics only. Cefiderocol demonstrated clinical cure in 42/80 (52.5%) of patients at test-of-cure compared to 19/38 (50%) of patients in the BAT group. These outcomes were similar. However, mortality among cefiderocol patients was 33.7% compared to 18.4% in the BAT arm. Independent adjudication of the causes of death was undertaken, and no direct cause of increased mortality was isolated. Upon further review, mortality considered related to antibiotic treatment failure was 15.8% in the cefiderocol arm and 8.2% in the BAT arm. Although these data are limited and do not imply causation, the difference was enough for the FDA to place a warning in the prescribing information for cefiderocol warning that it demonstrates increased mortality compared to BAT for infections due to carbapenem-resistant Gram-negative pathogens. Further study is eagerly anticipated to further define the clinical benefit of cefiderocol in these infections. A further study is currently recruiting patients to evaluate cefiderocol for the treatment of Gram-negative bloodstream infections.

As the body of evidence continues to grow, the exact place in therapy for cefiderocol will evolve. Even before there is an established role for infections other than cUTI, cefiderocol will be an attractive option for certain resistant Gram-negatives. Stenotrophomonas maltophilia harbors resistance to many antibiotics. Trimethoprim/sulfamethoxazole (TMP/SMX) remains a first-line treatment option due to high susceptibility rates. However, allergic reactions, adverse effects, and intolerance due to TMP/SMX limits its use certain populations. Cefiderocol remains active against many isolates of S. maltophilia, despite the organism’s β-lactamases, which inactivate most broad-spectrum β-lactam antibiotics, including carbapenems. Extensively drug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa are two other Gram-negatives for which cefiderocol may have a role. These organisms harbor carbapenemases, AmpC β-lactamases, and other mechanisms of resistance that limit therapeutic options. While some extensively drug-resistant A. baumannii and P. aeruginosa are still susceptible to polymyxins, cefiderocol represents a potentially safer and possibly more effective treatment option. Cefiderocol is even a welcome option for carbapenem-resistant Enterobacteriaceae, especially in light of resistance discovered to the novel β-lactam inhibitor combinations (ceftazidime/avibactam). With promising in vitro data and growing clinical data, cefiderocol may become the treatment of choice for patients with infections that would have historically received a polymyxin. Overall, cefiderocol represents a promising new antibiotic for cUTI and other infections caused by Gram-negative organisms. The novel mechanism of cell entry, spectrum of activity that includes organisms producing metallo-carbapenemases, oxacillin carbapenemases (OXA), and a safety profile similar to other cephalosporins makes cefiderocol a welcome addition to the arsenal of treatment options for multidrug-resistant Gram-negatives. Additional clinical trials will help define the best place in therapy for this novel antibiotic.

**Conclusions**

Cefiderocol, the first siderophore antibiotic to reach clinical trials, is an exciting and intriguing agent with the potential for clinical utility. It appears to be well-tolerated, it possesses predictable pharmacokinetics, and it demonstrates activity against a variety of resistant pathogens. There are still several studies to be accomplished with this agent, specifically targeting resistance that may develop upon cefiderocol exposure, that will help determine its place in the clinical armament. Thus far, however, cefiderocol represents a promising, novel therapeutic option for resistant gram-negative infections.
<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance</th>
<th>Dose</th>
<th>Frequency</th>
<th>Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;120 mL/min (augmented)</td>
<td>2,000 mg</td>
<td>Every 6 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>60-119 mL/min</td>
<td>2,000 mg</td>
<td>Every 8 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>30-59 mL/min</td>
<td>1,500 mg</td>
<td>Every 8 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>15-29 mL/min</td>
<td>1,000 mg</td>
<td>Every 8 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>ESRD with or without HD</td>
<td>750 mg</td>
<td>Every 12 hours</td>
<td>3 hours</td>
</tr>
</tbody>
</table>

Table 2. Cefiderocol dosing in various levels of renal impairment. Creatinine clearance estimated by Cockcroft-Gault equation. ESRD = end-stage renal disease; HD = hemodialysis. Doses should be given immediately after HD.

References
23. The University of Q, Shionogi. RCT Cefiderocol vs BAT for Treatment of Gram Negative BSI. 2022. "Generic"
About the authors

Jordan Smith is an Assistant Professor of Pharmacy Practice at High Point University. He is a graduate of the University of Michigan, completed residency at Moses Cone Hospital, and a two-year post-doctoral fellowship at the Anti-Infective Research Laboratory at Wayne State University.

Tyler Stone is a PGY2 infectious Diseases Pharmacy resident at Wake Forest Baptist Health where he also completed his PGY1 residency.

Instructions for Obtaining CE

The self-assessment quiz that can be found at the end of this article can be completed for 0.1 CEU of Continuing Pharmacy Education credit. The quiz may be completed online (http://madidtraining.org/newsletter/) at no cost for MAD-ID members. Non-members should print and mail the completed quiz, along with a $15.00 check made payable to MAD-ID to: MAD-ID, 537 Calico Retreat, Mt. Pleasant, SC 29464-2765. Your CE credit will be reported on CPE monitor within 4 weeks of receipt.

ACPE UAN# 0485-0000-20-019-H01-P (1.0 Contact Hour)

Knowledge-based activity.

Target audience: pharmacists and other healthcare providers (expires January 2022)

MAD-ID is accredited by the Accreditation Council for Pharmacy Education as the provider of continuing pharmacy education.
Self Assessment Questions

(To be completed online (http://mad-idtraining.org/newsletter/) or, in the case of non-MAD members, printed and mailed. You must achieve a grade of 80% of better to receive continuing education credit.)

1. Which of the following most likely best describes the ideation behind the brand name for cefiderocol, “Fetroja?” (objective 1)
   a) Fetroja is the last name of one of the discoverers of the drug
   b) Fetroja is derived from the Latin term for bacterial killer
   c) Fetroja is likely a combination of “Fe,” the chemical abbreviation for iron, and “troja,” which is short for Trojan horse
   d) Fetroja combines several elements of different names the drug was given during its development cycle

2. Which of the following descriptions of cefiderocol in vitro susceptibility data is most accurate? (objective 3)
   a) Cefiderocol demonstrates poor (<40% of isolates MIC <4 μg/mL) in vitro activity against ceftazidime/avibactam-resistant Enterobacteriaceae
   b) Cefiderocol demonstrates minimal (<20% of isolates MIC <4 μg/mL) in vitro activity against ceftolozane/tazobactam-resistant P. aeruginosa
   c) Cefiderocol demonstrates excellent (>96% of isolates MIC <4 μg/mL) in vitro activity against meropenem-resistant Acinetobacter spp.
   d) Cefiderocol demonstrates minimal (<30% of isolates MIC <4 μg/mL) in vitro activity against Stenotrophomonas maltophilia

3. Which of the following statements best describes the composite of clinical and microbiological outcomes of the phase 2 clinical trial comparing cefiderocol versus imipenem/cilastatin in the treatment of complicated UTI? (objective 4)
   a) Cefiderocol was found to be superior to imipenem/cilastatin
   b) Cefiderocol was found to be non-inferior to imipenem/cilastatin
   c) Cefiderocol was found to be inferior to imipenem/cilastatin
   d) Cefiderocol was found to be non-inferior to imipenem/cilastatin but was associated with an increased risk of adverse effects
4. Which of the following statements reflects a warning present in the FDA approval for cefiderocol? (objective 4)
   a) Cefiderocol demonstrated increased mortality compared to imipenem/cilastatin in the phase 2, cUTI trial
   b) Cefiderocol demonstrated increased mortality compared to best available therapy in a trial evaluating outcomes in patients with carbapenem-resistant pathogens
   c) Cefiderocol has an increased potential to prolong QTc interval compared to fluoroquinolone antibiotics
   d) Cefiderocol has the potential to deplete serum iron levels more than comparator agents

5. A 64-year-old female with a past medical history of lower extremity paralysis, decubitus ulceration, nephrolithiasis, and multiple episodes of UTI with extensive antibiotic exposure is admitted to the hospital with fever, flank pain, and pyuria. She is prescribed empiric meropenem, but urine cultures return positive for a P. aeruginosa isolate resistant to all antibiotics on the susceptibility panel, including meropenem, ceftolozane/tazobactam, ceftazidime/avibactam, ciprofloxacin, and aminoglycosides. What would likely be the most appropriate antibiotic choice pending additional susceptibility data? (objective 5)
   a) Plazomicin
   b) Delafloxacin
   c) Cefiderocol
   d) Eravacycline
Learning Activity Assessment

Please provide your honest assessment of the value of this learning activity so that we can continue to improve our offerings.

Please indicate your degree of agreement or disagreement with the following statements regarding this learning activity by indicating strong agreement (a), general agreement (b), no opinion (c), mild disagreement (d), or strong disagreement (e):

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Strong agreement</th>
<th>General agreement</th>
<th>No opinion</th>
<th>General disagreement</th>
<th>Strong disagreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>The information presented was relevant to my practice</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
</tr>
<tr>
<td>This program/session met the stated learning objectives</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
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</tr>
<tr>
<td>The information was presented in an objective and balanced manner without commercial bias</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
</tr>
<tr>
<td>The information presented will alter/affect my practice (usefulness)</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
</tr>
<tr>
<td>The educational materials enhanced my learning</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
</tr>
<tr>
<td>The learning method was effective</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
</tr>
<tr>
<td>The learning assessment activity (self-assessment quiz) was appropriate</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
</tr>
<tr>
<td>The faculty/authors were of appropriate quality</td>
<td>a</td>
<td>b</td>
<td>c</td>
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<td>e</td>
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</table>
OUR MISSION. The mission/purpose of the Foundation is to provide education, in the form of traditional continuing education, skills training, and other pertinent life-long learning methods, to pharmacists and other healthcare professionals concerning pharmacotherapy as it pertains to the prevention and treatment of infectious diseases and to do all things necessary or convenient to further these goals, with a special emphasis on antimicrobial stewardship.

MEMBERSHIP. Membership in MAD-ID is available to all healthcare providers, including students and post-graduate trainees, interested and/or practicing in the area of infectious diseases. For more information, visit our webpage (www.mad-id.org).

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John A. Bosso, PharmD, FCCP, FIDSA, FIDP
Medical University of South Carolina
Colleges of Pharmacy & Medicine
Charleston, SC

Eileen Carter, PhD, RN
Assistant Professor of Nursing
Columbia School of Nursing and Nurse Researcher New York – Presbyterian Hospital
New York, NY

Susan L. Davis, PharmD, FIDP
Eugene Applebaum College of Pharmacy & Health Sciences, Wayne State University and Henry Ford Hospital
Detroit, MI

Debra A. Goff, PharmD, FCCP
The Ohio State University Wexner Medical Center
Columbus, OH

Keith S. Kaye, MD, MPH, FIDSA, FSHEA, FACP
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St. Louis, MO

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Professor of Pharmacy, University of Rhode Island, Kingston, RI
Adjunct Professor of Medicine, Brown University, Providence, RI

Michael J. Rybak, PharmD, MPH, PhD, FCCP, FIDSA, FIDP
Eugene Applebaum College of Pharmacy & Health Sciences, Wayne State University
Detroit, MI

Edward J. Septimus, MD, FIDSA, FACP, FSHEA
Texas A&M Medical School
Houston, TX

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