Clostridioides difficile is an anaerobic, spore-forming, toxin-producing gram-positive rod that causes antibiotic-associated colitis. Over the last decade, the frequency and severity of C difficile infection (CDI) has been increasing worldwide, and it is now one of the most common hospital-acquired infections. We have

Emerging & Re-Emerging Infections

C Difficile: Are We Making Progress?
By Charles R. Bornmann, MD; and Yoav Golan, MD, MS, FIDSA

Clostridioides difficile is an anaerobic, spore-forming, toxin-producing gram-positive rod that causes antibiotic-associated colitis. Over the last decade, the frequency and severity of C difficile infection (CDI) has been increasing worldwide, and it is now one of the most common hospital-acquired infections. We have

HIV/AIDS

Novel Salvage Therapy for Multidrug-Resistant HIV Infection
By Maliha Ahmed, DO

Multidrug-resistant HIV, although less common than in the past, remains a problem among people living with HIV (PLWH). At least 2 fully active agents with novel mechanisms of action are recommended in the setting of salvage therapy. In this review, we will discuss these 2 recently approved antiretroviral medications, ibalizumab and fostemsavir, and their

Stewardship & Prevention

The Role of Antimicrobial Stewardship in the Treatment of C diff
By Helen G. Berhane, PharmD; and Jennifer N. Curello, PharmD, BCIDP

Biologics have traditionally been used to treat patients with cancer and various inflammatory diseases. More recently, biologics have emerged as a novel treatment modality in recurrent Clostridioides difficile infection (CDI). Currently, the recommended first-line treatment for CDI

ACUTE INFECTIONS

Holiday Guest List—When the Uninvited Arrive: COVID-19 and Coinfections
By Clayton Mowrer, DO, MBA; and Kelly Cawcutt, MD, MS, FACP

Winter, riding in on the coattails of autumn, is just starting to make its appearance. The leaves have tumbled gracefully from the trees, and the bite in the air and the possibility of snow on the ground has forced some of us to don our insulated clothing and cozy up indoors with the fireplace crackling in the background. Despite the familiarity and comfort during this time of year, there is also uncertainty—a foreign, obscure landscape that we are still learning to navigate: coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has upended our lives this year. Despite the continued threat of this pandemic, large family gatherings, holiday traveling, and crowding

(continued on page 16)
Fetroja—outsmarts pathogens by using iron to gain cell entry, like a Trojan horse.\textsuperscript{1,2}

Stable in vitro against all known classes of $\beta$-lactamases, including serine-carbapenemases (such as KPC and OXA) and metallo-$\beta$-lactamases (such as VIM, IMP, and NDM).\textsuperscript{3,4}

Active against pathogens with porin channel deletions and efflux pump up-regulation.\textsuperscript{1,2}

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with Fetroja than in patients treated with BAT [25/101 (24.8\%) vs 9/49 (18.4\%), treatment difference 6.4\%, 95\% CI (−8.6\%, 19.2\%)]. All-cause mortality remained higher in patients treated with Fetroja than in patients treated with BAT through Day 49 [34/101 (33.7\%) vs 10/49 (20.4\%), treatment difference 13.3\%, 95\% CI (2.5\%, 26.9\%)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as Acinetobacter baumannii complex, Stenotrophomonas maltophilia, and Pseudomonas aeruginosa, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed in Fetroja-treated patients in clinical trials. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.
Fetroja has an extensive Gram-negative spectrum that includes hard-to-treat pathogens

Fetroja has demonstrated activity against the following Gram-negative bacteria, both in vitro and in HABP/VABP:
- Acinetobacter baumannii complex, *Escherichia coli*, Enterobacter cloacae complex*, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens*

*Also included in cuti indication.

Fetroja is highly active in vitro vs Gram-negative carbapenem-NH pathogens

In this study, susceptibility of >38,000 Gram-negative clinical isolates from multiple countries (2013–2018) was tested against Fetroja

In vitro activity does not necessarily correlate with clinical efficacy.

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>P aeruginosa</th>
<th>A baumannii complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>[≥25 μg/mL]</td>
<td>[≥1 μg/mL]</td>
</tr>
<tr>
<td>Carbapenem-non-susceptible</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Overall</td>
<td>[≥1 μg/mL, 1 μg/mL]</td>
<td>[≥1 μg/mL]</td>
</tr>
<tr>
<td>Carbapenem-non-susceptible</td>
<td>100%</td>
<td>95%</td>
</tr>
</tbody>
</table>

In vitro susceptibility study design

Clinical isolates of Gram-negative bacteria were collected from 4 global surveillance studies (SIDERO-WT-2014, SIDERO-WT-2015, SIDERO-WT-2016, and SIDERO-WT-2018) that included Enterobacteriaceae* and non-fermenter strains. The global surveillance study (PROTEUS*) collected clinical isolates from 2013–2016, and were tested centrally (HLMA Inc., Schaumburg, IL, USA). Fetroja MICs were determined by broth dilution using non-depleted Mueller–Hinton broth (BD-CAMHB) as approved by the Clinical and Laboratory Standards Institute (CLSI) subcommittee on antimicrobial susceptibility testing in January 2016. FDA breakpoints were used for Enterobacteriales M. 14 μg/mL, *P. aeruginosa* MIC 1 μg/mL, and A. baumannii complex MIC 1 μg/mL, whereas CLSI investigative breakpoint was used for *S. maltophilia* MIC ≥4 μg/mL. Carbapenem-non-susceptible strain was defined as meropenem MIC ≥2 μg/mL, for Enterobacteriales strains (including *P. aeruginosa* and *A. baumannii* complex). FDA breakpoints used for Enterobacteriales M. 14 μg/mL, *P. aeruginosa* MIC 1 μg/mL, and A. baumannii complex MIC 1 μg/mL.

- **CLSI** investigational breakpoint used for *S. maltophilia* MIC ≥4 μg/mL.
- **EF cut-off** used *K. pneumoniae*, other *Klebsiella spp.*, Enterobacter spp., *Serratia spp.*, and *Citrobacter sp.*
- *Morganella morganii*, *P. mirabilis*, *Proteus vulgaris*, and *Providencia rettgeri*.
- *A. baumannii complex* consists of *A. baumannii*, *A. calcoaceticus*, *A. dhakensis*, *A. nosocomialis*, *A. pittii*, and *A. seotellae*.

**IMPORTANT SAFETY INFORMATION (continued)**

WARNINGS AND PRECAUTIONS (continued)

Hypersensitivity Reactions (continued)

Before therapy with Fetroja is instituted, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibiotic drugs. Discontinue Fetroja if an allergic reaction occurs.

Clostridoides difficile-associated Diarrhea (CDAD)

Clostridoides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Fetroja. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterial drugs not directed against *C. difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

In a seriously ill patient population with HABP or VABP, Fetroja exhibited non-inferiority to extended-infusion, high-dose meropenem

- **Study highlights:**
  - Meropenem was used as a comparator in the trial and was optimized (2 grams IV over 3 hours) for seriously ill patients with a multidrug-resistant Gram-negative infection in the ICU.
  - 60% of patients were ventilated, while approximately 33% had failed empiric treatment.
  - The top 5 baseline Gram-negative pathogens were *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *E. coli*, and *E. cloacae*.
  - At Day 14, all-cause mortality (primary endpoint) in the miTT population was 12.4% for Fetroja vs 12.2% for extended-infusion, high-dose meropenem (95% CI, -7.2, 7.7).

Fetroja exhibited comparable safety vs extended-infusion, high-dose meropenem in HABP/VABP

Study Design

Multicenter, double-blind, parallel-group, randomized, active-controlled Phase 3 study in approximately 300 adults with documented nosocomial pneumonia caused by Gram-negative bacteria. Subjects were randomized (1:1) to either cefiderocol, 2 grams, administered IV over 3 hours every 8 hours (q8h) or extended-infusion, high-dose meropenem, 2 grams, administered IV over 3 hours q8h. Randomization was performed by the stratified randomization method using their infection diagnosis (HABP, VABP, and HCABP) and Acute Physiology And Chronic Health Evaluation II (APACHE II) score (≥15 and ≥16) as allocation factors. Linezolid was administered for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant Staphylococcus aureus (MRSA), and to maintain the study blind.

Seizures and Other Central Nervous System (CNS) Adverse Reactions

Cephalosporins, including Fetroja, have been implicated in triggering seizures. Nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust Fetroja dosing based on creatinine clearance. Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether Fetroja should be discontinued.

Development of Drug-Resistant Bacteria

Prescribing Fetroja in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS

The most common adverse reactions occurring in ≥2% of patients receiving Fetroja compared to imipenem/cilastatin in the CUTI trial were: diaphragnic [4% vs 6%], infusion site reactions [4% vs 5%], constipation [3% vs 4%], rash [3% vs 4%], candidiasis [2% vs 3%], cough [2% vs 1%], elevations in liver tests [2% vs 3%], headache [2% vs 5%], hypokalemia [2% vs 3%], nausea [2% vs 4%], and vomiting [2% vs 1%]. The most common adverse reactions occurring in ≥4% of patients receiving Fetroja compared to meropenem in the HABP/VABP trial were: elevations in liver tests [16% vs 16%], hypokalemia [11% vs 15%], diarrhea [9% vs 9%], hypomagnesemia [5% vs 1%], and atrial fibrillation [5% vs 3%].

Please see a Brief Summary of Prescribing Information on following page.

References:
FETROJA (cefiderocol) for injection, for intravenous use

Initial U.S. Approval: 2019

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Complicated Urinary Tract Infections (cUTIs), Including Pyelonephritis

FETROJA is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Enterobacter cloacae complex. [see Clinical Studies (14.1) in the full prescribing information].

1.2 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

FETROJA is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens. [see Clinical Studies (14.2) in the full prescribing information].

1.3 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FETROJA and other antibacterial drugs, FETROJA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4 CONTRAINdicATIONS

FETROJA is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of FETROJA. [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Bacterial Infections

An increase in all-cause mortality was observed in patients treated with FETROJA as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with FETROJA than in patients treated with BAT (25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (1.8, 16.2%). All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 (34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI [-2.5, 26.9]). Generally, deaths were adjudicated patients with infections caused by Gram-negative organisms, including non-fermenters such as Acinetobacter baumannii complex, Pseudomonas maltophilia, and Pseudomonas aeruginosa, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

5.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs.

Hypersensitivity was observed in FETROJA-treated patients in clinical trials [see Adverse Reactions (6.1)]. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cefiderocol.

Before therapy with FETROJA is instituted, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibacterial drugs. Discontinue FETROJA if an allergic reaction occurs.

5.3 Clositudioides difficile-associated Diarrhea (CDAD)

Clositudioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including FETROJA. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Cefiderocol therapy may cause breakthrough CDAD due to overgrowth of C. difficile has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial drugs not directed against C. difficile may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of C. difficile, and institute surgical evaluation as clinically indicated.

5.4 Seizures and Other Central Nervous System (CNS) Adverse Reactions

Cephalosporins, including FETROJA, have been implicated in triggering seizures [see Adverse Reactions (6.1)]. Nonconvulsive status epilepticus (NCSÉ), encephalopathy, coma, astersia, neuromuscular excitability, and myclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust FETROJA dosing based on creatinine clearance [see Dosage and Administration (2.2) in the full prescribing information]. Anticonvulsant therapy should be continued in patients with known severe disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether FETROJA should be discontinued.

5.5 Development of Drug-Resistant Bacteria

Prescribing FETROJA in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Indications and Usage (1.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described in greater detail in the Warnings and Precautions section.

- Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.2)]
- Clositudioides difficile-associated Diarrhea (CDAD) [see Warnings and Precautions (5.3)]
- Seizures and Other Central Nervous System Adverse Reactions [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Complicated Urinary Tract Infections (cUTIs), Including Pyelonephritis

FETROJA was evaluated in an active-controlled, randomized clinical trial in patients with cUTI, including pyelonephritis (Trial 1). In this trial, 300 patients received FETROJA 2 grams every 8 hours infused over 1 hour (or a renally-adjusted dose), and 148 patients were treated with imipenem/cilastatin 1 gram every 6 hours infused over 1 hour (or a renally-adjusted dose). The median age of treated patients across treatment arms was 65 years (range 18 to 93 years), with approximately 53% of patients aged greater than or equal to 65. Approximately 96% of patients were White, most were from Europe, and 55% were female. Patients across treatment arms received treatment for a median duration of 9 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In Trial 1, a total of 14/300 (4.7%) cUTI patients treated with FETROJA and 12/148 (8.1%) of patients treated with imipenem/cilastatin experienced serious adverse reactions. One death (0.3%) occurred in 300 patients treated with FETROJA as compared to none treated with imipenem/cilastatin. Discontinuation of treatment due to any adverse reaction occurred in 5/300 (1.7%) of patients treated with FETROJA and 3/148 (2.0%) of patients treated with imipenem/cilastatin. Specific adverse reactions leading to treatment discontinuation in patients who received FETROJA included diarrhea (0.3%), drug hypersensitivity (0.3%), and increased hepatic enzymes (0.3%).

Common Adverse Reactions

Table 4 lists the most common selected adverse reactions occurring in ≥ 2% of cUTI patients receiving FETROJA in Trial 1.

Table 4 Selected Adverse Reactions Occurring in ≥ 2% of cUTI Patients Receiving FETROJA in Trial 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FETROJAa (N = 300)</th>
<th>Imipenem/Cilastatinb (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Infusion site reactionsa</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Rashb</td>
<td>3%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Candidiasisa</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>2%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Elevations in liver testsb</td>
<td>2%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Headache</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

(continued)
groups were elevated liver tests. Patients treated with FETROJA and 14/150 (9.3%) of patients treated with meropenem. Adverse reactions leading to death were reported in 39/148 (26.4%) treated with FETROJA and 45/150 (30%) of HABP/VABP patients treated with meropenem. 2 grams IV over 1 hour (with dosing adjustment based on renal function).

Table 5 lists the most common selected adverse reactions occurring in ≥ 4% of patients receiving FETROJA in the HABP/VABP trial.

Table 4 Selected Adverse Reactions Occurring in ≥ 2% of cUTI Patients Receiving FETROJA in Trial 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FETROJA* (N = 300)</th>
<th>Imipenem/Cilastatin* (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Other Adverse Reactions of FETROJA in the cUTI Patients (Trial 1)

The following selected adverse reactions were reported in FETROJA-treated cUTI patients at a rate of less than 2% in Trial 1:

Blood and lymphatic disorders: thrombocytopenia, neutropenia, anemia, leukopenia, lymphopenia
Cardiac disorders: atrial fibrillation, atrial flutter, ventricular arrhythmia, conduction disorder
Gastrointestinal disorders: nausea, vomiting, diarrhea, abdominal pain, pancreatitis, hepatic steatosis, upper gastrointestinal hemorrhage
Hematological disorders: neutropenia, anemia, lymphopenia
Hepatobiliary disorders: cholelithiasis, cholecystitis, gallbladder pain
Immune system disorders: drug hypersensitivity
Infections and infestations: C. difficile infection
Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), red blood cells, urine protein, creatinine, liver function test abnormal, hepatic enzyme increased, liver test abnormal
Psychiatric disorders: insomnia, restlessness
Skin and subcutaneous tissue disorders: rash, including rash erythematous
Vascular disorders: hypotension

Other Adverse Reactions of FETROJA in HABP/VABP Patients in Trial 2

The following selected adverse reactions were reported in FETROJA-treated HABP/VABP patients at a rate of less than 4% in Trial 2:

Blood and lymphatic disorders: thrombocytopenia, thrombocytosis
Cardiac disorders: myocardial infarction, atrial flutter, ventricular arrhythmia, conduction disorder
Gastrointestinal disorders: nausea, vomiting, abdominal pain, pancreatitis, cholelithiasis, cholecystitis
Hepatobiliary disorders: cholecystitis, cholelithiasis
Infections and infestations: C. difficile infection, oral candidiasis
Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), activated partial thromboplastin time (APTT)
Metabolism and nutrition disorders: hypocalcemia, hyperkalemia
Nervous system disorders: seizures, syncope
Renal and genitourinary disorders: acute interstitial nephritis
Respiratory, thoracic, and mediastinal disorders: cough
Skin and subcutaneous tissue disorders: rash including rash erythematous

7 DRUG INTERACTIONS

7.1 Drug/Laboratory Test Interactions

Cefiderocol may result in false-positive results in dipstick tests (protein, ketones, or occult blood). Use alternate clinical laboratory methods of testing to confirm positive tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on FETROJA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no available data on FETROJA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no available data on FETROJA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports have not identified an association with cefepime use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Developmental toxicity studies with cefiderocol administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses providing exposures of 0.9 times (rats) or 1.3 times (mice) higher than the average observed in patients receiving the maximum recommended daily dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 1% to 2%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Animal Data

Developmental toxicity was not observed in rats at intravenous doses of up to 1000 mg/kg/day or mice at subcutaneous doses of up to 2000 mg/kg/day given during the period of organogenesis (gestation days 6-17 in rats and 6-15 in mice). No treatment-related malformations or reductions in fetal viability were observed. Mean plasma exposure (AUC) at these doses was approximately 0.9 times (rats) and 1.3 times (mice) the daily mean plasma exposure in patients that received 2 grams of cefiderocol infused intravenously every 8 hours.

In a pre- and postnatal development study, cefiderocol was administered intravenously at doses up to 1000 mg/kg/day to rats from Day 6 of pregnancy until weaning. No adverse effects on parturition, maternal function, or pre- and postnatal development and viability of the pups were observed. In pregnant rats, cefiderocol-derived radioactivity was shown to cross the placenta, but the amount detected in fetuses was a small percentage (< 0.5%) of the dose.

8.2 Lactation

Risk Summary

It is not known whether cefiderocol is excreted into human milk; however, cefiderocol-derived radioactivity was detected in the milk of lactating women that received the drug intravenously. When a drug is present in human milk, it is likely that the drug will be present in human milk. No information is available on the effects of FETROJA on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for FETROJA and any potential adverse effects on the breastfed child from FETROJA or from the underlying maternal condition.

Other Adverse Reactions of FETROJA in HABP/VABP Patients in Trial 2

Table 5 Selected Adverse Reactions Occurring in ≥ 2% of HABP/VABP Patients Receiving FETROJA in Trial 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FETROJA* (N = 148)</th>
<th>Meropenem* (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevations in liver tests</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>5%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1 NABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia
2 2 grams IV over 3 hours every 8 hours (with dosing adjustment based on renal function).
3 Elevations in liver tests include alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, transaminases increased, hepatic enzyme increased, liver test abnormal.
4 Hypokalemia includes blood potassium decreased.
Cefiderocol-derived radioactivity was detected in milk following intravenous administration to lactating rats. The peak level in rat milk was approximately 6% of the peak plasma level.

### 8.4 Pediatric Use

Safety and effectiveness of FETROJA in pediatric patients younger than 18 years of age have not been established.

### 8.5 Geriatric Use

#### cUTI

Of the 300 patients treated with FETROJA in the cUTI trial, 158 (52.7%) were 65 years of age and older, and 67 (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

Of the 148 patients treated with FETROJA in the HABP/VABP trial, 83 (56.1%) were 65 years of age and older, and 40 (27%) were 75 years of age and older. The incidence of adverse reactions in patients treated with FETROJA was similar in patients under 65 years of age as compared to older patients (65 years of age and older and 75 years of age and older). The incidence of adverse reactions in older patients (65 years of age and older and 75 years of age and older) was also similar between treatment groups.

Clinical cure rates at the Test-of-Cure visit (TOC) in FETROJA-treated adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age and 75 years of age and older were 60.0%, 77.5%, and 60.0%, respectively. In comparison, the clinical cure rates at the TOC visit in the meropenem-treated patients for each of these subgroups were 65.5%, 64.4%, and 70.5%, respectively. The observed all-cause mortality rates at Day 14 in the FETROJA-treated patients for each of these subgroups were 12.3%, 7.5%, and 17.5%, respectively. In comparison, in the meropenem-treated patients for each of these subgroups, they were 10.3%, 17.8%, and 9.1%, respectively.

#### cUTI and HABP/VABP

FETROJA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. No dosage adjustment is required based on age. Dosage adjustment for elderly patients should be based on renal function [see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3) in the full prescribing information].

### 8.6 Renal Impairment

#### Patients with CLcr 60 to 89 mL/min

No dosage adjustment of FETROJA is recommended in patients with CLcr 60 to 89 mL/min.

#### Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Dose adjustment is required in patients with CLcr less than 60 mL/min, and in patients who are receiving HD. In patients requiring HD, complete HD at the latest possible time before the start of cefiderocol dosing [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]. Monitor renal function regularly and adjust the dosage of FETROJA accordingly as renal function may change during the course of therapy.

### Patients Receiving CRRT

A total of 16 patients treated with FETROJA received CRRT in clinical trials. Dosage adjustment of FETROJA is required in patients receiving CRRT including CVVH, CVVHD, and CVVHD. Dosage of FETROJA should be based on the effluent flow rate in patients receiving CRRT [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]. While on CRRT, a patient’s residual renal function may change. Improvements or reductions in residual renal function may warrant a change in FETROJA dosage.

#### Patients with CLcr 120 mL/min or Greater

CLcr 120 mL/min or greater may be seen in seriously ill patients, who are receiving intravenous fluid resuscitation. Dosage adjustment of FETROJA is required in patients with CLcr 120 mL/min or greater [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]. Monitor renal function regularly and adjust the dosage of FETROJA accordingly as renal function may change during the course of therapy.

### 8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of cefiderocol have not been evaluated. Hepatic impairment is not expected to alter the elimination of cefiderocol as hepatic metabolism/excretion represents a minor pathway of elimination for cefiderocol. Dosage adjustments are not necessary in patients with impaired hepatic function.

### 10 OVERDOSAGE

There is no information on clinical signs and symptoms associated with an overdose of FETROJA. Patients who receive doses greater than the recommended dose regimen and have unexpected adverse reactions possibly associated with FETROJA should be carefully observed and given supportive treatment, and discontinuation or interruption of treatment should be considered. Approximately 60% of cefiderocol is removed by a 3- to 4-hour hemodialysis session [see Clinical Pharmacology (12.3) in the full prescribing information].

Manufactured by
Shionogi Inc.
Florham Park, NJ
USA, 07932

FET-PI-02A
USP-247 09/20
or advertisements, contained in this publica-
ration of any kind about the completeness,
Right: to alter or correct any error or omission
further disclaims any and all liability for
squares, and other damages arising from
The reader is encouraged to confirm the
Any direct, indirect, consequential, special,
expressed in this publication are those of the
The content contained in this publication is
The copyright holder reserves the
reserves the
Copyright © 2020 by Intellisphere, LLC. All
Shari Lundenberg
Executive Vice President, Mergers &
EDMOND A. HOOKER, MD, DRPH
Xavier University, Cincinnati, Ohio
KIRK HEVENER, PHARMD, PhD
College of Pharmacy
Memphis, Tennessee
EDMUND A. HOOKER, MD, DRPH
Xavier University, Cincinnati, Ohio
KING ABDULAZIZ UNIVERSITY
Jeddah, Saudi Arabia
KHALID ELJALALY, PHARMD, BCPS, CAPPS
College of Pharmacy
The University of Arizona
Tucson, Arizona
ROBERT BRANSFIELD, MD, DLFAPA
Robert Wood Johnson Medical School
Rutgers University
New Brunswick, New Jersey
MARTA CAVALCANTI, MD, PHD
Infectious Disease Clinic Hospital Universitario Clementino Fraga Filho Department of Immunology Instituto de Microbiologia de Paulo de Goes Universidade Federal do Rio de Janeiro
Rio de Janeiro, Brazil
KELLY CAMCUTT, MD, MS, FACP
Infectious Diseases & Critical Care Medicine University of Nebraska Medical Center
Omaha, Nebraska
CARLOS DEL RIO, MD
Emory Vaccine Center
Emory Center for AIDS Research Atlanta, Georgia
DAVID VAN DUIN, MD, PHD
University of North Carolina School of Medicine
Chapel Hill, North Carolina
KHALID ELJALALY, PHARMD, BCPS, CAPPS
College of Pharmacy
The University of Arizona
Tucson, Arizona
JASON POUGUE, PHARMD, BCPS, BCIDP
University of Michigan College of Pharmacy
Ann Arbor, Michigan
MADELINE KING, PHARMD, BCIDP
Philadelphia College of Pharmacy University of the Sciences Philadelphia, Pennsylvania
JAMES S. LEWIS, PHARMD, FIDSA
Oregon Health and Science University
Portland, Oregon
CONAN MACDOUGALL, PHARM, MAS, BCPS, BCIDP
University of California
San Francisco
San Francisco, California
MONICA V. MAHONEY, PHARMD, BCPS-AQ ID
Beth Israel Deaconess Medical Center
Boston, Massachusetts
BRIONNA MATT, DO
Infectious Disease Physician
Temple University Hospital Philadelphia, Pennsylvania
CHRISTOPHER MCCOY, PHARMD, BCPS-AQ ID, BCIDP
Beth Israel Deaconess Medical Center
Boston, Massachusetts
JOHN MOHR, PHARMD
Medical Affairs Strategic Solutions Acton, Massachusetts
Medical Affairs scPharmaceuticals
Lexington, Massachusetts
MARCIAL NAILOR, PHARMD, BCPS-AQ ID
School of Pharmacy
University of Connecticut
Storrs, Connecticut
PAYAL K. PATEL, MD, MPH Institute for Healthcare Policy & Innovation University of Michigan
Ann Arbor, Michigan
ELIZABETH PHILLIPS, MD, FACP, FRCPC, FRACP
Division of Infectious Diseases University of Michigan College of Medicine
Ann Arbor, Michigan
MICHAEL J. RYBAK, PHARMD, MPH, PhD
Anti-Infective Research Laboratory Eugene Applebaum College of Pharmacy & Health Sciences Wayne State University
Detroit, Michigan
CASSANDRA D. SALGADO, MD, MS
Department of Internal Medicine Medical University of South Carolina Charleston, South Carolina
PAUL E. SAX, MD Brigham and Women's Hospital Harvard Medical School Boston, Massachusetts
JASON J. SCHAFER, PHARMD, MPH, BCIDP, AHIHP
Jefferson College of Pharmacy
Thomas Jefferson University Philadelphia, Pennsylvania
ADRIANO DE BERNARDI SCHNEIDER, PHD
Postdoctoral Scholar Department of Medicine University of California, San Diego
SARA SCHULTZ, MD, FACP Division of Infectious Diseases & Human Virology Drexel College of Medicine Philadelphia, Pennsylvania
OTTO SCHWAKE, PHD Department of Civil and Environmental Engineering Virginia Tech Blacksburg, Virginia
DAVID A. SCHWARTZ, MD, MS HYG, FCAP Medical College of Georgia Augusta University Augusta, Georgia
EDWARD J. SEPTIMUS, MD, FIDSA, FACP, FSHEA Department of Population Health Harvard Medical School Boston, Massachusetts
SHMUEL SHOHAM, MD Transplant and Oncologic Infectious Diseases Program Johns Hopkins University School of Medicine Baltimore, Maryland
KATHLEEN SQUIRES, MD Merck Research Laboratories Philadelphia, Pennsylvania
AUDREY STEVENSON, PHD, MPH, MSN, FNP-BC Salt Lake County Health Department Salt Lake City, Utah
GLENN TILLOTSON, PHD, FIDSA Consultant Microbiologist Henrico, Virginia
PEDRO FERNANDO DA COSTA VASCONCELOS, MD, PHD WHO Collaborating Center for Arboviruses and Research Instituto Evandro Chagas Ananindeua, Brazil
JOSE A. VAZQUEZ, MD, FACP, FIDSA Division of Infectious Diseases Medical College of Georgia at Augusta University Augusta, Georgia
CARMEN ZORRILLA, MD School of Medicine University of Puerto Rico San Juan, Puerto Rico
Questions related to editorial content and submissions should be sent to Editorial Director Alexandra Ward, MA, AWARD@MJHLIFESCIENCES.COM.
† Active members of the Society of Infectious Diseases Pharmacists (SIDP)
† Active member of MAD-ID (Making a Difference in Infectious Diseases)
† Contagion® Section Editor

WENDY M. BAMBERG, MD†
Medical Epidemiology Consulting Denver, Colorado
BRANDON BOOKSTOWER, PHARM, FCP, FIDSA, BCPS, AHIHP†
College of Pharmacy
University of South Carolina Columbia, South Carolina
ROBERT BRANSFIELD, MD, DLFAPA
Robert Wood Johnson Medical School Rutgers University New Brunswick, New Jersey
MARTA CAVALCANTI, MD, PHD
Infectious Disease Clinic Hospital Universitario Clementino Fraga Filho Department of Immunology Instituto de Microbiologia de Paulo de Goes Universidade Federal do Rio de Janeiro Rio de Janeiro, Brazil
KELLY CAMCUTT, MD, MS, FACP
Infectious Diseases & Critical Care Medicine University of Nebraska Medical Center Omaha, Nebraska
CARLOS DEL RIO, MD
Emory Vaccine Center Emory Center for AIDS Research Atlanta, Georgia
DAVID VAN DUIN, MD, PHD
University of North Carolina School of Medicine Chapel Hill, North Carolina
KHALID ELJALALY, PHARMD, BCPS, CAPPS
College of Pharmacy The University of Arizona Tucson, Arizona
King Abdulaziz University Jeddah, Saudi Arabia
DEBRA A. GOFF, PHARMD, FCCP
The Ohio State University Wexner Medical Center Columbus, Ohio
JEAN PAUL J. GONZALES, MD, PHD Center of Excellence for Emerging & Zoonotic Animal Disease Kansas State University Manhattan, Kansas
ALAN GROSS, PHARMD, BCPS-AQID
College of Pharmacy University of Illinois at Chicago Chicago, Illinois
EMILY HEIL, PHARMD, BCPS-AQ ID, BCIDP† School of Pharmacy University of Maryland Baltimore, Maryland
KIRK HEVENER, PHARMD, PhD† College of Pharmacy University of Tennessee Memphis, Tennessee
EDMUND A. HOOKER, MD, DRPH Xavier University Cincinnati, Ohio
KENG O INAGAKI, MD University of Michigan Ann Arbor, Michigan
NORMAN B. JAVITT, MD, PHD NYU School of Medicine New York, New York
MEGHAN JEFFRES, PHARMD Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Aurora, Colorado
LEAH JOHNSON, PHD RTI International Research Triangle Park North Carolina
JULIE ANN JUSTO, PHARMD, MS, BCPS-AQ ID University of South Carolina College of Pharmacy Columbia, South Carolina
KEITH S. KAYE, MD, MPH† Division of Infectious Diseases University of Michigan Medical School Ann Arbor, Michigan
MADELINE KING, PHARMD, BCIDP Philadelphia College of Pharmacy University of the Sciences Philadelphia, Pennsylvania
JAMES S. LEWIS, PHARMD, FIDSA Oregon Health and Science University Portland, Oregon
CONAN MACDOUGALL, PHARM, MAS, BCPS, BCIDP† University of California San Francisco San Francisco, California
MONICA V. MAHONEY, PHARMD, BCPS-AQ ID† Beth Israel Deaconess Medical Center Boston, Massachusetts

Copyright © 2020 by intellisphere, LLC. All rights reserved.
The content contained in this publication is for general information purposes only. The reader is encouraged to confirm the information presented with other sources. Contagion® makes no representations or warranties of any kind about the completeness, accuracy, timeliness, reliability, or suitability of any information, including content or advertisements, contained in this publication and expressly disclaims liability for any errors and omissions that may be presented in this publication. Contagion® reserves the right to alter or correct any error or omission in the information it provides in this publication, without any obligations. Contagion® further disclaims any and all liability for any direct, indirect, consequential, special, exemplary, or other damages arising from the use or misuse of any material or information presented in this publication. The views expressed in this publication are those of the authors and do not necessarily reflect the opinion or policy of Contagion®.

Subscription to Contagion® at Contagionlive.com, or use a smartphone to scan this QR code.

2 Clarke Drive, Suite 100 Cranbury, NJ 08512 • (609) 716-7777
## TABLE OF CONTENTS

### ACUTE INFECTIONS

**Holiday Guest List—When the Uninvited Arrive: COVID-19 and Coinfections**

*The confluence of seasonal viruses and COVID-19 leaves clinicians uncertain about the coming months.*

**BY CLAYTON MOWRER, DO, MBA; AND KELLY CAWCUTT, MD, MS, FACP**

### EMERGING & RE-EMERGING INFECTIONS

**C Difficile: Are We Making Progress?**

*A review of progress made and some newer therapies.*

**BY CHARLES R. BORNMANN, MD; AND YOAV GOLAN, MD, MS, FIDSA**

### HIV/AIDS

**Novel Salvage Therapy for Multidrug-Resistant HIV Infection**

*An examination of 2 agents with novel mechanisms of action.*

**BY MALIHA AHMED, DO**

### MULTIDRUG-RESISTANT INFECTIONS

**IDSA Guidance on the Treatment of Antimicrobial Resistant Gram Negative Infections**

*The new guidance is a living document with updated recommendations and revisions.*

**BY CORNELIUS J. CLANCY, MD; AND SAMUEL L. AITKEN, PHARM D**

### STEWARDSHIP & PREVENTION

**The Role of Antimicrobial Stewardship in the Treatment of Clostridioides difficile Infection**

*An examination of therapies.*

**BY HELEN G. BERHANE, PHARM D, AND JENNIFER N. CURELLO, PHARM D, BCIDP**

### PEER EXCHANGE

**Emerging Options for Treatment and Prevention of HIV Infection**

**BY GINA BATTAGLIA, PHD**

### MEETING COVERAGE

**Catch up on session coverage and featured interviews from IDWeek 2020.**

### CASE STUDY

**A Case of Pneumonia and Bacteremia in a Trauma Patient Caused by Bordetella hinzii**

**BY ELIZABETH NOVICK, MD, AND REBECCA MOON**

---

**IN THE LITERATURE**

**Entering the Phase of Phase: A Closer Look at Bacteriophage Therapy**

**BY MEAGAN ADAMSICK, PHARM D**

**Afabinicin: A Novel, Narrow-Spectrum Antistaphylococcal Agent**

**BY HUMNA N. MEER, PHARM D CANDIDATE; AND KIRK E. HEVENER, PHARM D, PHD**

**Learn more on the latest clinical innovations and challenges in COVID-19 care.**

**NEWS & BREAKTHROUGHS**

**Fostemsavir for Multidrug Resistant HIV-1: It’s Time for HIV to Overcome its Attachment Issues With Our CD4 Cells**

**BY AMY L. BROTHERTON, PHARM D, AAHIVP, BCIDP; AND RAJEEV SHAH, PHARM D, AAHIVP, BCIDP**

**CONNECT WITH US ON SOCIAL MEDIA**

- @Contagion_Live
- @Contagion_Live
- @Contagion_Live
- @Contagion_Live
- @Contagion_Live

**COVER IMAGE CREDIT TO ANGLELU, VALENIKER, SIRICHAI/ ADOBE STOCK**

**ILLUSTRATION BY PATRICK WELSH**

*PAT@PATRICKWELSH.COM**
Return to Stewardship: A 2021 Resolution

A SECONDHAND EFFECT of the coronavirus disease 2019 (COVID-19) pandemic on the infectious disease community this year came not from the disease itself, but from the mystery of its mechanism.

Undoubtedly, as we reflect on this year in medicine, we will instinctually look to how COVID-19 burdened our health care systems and attacked our previously unchallenged systemic means of fighting, managing, and preventing diseases. This was the year of the modern pandemic; that will always headline discussion about 2020.

Beyond the totality of the virus, the infectious disease community is now tasked with righting course on a goal nearly derailed by the pandemic: stewardship.

At IDWeek 2020, among the hallmark meetings for annual infectious disease collaboration, experts repeated a message on returns to stewardship. The earliest weeks of COVID-19 in the US, when hospitals were overwhelmed, testing was limited and resources were exhausted, antibiotic prescribing expanded. Some data suggest the lack of efficacious antiviral options at the beginning of COVID-19 was enough to effect 4 consecutive years’ worth of antibiotic stewardship.

Still, in just 10 months, we are far more capable to manage this virus. We enter 2021 with evidenced guidance, better mitigation strategies, and appropriate therapies. There’s no reason why, as we continue to combat the pandemic, we cannot pursue a return to excellence in stewardship.

In fact, given the incredible effort and collaboration shown by the infectious disease community shown this year, it seems to be an inevitable return to form in 2021.

In this issue of Contagion®, we highlight novel oral agent fostemsavir for multidrug-resistant HIV, the burden of COVID-19 and other respiratory infections during the holiday season, and a unique pneumonia and bacterialemia case in a young adult trauma patient.

Thank you for reading Contagion® this year.

Mike Hennessy Sr
Chairman and founder

Emergency Use Authorizations for COVID-19 Therapeutics: The Good, the Bad, and the Data-Deficient

THIS MONTH FINDS US entering a dark period of the coronavirus 2019 (COVID-19) pandemic with increasing rates of cases, hospitalizations, and deaths, while we await the availability of the vaccines that are increasingly looking effective.

It is also a timely occasion to consider the merit and faults of the primary way that COVID-19 therapeutics have been delivered, through the US Food and Drug Administration’s (FDA’s) Emergency Use Authorization (EUA) process.

The EUA process was created as part of the Project BioShield Act of 2004, to allow the FDA to respond to chemical, biological, radiological, and nuclear threats. Further legislation has expanded the use of EUAs to their current form, which includes uses in pandemics and by the US military. They are designed to allow rapid access to therapeutic agents, and these have been for therapeutic agents, and these have had decidedly mixed results.

The first therapeutic EUA this year was the most disastrous: hydroxychloroquine, which was the subject of my column in August. This authorization came with almost no supporting evidence after millions of doses were purchased for the Strategic National Stockpile. While in vitro activity of hydroxychloroquine against SARS-CoV-2 warranted investigation of this agent, it did not translate into clinical success, and the FDA revoked its EUA in June.

Remdesivir followed, and I believe it is an example of a justified EUA through a well-conducted process after results from the ACTT-1 study showed efficacy. Trials that have followed have had mixed results and while the WHO’s SOLIDARITY study did not show a mortality benefit for remdesivir, the results that led to the EUA have not been invalidated.

Convalescent plasma and bamlanivimab have since received EUAs. Convalescent plasma may well have a niche in COVID-19 treatment (or prevention), but the few randomized controlled trials conducted with it have not been promising. The EUA was influenced by the large, noncomparative early access program conducted by the Mayo Clinic, which had mixed utility.

Bamlanivimab was approved after a phase 2 outpatient study looking primarily at reductions in viral load also found lower rates of combined hospitalization and emergency room visits (1.6% vs. 6.3%). Neither of these agents have impres-
Bacteriophages are viruses that lead to the exponential lysis of bacterial cells by infecting specific bacterial hosts, and although bacteriophage therapy (BT) for the treatment of multidrug resistant (MDR) infections seems novel to most people, the concept of phages far precedes the antibiotic era. Phages were initially described in the 1920s and 1930s for the treatment of dysentery, urinary tract infections, and upper respiratory tract infections. However, the introduction of penicillin in the 1940s shifted focus away from BT to antibiotics for the management of infections. As we progress through the antibiotic era and see the increasing emergence of infections caused by pandrug-resistant pathogens, clinicians are again turning to phages as a potential treatment option.

Patients excluded was vast, mostly due to IPATH’s decision that BT was not indicated (n = 525). A hunt for susceptible phages was only recommended in 119 cases (18.5%). Subsequent exclusions were due to no susceptible phages being identified (n = 31) and death of the patient before completion of the phage hunt (n = 10), among others (n = 11). Ultimately, 47 cases had susceptible phages identified and 17 patients were treated with BT.

The process from request to administration is lengthy and serves as a critical barrier to BT in some patients. The range of days between phage request and BT administration was 28 to 386 (median, 170.5 days), underscoring the importance of appropriate patient selection. Patients in septic shock or with a limited life expectancy may not be the best candidates, given the need to allow for a phage hunt and satisfy regulatory requirements. Due to the investigational nature of BT, each case requires a single-use investigational new drug (IND) application to the FDA and approval by the local Institutional Review Board. The IND application requires evidence of clinical need, proof of in vitro bacterial susceptibility to the phage, characterization of genes with known mechanisms of resistance, lack of lysogenic activity, proof of sterility of the product, and minimal exotoxin concentration. All the requirements can be time consuming and generate a significant lag time from phage identification to administration of therapy to the patient.

Seven of the 10 patients discussed in the study achieved clinical success via concurrent BT and systemic antibacterial therapy. Pathogens the investigators identified included Pseudomonas aeruginosa, Acinetobacter baumannii, and Staphylococcus aureus. The authors include the breakdown of pathogens for all requests made to IPATH, and the subset of patients that received BT is shown in the Table. All patients received intravenous (IV) BT, and 1 patient received nebulized BT in conjunction with IV BT.

The authors also described the development of phage resistance while on therapy in 3 of the 10 cases. Fortunately, they were able to identify alternative phages to overcome the new resistance, but additional experience is needed to determine the best methods for preventing the development of phage resistance. The concept of synergy between antibiotics and phage therapy is of great interest in developing optimal treatment regimens.

Identifying the appropriate time and place in therapy for phages is the most challenging aspect. Patients with limited antibiotic options for chronic MDR infections, with a life expectancy longer than the median time to administration of BT, seem to be the best candidates. Clinicians considering BT for patients should make a request to IPATH early in the patient’s chronic infection course to help mitigate some of the delays to administration shared by the authors. Although most patients received IV hospital-administered BT alongside systemic antibiotic therapy, additional experience will be necessary to confirm the safety of both nebulized and self-administered BT given the limited numbers for each in the study’s 10 cases, although current experience suggests feasibility and safety.

### Table. Distribution of Phage Requests and Outcomes

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of requests</th>
<th>Phage hunt initiated</th>
<th>Lytic phage(s) found</th>
<th>Phage therapy administered</th>
<th>Median time from request to admin (range), d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>92</td>
<td>26</td>
<td>18</td>
<td>5</td>
<td>156.5 (58-374)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>39</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>260 (165-355)</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>252</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>77</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>127 (50-204)</td>
</tr>
<tr>
<td>Mycobacterium abscessus</td>
<td>47</td>
<td>18</td>
<td>9</td>
<td>4</td>
<td>176 (87-386)</td>
</tr>
<tr>
<td>Mycobacterium chimeric</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>168</td>
</tr>
</tbody>
</table>

Adapted from Table 1 from Aslam et al.
Afabinic: A Novel, Narrow-Spectrum Antistaphylococcal Agent

BY HUMNA N. MEER, PHARMD CANDIDATE; AND KIRK E. HEVENER, PHARMD, PHD

The alarming rise in bacterial resistance has led to a growing need for new antibacterial drug targets. According to the World Health Organization, approximately 60% of hospital infections are resistant to at least 1 first-line therapy, leading to longer hospital stays and increased mortality and morbidity. Designated a “serious threat” in the CDC’s 2019 report Antibiotic Resistance Threats in the United States, methicillin-resistant Staphylococcus aureus (MRSA) accounts for more than 323,000 cases annually and causes over 10,000 deaths in the United States. The extensive resistance of MRSA to several antibacterial classes, along with less than ideal dosing of and therapeutic monitoring requirements for the first-line agent, vancomycin, has led to significant interest in the discovery of new antistaphylococcal agents with novel bacterial targets.

Wittke et al reported the phase 2 clinical trial results of afabinic for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by S. aureus (NCT02426918). Afabinic (AFN-1720, Debio-1450) is a first-in-class antistaphylococcal agent that works by inhibiting a key enzyme—enoyl-acyl carrier protein (ACP) reductase, or FabI—in the bacterial fatty acid synthesis pathway (FAS-II). This enzyme is responsible for producing the essential fatty acids needed for a functional cell membrane. Because the bacterial FAS-II pathway is distinct from eukaryotic fatty acid synthesis (FAS-I), enzymes in this pathway have held considerable interest for investigators as selective antibacterial drug targets. The FabI enzyme is a critical, rate-limiting enzyme in the FAS-II pathway. Importantly, FabI is one of several known enoyl-ACP reductase isozymes that are both species-specific and mechanistically distinct. This, coupled with the ability of some organisms to bypass FAS-II inhibition using fatty acids from the host, makes FabI a narrow-spectrum antibacterial target (see Table online). Afabinic is a phosphate prodrug that is converted to the active dephosphono moiety in vivo after oral or intravenous (IV) administration (Figure).

The investigators reported results from a randomized, double-blind, double-dummy study consisting of 330 participants across 15 study centers for the treatment of ABSSSIs. A microbiological intent-to-treat (mITT) population included 284 patients with baseline S. aureus or pathogenic coagulase-negative staphylococcus isolated from blood or primary lesion. Participants were divided into 1 of 3 cohorts and treated for 7 to 10 days. Cohort 1 received 80 mg IV afabinic followed by 120 mg oral afabinic twice daily. Cohort 2 received 160 mg IV afabinic followed by 280 mg oral afabinic twice daily. Cohort 3 received 15 mg/kg IV vancomycin followed by 600 mg oral linezolid twice daily. There was no separate cohort for patients with polymicrobial infections with staphylococcal and non-staphylococcal species (21.1% of the mITT population), although the investigators tracked and reported the data. The primary efficacy end point in this study was early clinical response, defined as a reduction in lesion area, erythema, and edema at 2 to 3 days post initiation. Of note, MRSA was the primary causative agent for approximately half the population in each group. Investigators reported that the early clinical response in the afabinic cohorts 1 and 2 was noninferior to that of the vancomycin/linezolid cohort 3 (94.6% and 90.1% vs 91.1%). Commonly reported adverse events in both the high-dose and low-dose afabinic groups were headache, nausea, vomiting, and diarrhea. Interestingly, the diarrhea rate in the afabinic cohorts was 50% less than that in the vancomycin/linezolid cohort.

The results of this clinical trial suggest that afabinic has the potential to be an antistaphylococcal drug of similar efficacy to vancomycin. The availability of oral and IV formulations, as with linezolid, would alleviate the complexities associated with switching from IV to oral antibiotics for severe infections. However, although linezolid has broad gram-positive activity, afabinic possesses narrow-spectrum activity, which will limit the use of the drug to confirmed staphylococcal infections, including MRSA. Additionally, this drug is unlikely to be effective against gram-negative bacteria due to difficulties with cell penetration. With limited potential as an empiric treatment, it is likely that rapid diagnostic tests would be needed with afabinic, although this could result in quicker time to targeted therapy. Anticipated advantages of afabinic’s narrow-spectrum activity include a limited microbiome impact, mitigation of antibiotic resistance, and decreased prevalence of infections from opportunists such as Clostridioides difficile. Afabinic, if approved, would certainly have a place in the clinic as a Staphylococcus-targeted, narrow-spectrum antibacterial agent. However, additional clinical trials with larger sample sizes are needed to further assess the drug’s safety and long-term effects.

References and table are available at ContagionLive.com.

Highlighted Study
Physician Liability During COVID-19

BY TODD SHRockey

The coronavirus disease 2019 (COVID-19) pandemic has brought a lot of unknowns into the practice of medicine. Doctors are already dealing with diagnosing and treating people affected by the deadly virus while trying to keep themselves and their staff safe from infection. But with the threat of infection comes the threat of being sued for not taking the proper precautions against it. Medical Economics spoke with Stephanie Sheps, a medical liability insurance provider, to discuss liability risk in the age of COVID-19. (Editor’s note: The following transcript has been edited for clarity and brevity.)

MEDICAL ECONOMICS®: What new liability threats have emerged from COVID-19?
Stephanie Sheps: First, there are the obvious risks that include transmission of COVID-19, both to patients and to staff. It’s a novel issue because we’re not fully understanding this virus yet, so things continue to evolve daily. Based on patient and provider awareness and precautionary measures taken to mitigate these risks, I believe that the greater liability actually stems from pandemic-related or contextual realms. And so, pandemic risks are those that do not involve the diagnosis or treatment of COVID-19, or the transmission of it, but are related to the changes in how health care is currently being delivered or not delivered. These risks include the denial of services to patients because of lack of capacity or the availability of PPE [personal protective equipment], and providers and facilities that delay elective surgeries because of capacity issues, etc. Another significant area of risk stems from the fact that many providers have [deferred] and continue to defer their primary care visits, their annual checkups of patients, [and] routine screenings like mammograms and colonoscopies, things that we do to manage chronic conditions. And the fact that those are being deferred or if they’re being held…virtually does present some risk. I mean, there’s a reason we see our providers in person; they get to put eyes on the patient, they get to take labs, they get to really assess the patient using all of their senses.

And so, when that is being limited by doing these types of visits through telehealth, I think that could present some greater risk in the future. And just one final note is that on the patient side, many people are making the choice to delay or defer treatment because they’re fearful of going into the doctor’s office or a hospital, or they’re trying to be a good citizen and think their issue isn’t that serious. [They say] ‘Other people need the facilities more, I will just hang back.’ And because they make those decisions, sometimes we’ve seen increased risks of heart attacks and strokes [in patients who] are having greater morbidity and mortality, because people are waiting it out at home. You’ve even seen some cases of delayed setting of fractures, because people just thought ‘I’ll wait this out, it’s not that bad.’ And the longer they wait to deal with those issues, the more morbidity there could be.

Is following CDC guidelines, as far as safety goes, enough to protect the practice from lawsuits?
Well, I think it’s a good starting place, and of course would advise everybody to continue to follow those guidelines, but it’s not the panacea to prevent claims and suits. In essence, the standard of care is going to come from the region, ...whatever...is the common law, the statutory law in that jurisdiction, that will define the standard of care. ...We’re functioning under what we like to think of as a crisis standard of care right now, but only time will tell how things are perceived and adjudicated in the courts. So it’s always a good idea to follow the CDC guidelines. But unfortunately, I can’t say that it will be totally preventative of claims.

Are there common mistakes or oversights that make practices more vulnerable to COVID-19–related lawsuits?
I would say yes and no. And the reason I equivocate there is that these are common issues that would have existed before COVID-19. So the failure to document informed consent or informed refusal of treatment, those are risks that exist no matter what. Obviously, there are these specific risks that patients will get the disease or transmit the disease to your staff while they’re there. But I think, to me, the greatest risk right now is that providers are so focused on making sure that they are safe, that their patients are safe, and their staff members are safe from contracting COVID-19 that they may overlook traditional typical patient safety and risk mitigation efforts.

Have there been any court cases that offer any insight into how the courts will look at these COVID-19 issues?
We are not yet really there, as it is a little bit early in the lifecycle of what are potential suits or suits related to COVID-19. Not many have been filed yet that are very specific to COVID-19 and that aren’t just contextual or pandemic related. But it takes some time for things to wind their way through the court system. There was one decision in the federal district court in New York that actually remanded a case that was filed in the federal courts extensively, to bring certain allegations that were federal in nature, but it was remanded back to the states so that it wouldn’t have the protections of the PREP [Public Readiness and Emergency Preparedness] Act.

Is there a particular type of practice that might be more vulnerable than another?
The...answer to that question is long-term care facilities are obviously at heightened risk because they contain a very vulnerable patient population. And there have been numerous incidents and cases of COVID-19 and mortalities in those settings. It’s really any place where patients are in inpatient care, so that could be behavioral health facilities or hospitals; any of those locations have greater risk because of the density of patients and just the multitude of staff and interactions that the patients are having. ▲

To read more, visit https://bit.ly/3pXUZZQ
Remdesivir Fails to Benefit COVID-19 Hospitalization, Death Risk in WHO Study

BY KEVIN KUNZMANN

Interim results from the ongoing World Health Organization (WHO) Solidarity Trial show that remdesivir has provided little to no benefit for patients hospitalized with coronavirus disease 2019 (COVID-19), on metrics of overall mortality, ventilation need, and duration of hospital stay.

The findings come a week after results from the ACTT-1 and ACTT-2 trials (NCT04280705, NCT04401579) indicated that the antiviral therapy, used alone and in combination, was associated with reduced time to recovery and mortality risk versus placebo among patients hospitalized with COVID-19.

The results also come 2 weeks following President Trump’s hospitalization, during which he began a 5-day regimen of remdesivir plus corticosteroid dexamethasone, along with an investigative monoclonal antibody cocktail, giving the Gilead therapy a national media spotlight.

But these newest findings from WHO, in a robust, real-world, global series of randomized trials for 4 antiviral drugs in patients hospitalized for COVID-19, indicated minimal benefit with remdesivir. The study investigators observed similar outcomes for the Solidarity Trial’s 3 other assessed agents: hydroxychloroquine, lopinavir, and interferon.

"The main outcomes of mortality, initiation of ventilation and hospitalization duration were not clearly reduced by any study drug," the investigators wrote. "Although ACTT-1, with placebo control, reported remdesivir moderately reduced time to recovery, in the present study there were no material effects on ventilation initiation or time to discharge."

The Solidarity investigators randomized patients with COVID-19 equally between whichever of the 4 study drugs were locally available and open control: remdesivir, hydroxychloroquine, lopinavir fixed-dose combination with ritonavir, and subcutaneous interferon-

They compared study drugs versus control, with an intent-to-treat primary analysis of in-hospital mortality, as per unstratified Kaplan-Meier 28-day risks and age- and ventilation-stratified log-ran death rate ratios (RRs).

Their findings included 11,266 adults randomized to remdesivir (n = 2750), hydroxychloroquine (954), lopinavir (1411), interferon plus lopinavir (651), lone interferon (1412), or no study drug (4088). Investigators observed a compliance rate between 94% to 96% through treatment.

The team reported 1253 (11.1%) deaths, at a median duration of 8 days (interquartile range, 4-14). The unstratified Kaplan-Meier 28-day mortality was 12%, and spiked to 39% among patients ventilated at the time of randomization.

Death RR were consistently underwhelming for each observed regimen:

- Remdesivir RR, 0.95 (95% CI, 0.81-1.11; P=0.50)
- Hydroxychloroquine RR, 1.19 (95% CI, 0.89-1.59; P=0.23)
- Lopinavir RR, 1.00 (95% CI, 0.79-1.25; P=0.97)
- Interferon RR, 1.16 (95% CI, 0.96-1.39; P=0.11)

The investigators observed no definite reduction in mortality, initiation of ventilation, or hospitalization duration with any of the studied therapies.

The infectious disease community responded with disappointment to the newest Solidarity findings—particularly for remdesivir, which to a point has served as a viable option for patients severely ill with COVID-19.

Jason Pogue, PharmD, BCPS, BCIDP, a clinical pharmacist specialist in infectious diseases and clinical professor in pharmacy at the University of Michigan College of Pharmacy, told Contagion® there is "no way around" these newest findings.

"This is a very disappointing result," he said. "It really throws into question what role, if any, remdesivir has in the [treatment] of hospitalized patients with COVID-19, particularly at its current price point."

The Solidarity Trial will continue to recruit and assess an additional 2000 hospitalized patients with COVID-19 monthly. Investigators aim to progress toward an assessment of immunomodulators and specific monoclonal antibodies that target severe acute respiratory syndrome coronavirus 2. Their hope is to improve on the minimal impact by remdesivir, hydroxychloroquine, lopinavir, and interferon.

"The unpromising overall findings from the regimens tested suffice to refute early hopes, based on smaller or nonrandomized studies, that any will substantially reduce inpatient mortality, initiation of ventilation or hospitalization duration," they wrote. "Narrower confidence intervals would be helpful (particularly for remdesivir), but the main need is for better treatments."
Tuberculosis Vaccine Could Play Role in COVID-19 Prevention

BY KILLIAN MEARA

A group of researchers at Cedars-Sinai Medical Center in Los Angeles have found evidence that a tuberculosis vaccine has been associated with a reduced likelihood of contracting coronavirus 2019 (COVID-19). The research also found that the vaccine could help in reducing the level of severity of the disease.

The Bacillus Calmette-Guérin (BCG) vaccine was first developed approximately 1921 to treat bladder cancer and for people who are at a higher risk of contracting tuberculosis. The vaccine is FDA approved and is administered to over 100 million children every year around the globe.

The Study, published in The Journal of Clinical Investigation, tested for evidence of SARS-CoV-2 in more than 6,000 healthcare workers in the Cedars-Sinai Health system and also asked about their medical and vaccination histories. The study found that 30% of those who had received the BCG vaccine at some point in the past were significantly less likely to test positive for antibodies of SARS-CoV-2. They were also less likely to have reported having had an infection of COVID-19 or having COVID-19 related symptoms.

“It appears that BCG-vaccinated individuals either may have been less sick and therefore produced fewer anti-SARS-CoV-2 antibodies, or they may have mounted a more efficient cellular immune response against the virus,” said Moshe Arditi, MD, co-senior author on the study.

The findings of the study do not represent a view that the BCG vaccine will be more effective than a specific COVID-19 vaccination. However, the BCG vaccine could be approved more quickly and be made more readily available, considering its years of being an approved therapy. The vaccine could be a potential bridge offering some benefit until a more effective and safer COVID-19 vaccine is made widely available.

“Given our findings, we believe that large, randomized clinical trials are urgently needed to confirm whether BCG vaccination can induce a protective effect against SARS-CoV2 infection,” said Susan Chang, MD, MPH, MMSc, the other co-lead author of the study.

Numerous randomized clinical trials are already in the works studying the potential of the BCG vaccine for COVID-19. Along with Cedars-Sinai, Baylor College of Medicine and Texas A&M University are leading the research.

“It would be wonderful if one of the oldest vaccines that we have could help defeat the world’s newest pandemic,” Arditi said. ▲

Vaccinations Equally Effective for Preterm and Full-Term Infants

BY RACHEL LUTZ

Preterm infants with routine vaccination schedules during their first year of life achieve protective antibody levels comparable to term infants after the primary series and the booster shot, according to a paper published in JAMA.

Investigators from the Netherlands compared preterm infants to healthy control infants in order to evaluate the immunogenicity of routine vaccinations administered to preterm infants. The investigators recruited 296 infants from 8 hospitals across the Netherlands between October 2015 and October 2017 and used 66 healthy control infants for their study. The study authors categorized infants in their first year of life into 3 gestational age groups: less than 28, 28 to less than 32, and 32 to 36 weeks. They followed up with the babies throughout their first year, until as late as October 2018.

All the infants received vaccinations according to the normal practice, the study authors said. The vaccines for diphtheria-tetanus toxoids-acellular pertussis-inactivated poliomyelitis-Haemophilus influenzae type b and hepatitis B were administered at 6 to 9 weeks, 3 months, 4 months, and 11 months, which is aligned with the national program in the Netherlands.

The babies in the study were 56% male with a mean gestational age of 30 weeks, the study authors noted. According to the authors, preterm infants have an increased susceptibility to infections due to the decreased transfer of protective maternal antibodies, as well as a possible relative immaturity of the immune system compared with term babies.

A total of 220 preterm infants completed blood samples prior to vaccination, 1 month post vaccination, and 1 month after the booster, the investigators said.

In all 3 preterm categories, the mean immunoglobulin G levels for the different vaccine antigens prior to vaccination were low (between 1.5% and 54.9%). The prevaccination concentrations were lowest in the group with gestational age less than 28 weeks, and significantly lower for almost all antigens compared with the other 2 categories.

After the primary series of vaccinations, the investigators found protective antibody levels against pertussis toxin, diphtheria toxoid, and tetanus toxin in between 93% and 100% of the preterm infants. Furthermore, the level of diphtheria toxin antibodies was greater than 99% across all preterm groups and did not differ from control infants.

Haemophilus influenzae type b protective antibodies were significantly lower in the preterm infants compared with the control infants (40% vs 83%, respectively), the investigators said. The levels were lowest in the group with the shortest gestational age (34%).

After the booster vaccinations, nearly all of the preterm infants reached protective antibody status for all antigens, except for Haemophilus influenzae type b, for which the levels were as follows: 88% in the overall preterm infants group and 87% in the group aged between 28 and 32 gestational weeks (lower than the group aged 32 to 36 gestational weeks, as well as term infants).

“Among preterm infants, administration of routine vaccinations during the first year of life was associated with protective antibody levels against most antigens in the majority of infants after the primary series and booster, except for Haemophilus influenzae type b,” the study authors concluded, adding that it is possible to generalize these results across preterm infants in similar communities. “However, antibody concentrations were generally lower among preterm infants compared with historical controls.” ▲
Review the historical background on tetracycline discovery, emerging resistance, mechanism of action, and their spectrum of activity.

Learn about pharmacokinetic and pharmacodynamic similarities and differences of tetracyclines.

Discuss the clinical data supporting tetracycline use for common bacterial infections.

Identify applications for tetracycline-class antibiotics after assessing a patient case.

Watch this iPub® to learn more about the tetracyline-class antibiotics in an era of antimicrobial resistance.

Program Objectives

- Review the historical background on tetracycline discovery, emerging resistance, mechanism of action, and their spectrum of activity.
- Learn about pharmacokinetic and pharmacodynamic similarities and differences of tetracyclines.
- Discuss the clinical data supporting tetracycline use for common bacterial infections.
- Identify applications for tetracycline-class antibiotics after assessing a patient case.

Faculty Information

Kerry Laplante, PharmD, FCCP, FIDSA
Professor of Pharmacy
University of Rhode Island
Kingston, RI

Abhay Dhand, MD
Infectious Disease Physician
Westchester, NY
Fostemsavir for Multidrug Resistant HIV-1: It’s Time for HIV to Overcome Attachment Issues With CD4 Cells

Fostemsavir, an HIV-1 attachment inhibitor, is a novel therapeutic option for multidrug-resistant (MDR) human immunodeficiency virus (HIV). It represents the first oral agent developed for this indication in over a decade and provides promise for patients with limited remaining treatment options.

BY AMY L. BROTHERTON, PHARMD, AAHIVP, BCIDP and RAJEEV SHAH, PHARMD, AAHIVP, BCIDP

Significant advancements in drug development have transformed the prognosis of HIV from a deadly disease to a chronic condition that can be easily managed with combination antiretroviral therapy (ART), often coformulated into a single tablet. Despite this progress, there are many reasons why virologic failure can still occur, including suboptimal adherence, poor tolerability, and drug-drug interactions (DDIs). In the presence of viremia, HIV drug resistance can emerge across multiple agents and classes. For individuals with multidrug drug resistance and few remaining treatment options, novel agents and mechanistic classes are needed to construct a fully suppressive regimen. In the United States alone, there are approximately 25,000 individuals with MDR HIV and 12,000 individuals in need of novel therapies to achieve virologic control.1 Without viable treatment options, there is a risk for disease progression, increased mortality, and increased rates of MDR HIV transmission.

Fostemsavir (Rukobia) is a first-in-class HIV-1 attachment inhibitor approved by the FDA in July 2020 for the treatment of MDR HIV-1 infection in heavily treatment-experienced (HTE) adults who are failing their current regimen due to resistance, safety, or intolerance.2 Fostemsavir (FTR) is available as a 600-mg extended-release tablet and is administered orally every 12 hours. This article will review its mechanism of action, pharmacokinetic properties, safety and efficacy data, and role in the treatment of MDR HIV-1 infection.

**MECHANISM OF ACTION**
FTR is an oral prodrug of tamsuvir (TMR), an HIV-1 envelope glycoprotein 120 (gp120) attachment inhibitor, which prevents viral attachment and entry into host CD4+ T cells. Once FTR is converted to the active moiety, TMR binds directly to the viral gp120 subunit near its CD4-binding site. This results in a conformational change that inhibits attachment to CD4+ T cell–surface receptors and subsequent viral replication.3

**PHARMACOKINETICS**
FTR is rapidly hydrolyzed to TMR upon oral administration. The half-life of TMR is 11 hours, and it can be administered without regard to meals. The extended-release tablets should not be split, crushed, or chewed, limiting use to those who are able to swallow tablets whole.4 The metabolism of TMR occurs primarily through esterase-mediated hydrolysis with minor contribution of cytochrome P450 (CYP) 3A4. TMR is also a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and inhibits organic anion transporter (OATP) 1B1/3 and BCRP.5 Less than 2% of TMR is eliminated unchanged in the urine. There were no clinically relevant differences in the pharmacokinetics of TMR in individuals with mild to severe renal or hepatic dysfunction, and TMR is not significantly removed by hemodialysis. Consequently, dose adjustments are not required in renal or hepatic impairment.

**DRUG-DRUG INTERACTIONS**
FTR has a low potential for DDIs; however, there are a few notable exceptions. Coadministration with strong CYP3A4 inducers, such as rifampin, is contraindicated and may lead to virologic failure. In the setting of mycobacterial coinfection, rifabutin may be combined with FTR without dose adjustments. Additionally, CYP3A4 inhibitors can be combined with FTR without concern for toxicity.6,7 TMR may increase levels of grazoprevir and voxilaprevir, increasing the risk for ALT elevations; however, simultaneous use with glecaprevir is not anticipated to significantly alter glecaprevir concentrations.3 Concomitant use with HMG-CoA reductase inhibitors may result in significantly increased statin levels and potential for toxicity. For example, rosuvastatin maximum concentration (Cmax) and area under the curve were increased by 78% and 69%, respectively, when combined with TMR. TMR increased ethinyl estradiol Cmax by 40%7; therefore, the dose of ethinyl estradiol should not exceed 30 μg when combined with FTR.4
PHASE 3 CLINICAL TRIALS
Investigators evaluated the safety and efficacy of FTR for the treatment of MDR HIV-1 in a partially randomized, multicenter, double-blind, placebo-controlled 96-week trial (BRIGHTE Study, NCT02362503), which enrolled 371 HTE adults with HIV-1 and documented failure of current ART (HIV-1 ribonucleic acid [RNA], ≥ 400 copies/mL). Patients were included if at least 3 ART classes were exhausted due to resistance, intolerability, contraindications, or patient refusal. Individuals with chronic untreated hepatitis B virus (HBV), decompensated cirrhosis, congestive heart failure, or congenital prolonged QT syndrome were excluded. Additionally, those with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than 7 times the upper limit of normal (ULN) or a bilirubin level at or greater than 1.5 times the ULN were also excluded. Participants with 1 to 2 fully active agents (FAAs) from 2 or fewer classes remaining (n = 272) were randomized 3:1 to receive blinded FTR 600 mg every 12 hours or placebo in addition to their failing regimen on days 1 to 8 (functional monotherapy), followed by open-label FTR plus optimized background therapy (OBT) after day 8. Participants with zero FAAs remaining were placed in a nonrandomized cohort (n = 99) and were initiated on FTR plus OBT on day 1. The primary outcome was mean change in log_{10} HIV-1 RNA from day 1 to 8 in the randomized cohort (7%). The most common adverse effects experienced by those taking FTR plus OBT were nausea (10%), diarrhea (4%), and headache (4%). The OBT, which often contained a protease inhibitor, may have contributed to the incidence of gastrointestinal adverse effects, as the incidence was similar in both groups. Adverse effects leading to discontinuation were not commonly related to FTR and were largely due to infections. QTc prolongation is a rare adverse effect, which occurred in less than 2% of patients but did not require intervention or discontinuation. QTc prolongation (mean increase, 11.2 milliseconds) was observed in a phase 1 study only at supratherapeutic doses (2400 mg twice daily).6 Grade 3 or 4 elevations in hepatic laboratory parameters that were significantly higher than the placebo arm included increased direct bilirubin (14% vs 7%) and bilirubin (7% vs 4%) levels. Elevations in ALT and AST levels were more common in patients who were coinfected with viral hepatitis. However, a portion of those elevations were attributed to patients who had HBV reactivation as a result of their change in ART.5

ADVERSE REACTIONS, WARNINGS, AND PRECAUTIONS
Similar to other clinical trials with HTE patients, adverse effects occurred frequently (92%) in BRIGHTE Study patients, but very few led to treatment discontinuation in the randomized cohort (7%). The most common adverse effects experienced by those taking FTR plus OBT were nausea (10%), diarrhea (4%), and headache (4%). The OBT, which often contained a protease inhibitor, may have contributed to the incidence of gastrointestinal adverse effects, as the incidence was similar in both groups. Adverse effects leading to discontinuation were not commonly related to FTR and were largely due to infections. QTc prolongation is a rare adverse effect, which occurred in less than 2% of patients but did not require intervention or discontinuation. QTc prolongation (mean increase, 11.2 milliseconds) was observed in a phase 1 study only at supratherapeutic doses (2400 mg twice daily).6 Grade 3 or 4 elevations in hepatic laboratory parameters that were significantly higher than the placebo arm included increased direct bilirubin (14% vs 7%) and bilirubin (7% vs 4%) levels. Elevations in ALT and AST levels were more common in patients who were coinfected with viral hepatitis. However, a portion of those elevations were attributed to patients who had HBV reactivation as a result of their change in ART.5

RESISTANCE DATA
Investigators observed virologic failure in 25% of patients in the randomized cohort and 51% in the nonrandomized cohort at week 96. As expected, higher rates of virologic failure occurred in the nonrandomized cohort. Approximately half of patients in the randomized cohort and three-fourths of those in the nonrandomized cohort who were experiencing virologic failure developed treatment-emergent resistance mutation(s) at the 4 key sites in the gp120 region. The 4 substitutions associated with significant changes in TMR effective concentrations were S375N, M426L/I, M434I/L, and M475I/L/V.9 There does not appear to be cross-resistance with other entry inhibitors, including ibalizumab and maraviroc; however, this conclusion is based on a small number of patients.1,0 Although investigators have observed reduced susceptibility to TMR in HIV subtype AE, it is uncommon in subtype B, which is the prevalent subtype in the Americas. Baseline resistance testing (including viral tropism) is not recommended.2

PLACE IN THERAPY
Fostemsavir is an exciting new addition to the limited repository of salvage therapy for MDR HIV. It represents the first orally administered novel class developed for this indication since the approval of maraviroc and raltegravir in 2007 and has low potential for cross-resistance to other agents and classes. Furthermore, clinical data have demonstrated that it is well tolerated, has minimal DDIs, and can be conveniently administered without renal or hepatic dose adjustments. Based on the available data, the patients most likely to derive clinical benefit from FTR are those with at least 1 additional remaining FAA. Although the twice daily dosing of fostemsavir may be difficult for some patients, it aligns well with twice daily administration of medications that are common components of salvage regimens, such as dolutegravir, darunavir/ritonavir, maraviroc, and etravirine. Unfortunately, the investigators studied fostemsavir in a limited number of patients, and long-term adverse effects are not yet known. Patients are also required to swallow the tablet whole, as crushing is not permitted due to the extended-release formulation. Resistance testing is not yet commercially available, and the implications of fostemsavir resistance are not yet well understood. ▲
Holiday Guest List—When the Uninvited Arrive: COVID-19 and Coinfections

The confluence of seasonal viruses and COVID-19 leaves clinicians uncertain about the coming months.

BY CLAYTON MOWRER, DO, MBA; AND KELLY CAWCUTT, MD, MS, FACP

(continued from cover page)

Together in celebration for sporting events (read: Chiefs or in Nebraska, Huskers) are all taking place. Although SARS-CoV-2 has become the elephant in the room during such gatherings, it isn’t alone; there are also the frequent sniffs, sneezes, and coughs from the variety of seasonal respiratory viruses that arrive as unwanted party guests.

Typically, it is at this time of year that we tend to see many respiratory viruses surface. Influenza has been of most concern, historically, with its ability to cause life-threatening disease and its tendency to mutate and spread rapidly, which has resulted in past pandemics. But now we have a new guest—SARS-CoV-2—and we realize that we are unsure how it will play with the others. Will it start to peak in a similar fashion? What about its impact on coinfections that are known to occur with the other seasonal respiratory viruses? Let’s first take a look at how SARS-CoV-2 compares with our standard seasonal viruses.

SARS-COV-2 VS OTHER SEASONAL VIRUSES

COVID-19 and other respiratory viruses have similar clinical presentations, creating difficulty in differentiating them without a diagnostic test. Although asymptomatic infections do occur, these infections, including COVID-19, generally exhibit an overlapping influenza-like illness: cough, shortness of breath, muscle aches, fatigue, sore throat and runny nose, headaches, and fever are among the more common symptoms. There are also some less common, though notable symptoms such as loss of taste and smell, or gastrointestinal complaints such as nausea and diarrhea, that are more specific to COVID-19 and thus may help differentiate it. However, this becomes even more difficult to distinguish based on symptoms alone with coinfections.

Overall, most respiratory viruses cause a relatively mild illness, though there are several (Respiratory syncytial virus [RSV] and influenza) that can have a more severe course. Whereas many people recover without complications, there are certain groups of people who are at higher risk for developing more severe disease or complications from infection, especially with SARS-CoV-2 and influenza: older adults and those with certain underlying medical conditions are among the highest-risk populations.

All the above can be summarized thusly: although there are some differences between COVID-19 and other common seasonal respiratory viruses, there are plenty of similarities with significant overlap, and the courses of such viruses are relatively well understood. But one aspect with which we still don’t have much experience and which we may start to encounter shortly concerns when a person becomes infected with...
COVID-19 and another respiratory virus (especially influenza), a phenomenon we refer to as coinfection.

**RESPIRATORY COINFECTIONS AND COVID-19**

We know that infection with different, yet simultaneously occurring, respiratory viruses does happen.\(^9-10\) Virus-specific interactions play a key role in the morbidity and mortality of respiratory viral coinfections, but our understanding of this concerning even typical pathogens is limited and the introduction of SARS-CoV-2 raises even more questions.\(^11-12\) Early in the COVID-19 pandemic, there were reports of coinfection in various parts of the world. One particular study in northern California revealed that of 116 patients with COVID-19, 21% exhibited coinfections, with the most common being rhinovirus, RSV, and other types of coronaviruses.\(^13\)

Additionally, there were some reports of coinfection with influenza in particular that demonstrated a subset of patients progressing to severe disease.\(^1,2,14\)

Although the data are far from definitive due to the limited number of patients and the varying treatment modalities employed for them, there were suggestions in these cases that persons who were coinfected with SARS-CoV-2 and another respiratory virus had severe disease and poor outcomes.

Ultimately, it is unclear if influenza and COVID-19 will peak at the same time this season, nor do we fully understand the interactions between the 2 viruses within an individual. Yet reason for concern remains as both viruses cause life-threatening illness in certain populations and have very different ways in which clinicians approach their treatment, potentially impacting those who develop coinfection with influenza and COVID-19.

Due to the differences in treatment, rapid, easily accessible, and reliable testing for a broad variety of respiratory viruses has been a focus of diagnostics, leading to both the development of a combination SARS-CoV-2/influenza multiplex PCR assay and the inclusion of SARS-CoV-2 on a revised respiratory pathogen panel that detects nearly 2 dozen viral and bacterial pathogens.\(^15\)

**PREVENTION AND MANAGEMENT OF COINFECTION WITH COVID-19**

Most seasonal respiratory viruses are self-limited (that is, people tend to recover without the assistance of medication that targets the virus). Influenza and SARS-CoV-2 can be exceptions, as there are certain circumstances and specific populations in which treatment is recommended. For influenza, this is typically with the antiviral oseltamivir (Tamiflu), which is given to patients who require hospitalization, especially those with severe disease, or to high-risk populations. For COVID-19, on the other hand, although there are many ongoing trials to determine what works best, the most recent National Institutes of Health guidelines recommend the use of the antiviral remdesivir, often with dexamethasone, in hospitalized patients.\(^16\)

The effects of administering oseltamivir and remdesivir to those who are simultaneously infected with both viruses are unknown, but clinicians have found that steroids, which have become important in the treatment of COVID-19, worsen outcomes with influenza. This makes treatment decisions in coinfection more convoluted, as the optimal treatment is currently unknown.

Most important as we move into this season will be our efforts to mitigate the spread of infection. Social distancing, hand hygiene, and wearing masks remain crucial to preventing the spread of COVID-19, with similar effects on seasonal respiratory viruses. Vaccinations also have an important role in mitigation efforts; we do have a safe and reasonably effective influenza vaccine, which will become that much more important to receive this year, particularly while we await the completion of COVID-19 vaccination trials.

**CONCLUSIONS**

We have witnessed the severity and intensity with which both influenza and COVID-19 can strike, and we are uncomfortably aware of how quickly and efficiently both can permeate a population.\(^X,17\) Therefore, as we enter the season when influenza and other respiratory viruses are most prominent, while remaining very much in the midst of the COVID-19 pandemic, we must become more vigilant in our public health and research efforts to prepare for a rise in such coinfections. ▲

**References are available at ContagionLive.com.**

---

**Are you a clinician or interested stakeholder in this topic?**

Contagion® has developed its ebook, COVID-19 and the Flu: What Clinicians Need to Know, which provides insights from medical experts and offers potential strategies in dealing with the confluence of the influenza season and the existing COVID-19 pandemic.

Scan the QR code to find more information on the book.
more reliable surveillance data on CDI from the Centers for Disease Control and Prevention (CDC) in part because it has been a reportable infection for all health care facilities participating in Medicare and Medicaid since 2013. In 2017, there were an estimated 223,900 hospitalized cases and 12,800 deaths in the United States from *C difficile*. The national incidence of community-associated CDI saw no change, whereas health care-associated (HA) CDI decreased by 36% from 2011 to 2017. This decline in HA infections can be attributed to antibiotic stewardship programs, reduced use of fluoroquinolones, and testing protocols that limit false-positive results. With an aging population and increased numbers of persons with underlying comorbidities, *C difficile* remains a major concern for the US health care system.

Most recently, the coronavirus disease 2019 (COVID-19) pandemic has led to an extensive use of broad-spectrum antibiotics due to concern of secondary bacterial infections, and 1 study showed that 91% of patients with COVID-19 received antibacterial therapy. A retrospective study in Italy during the pandemic found a significant decrease in the incidence of HA-CDI in 2020 when compared with the 3 prior years, possibly related to enhanced pandemic precautions. It is interesting to note that COVID-19 wards actually had a higher incidence of HA-CDI when compared to the non-COVID-19 wards, but this difference was not statistically significant. One case series of 9 patients coinfected with both severe acute respiratory syndrome coronavirus 2 and *C difficile* reports that all 9 patients received antibiotics during their hospitalization. These reports highlight the importance of focusing efforts on infection control and antibiotic stewardship to prevent further emergence of CDIs.

The North American pulsed-field gel electrophoresis type 1 (NAP1) strain of *C difficile*, also known as ribotype 027, is one of several described hypervirulent strains. The NAP1 strain has been implicated in outbreaks for almost
20 years.6 Most pathogenic strains of *C. difficile* produce 2 toxins, an enterotoxin tdA and a cytoxin tdB. The NAP1 strain has a deletion of the tdC inhibitory gene, which results in higher toxin A and B production. Risk factors for NAP1 include advanced age, fluoroquinolone use, and admission to long-term care facilities.7 The CDC’s emerging infections program reported a significant decline in HA isolates of the NAP1 strain from 21% in 2012 to 15% in 2017, but the strain remained the most prevalent.8 This decrease in the proportion of infections caused by NAP1 is associated with decreased fluoroquinolone use likely due to awareness and antimicrobial stewardship.9

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) updated their treatment guidelines in 2017. The guidelines recommend that the initial treatment of nonsevere disease is 10 days of either oral fidaxomicin (200 mg twice daily) or oral vancomycin (125 mg 4 times daily).10 Both fidaxomicin (200 mg twice daily) or oral vancomycin (125 mg 4 times daily).10 Both options are equally effective, but recurrence rates are lower with fidaxomicin than with vancomycin (15% vs 25%).11 Metronidazole is no longer recommended unless vancomycin or fidaxomicin is unavailable, a situation that is unlikely to occur in the United States. Metronidazole also has a role in the initial treatment for fulminant disease, for which clinicians recommend vancomycin 500 mg orally every 4 times daily along with metronidazole 500 mg intravenously every 8 hours.

IDSA-SHEA included fidaxomicin in their updated guidelines for the first time, as it was approved by the FDA in 2011. It is important to note that the FDA has approved no new antibiotics since fidaxomicin almost a decade ago.

Relapse is a major concern for CDI, as up to 25% of patients experience recurrence, usually within 30 days of stopping treatment.12 The IDSA-SHEA guidelines recommend the first recurrence be treated with 10 days of oral fidaxomicin or with a prolonged tapering course of oral vancomycin for 6 to 12 weeks. In 2016, the FDA approved bezlotoxumab, a monoclonal antibody directed against the toxin B produced by *C. difficile*, for patients at high risk for recurrence. In a randomized controlled trial, patients given one dose of bezlotoxumab had a lower risk of disease relapse within 12 weeks (16%) than patients given placebo (26%).13 Relapse rates were particularly lower among the elderly and among cancer patients who were treated with bezlotoxumab.13 Clinicians should consider the addition of bezlotoxumab to antibiotic treatment in patients at high risk for *C difficile* recurrence, including older patients, those with a recent history of *C difficile*, and those with kidney dysfunction.

Systemic antibiotics are well known to alter the microbiome of patients, leading to a decrease in bacterial diversity.14 Results from studies show that these effects after 1 course of antibiotics last for months,15 and even up to 4 years.16 This has generated much interest in biome-based solutions to treatment, such as fecal microbiota transplantation (FMT) and microbiome-based treatment. FMT refers to giving fecal bacteria from a healthy donor or a pool of healthy donors (stool bank) to the patient with recurrent infection via freeze-dried stool capsules, nasoenteric tube, or colonoscope. Results from randomized studies have shown a higher resolution of *C difficile* diarrhea with FMT (94%) than with vancomycin (31%),17 and with FMT (92%) versus fidaxomicin (42%) or vancomycin (19%).18 In 2019, investigators reported 2 cases of immunocompromised patients infected with extended-spectrum β-lactamase–producing *Escherichia coli* after FMT; 1 of the 2 patients died.19 In 2020, there were also reports of 2 patients developing enteropathogenic *E coli* after FMT, and 4 patients were infected with shiga toxin–producing *E coli*.20 There is concern that safety issues with FMT are underreported, but a prospective cohort study using propensity-score matching showed that patients with recurrent CDI who were treated with FMT had a 23% lower risk of developing primary blood stream infections than those treated with antibiotics.21 Study investigators are currently examining oral partial microbiome fractions. One gut microbiota capsule, SER-109, recently met its primary end point in a phase 3 trial in recurrent CDI and showed a lower proportion of recurrent CDI within 8 weeks with SER-109 (11.1%) compared with placebo (41.3%).22 Another microbiota-based therapy, RBX2660, is currently under study in a phase 3 clinical trial for the prevention of recurrent CDI; it showed 87.1% efficacy, defined as absence of diarrhea through 8 weeks, in its phase 2 trial data.23

More recent developments related to treatment of *C difficile* that are being investigated include new antibiotics and vaccine efforts. Study results show that ridinilazole, a newer antibiotic, has limited systemic absorption and preserves the gut microbiome diversity when compared with fidaxomicin.24 Early data for ridinilazole suggest the agent could become a new treatment against CDI, but phase 3 trials are ongoing. According to a phase 2 clinical study, another antibiotic, MGB-BP-3, met its safety and efficacy end points earlier this year. Immunization against the toxins produced during infection is another area of interest. One vaccine, PF-06425090, entered phase 3 testing in 2017 after a phase 2 trial showed it was safe and well tolerated with a robust immune response.25 VLA48, an additional toxin vaccine, has successfully completed a phase 2 study.26 Antibodies directed against toxins are not likely to prevent colonization or transmission. There are early studies looking at vaccines directed against surface antigens of *C difficile*, which would reduce colonization and thus help with transmission.

Although its incidence has decreased over the past 10 years, *C difficile* remains prevalent in health care institutions and the community. The 2 major challenges are the treatment of severe and fulminant *C difficile* and the prevention of infection and relapse. Expansion and improvement of infection control and antibiotic stewardship programs have been successful in reducing *C difficile* disease burden, but additional measures are required. The development of an effective vaccine is an important next step in disease prevention. There is ongoing development of additional narrow-spectrum antibiotics to treat *C difficile*. Furthermore, the recommendation of fidaxomicin in guidelines, as well as the option of bezlotoxumab, should substantially decrease relapse rates and prevent relapse-related secondary cases. Microbiota-based and metabolomic-based therapies will help restore gut hostility toward *C difficile* in a safe way and are expected to prevent disease and relapse. Several ongoing programs show promise. Additional efforts to develop testing that is more specific, while retaining high sensitivity, are required to better identify persons at higher risk of *C difficile* infection and relapse.

References are available at ContagionLive.com.
Novel Salvage Therapy for Multidrug-Resistant HIV Infection

An examination of 2 agents with novel mechanisms of action.

BY MALIHA AHMED, DO

(continued from cover page)

role as salvage therapy in multidrug-resistant HIV.

FOSTEMSAVIR

Mechanism of action

Fostemsavir (FTR) is a CD4 attachment inhibitor, specifically for heavily treatment-experienced adults with multidrug-resistant HIV-1 who have failed their current regimen. FTR is a prodrug of the active tamsavir, which binds to the HIV-1 viral envelope glycoprotein 120 (gp120) and prevents interaction between the virus and the correlating CD4 receptor.2

Pharmacokinetics

FTR is dosed at 600 mg orally twice daily.2 It is quickly metabolized into its active form, tamsavir, and has a half-life of about 7 to 14 hours. It is excreted mostly in urine (44%-51%) and feces (33%), and minimally in bile (5%).2 The pill should not be crushed or split. High-fat meals enhance bioavailability and absorption time but do not affect the maximum concentration achieved.2 Stomach acid–lowering agents have not been found to change dosing needs to reach maximum efficacy.2 No dosing changes are necessary for patients on hemodialysis or with renal dysfunction.2 Mild hepatic impairment can cause an increase in drug levels, but patients with severe hepatic impairment have not been studied.2

Clinical trials

The pivotal FDA registration trial was the multiphase, 2-cohort BRIGHTE study.3 Cohorts were assigned based on the participants’ remaining treatment options. The first (randomized) cohort included participants who still had the option of 1 or 2 fully active, approved antiretroviral agents (ARVs).3 They were randomized into 2 groups: 1 received FTR 600 mg twice daily in addition to their regimen, and the other received placebo in addition to their regimen.3 After 8 days, both groups of this cohort were then placed on an optimized regimen plus FTR 600 mg twice daily.3 The second (nonrandomized) cohort included participants with no fully active ARVs left as options.3 They were placed on an optimized ARV regimen plus FTR 600 mg twice daily.3 After 8 days of treatment, the treatment group of the randomized cohort had a statistically significant drop in log10 HIV RNA.5,5 At 48 weeks, 54% of the randomized cohort reached a viral load of less than 40 copies, and 38% of the nonrandomized cohort also reached viral suppression with less than 40 copies.5 After 96 weeks, these percentages were 60% and 37% in the treatment group of the randomized cohort and in the nonrandomized cohort, respectively.2

Safety, drug interactions, adverse effects

The most common adverse effects (AEs) reported in the BRIGHTE trial were nausea, diarrhea, and headache.7 During a 96-week safety analysis, serious AEs were noted in 12% of the treatment group and 14% of the control group. Of the FTR group, 2.5% discontinued treatment due to AEs, compared with 10% of the control group.2 As a substrate of the CYP3A enzyme, FTR is contraindicated with any strong CYP3A inducers.2

Cost

As of August 2020, the list cost for FTR is $7650 for a 30-day supply.4 Compassionate use of FTR through ViV Healthcare is available only outside of the United States.4

Although less common today, multidrug-resistant HIV remains a challenge in this population.
Comparison of Fostemsavir and Ibalizumab

<table>
<thead>
<tr>
<th>MECHANISM OF ACTION</th>
<th>DOSING</th>
<th>ADVERSE</th>
<th>COST</th>
<th>RESISTANCE MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fostemsavir</td>
<td>CD4 attachment inhibitor</td>
<td>600 mg orally</td>
<td>Nausea, diarrhea, headache</td>
<td>$7650 30 day supply</td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>Postattachment inhibitor</td>
<td>2000 mg loading dose</td>
<td>Diarrhea, nausea, dizziness, rash</td>
<td>$8930 28 day supply</td>
</tr>
</tbody>
</table>

Resistance
Study results published in 2020 analyzed HIV-1 env full gp120 sequences of 1997 individuals from the Los Alamos HIV database and identified several genomic positions with mutations associated with decreased susceptibility to fostemsavir. The BRIGHTTE trial did not find consistent associations between virologic failure and the presence of these genotypic mutations. In the nonrandomized group, these genotypic mutations were identified in 70% of the participants who met the criteria for virologic failure (greater than 40 viral copies/mL at week 48). Conversely, in the randomized group, more than 50% of participants with virologic failure did not have these genotypic mutations identified.

IBALIZUMAB

Mechanism of action
Ibalizumab (IBA) is an immunoglobulin G4 monoclonal antibody that acts as a postattachment inhibitor. Usually, gp120 attaches to domain 1 of the CD4 receptor to begin HIV’s entry process. IBA binds to domain 2 of the CD4 receptor, causing steric hindrance and blocking HIV entry after gp120 attachment. Importantly, the binding of IBA to CD4 cell receptors does not interfere with normal CD4-related immune functions.

Pharmacokinetics and administration
IBA is administered intravenously (IV); the loading dose is 2000 mg, followed by subsequent doses of 800 mg IV every 2 weeks. It is not thought to distribute to the extravascular space. The half-life is 72 to 84 hours, and there is no effect on serum levels based on renal or hepatic impairment. At 21 days of therapy, 97% of patients had a CD4 cell receptor occupancy of 85% or higher. At week 25, it was 81%. IBA must be administered IV, and after diluting the drug, it can be stored up to 4 hours at room temperature, 20 °C to 25 °C, and up to 24 hours if refrigerated. It must be at room temperature prior to administration.

Clinical trials
TMB-301 (NCT02475629) was a single-group trial of adults with multidrug-resistant HIV-1 who had failed ART regimens, had a viral load of more than 1000 copies/mL, and had resistance across at least 3 different drug classes, with sensitivity to at least 1 drug class. The study was split into 3 phases: 1 week of observation on the patients’ current therapy, 1 week of observation on their ART plus loading dose of IBA, and then observation for 23 weeks on maintenance-dose IBA plus optimized ART regimen. The percentage of participants with a great tan 0.5 log10 decrease in viral load after weeks 1, 2, and 25 was 3%, 83%, and 63%. The percentage of participants with greater than 1 log10 decrease in viral load after weeks 1, 2, and 25 was 0%, 60%, and 55%. At week 25, 43% of participants had a viral load of less than 50 copies/mL, and mean CD4 counts increased from 150 to 240 between week 1 and week 25.

The TMB-311 trial was a single-group extension trial that included 2 cohorts. The first cohort included participants from TMB-301 and from TMB-202, a phase 2b trial; the second cohort included IBA-naïve patients who had HIV viral load greater than 1000 copies/mL, resistance to at least 3 drug classes of ART, and full sensitivity to at least 1 class of ART. Participants from TMB-301 and TMB-202 continued to receive the same regimens they were receiving within their trials (which included FTR in some cases), and cohort 2 was started on a loading dose of IBA (2000 mg), followed by a maintenance dose of 800 mg IV every 2 weeks. Results showed that at weeks 24, 48, and 96 for cohort 1, 59%, 59%, and 56% of participants reached an HIV viral load of less than 50 copies/mL. In cohort 2, at weeks 24 and 48, 46% and 47% reached virologic suppression with less than 50 copies/mL, respectively.

Safety, drug interactions, adverse effects
IBA carries the theoretical risk of infusion-related hypersensitivity reactions and anaphylactic shock; however, these have not been described in any clinical trials. IBA is well tolerated overall; common AEs reported in TMB-301 were diarrhea, nausea, dizziness, and rash. All other serious reactions noted were not due to IBA. The longer-term TMB-311 trial did not note any new AEs, and tolerability was maintained over 96 weeks. Investigators saw no adverse interactions between IBA and other ARTs, and no significant drug-drug interactions have been noted with IBA.

Cost
The cost of IBA is $8930 for a 28-day supply of the maintenance dose. Due to its high price, this medication was not found to be cost-effective in 1 analysis. However, the overall impact of cost will be limited by the relatively small number of patients who will require this medication.

Resistance
Resistance is conferred by decreased viral expression of specific binding sites in the gp120 envelope protein, which overcomes the steric hindrance produced by IBA. In the TMB-301 trial, 7 patients met criteria for virological failure, and 3 had virologic rebound after initial suppression. Investigators identified this mechanism of resistance as the cause of failure in 8 of these 10 patients. Currently, no commercially available resistance panel includes IBA.

CONCLUSIONS
FTR and IBA have recently been FDA approved for use in heavily treatment-experienced individuals with multidrug-resistant HIV, and each medication brings a new mechanism of action to the arsenal of ARVs currently available. Data from the trials outlined above are promising in the ongoing effort to control HIV globally, particularly for heavily treatment-experienced PLWH with multidrug resistance and limited ARV options. ▲

References are available at ContagionLive.com.
GUIDANCE BACKGROUND

Antimicrobial-resistant (AMR) bacteria pose grave threats to global public health. In the United States, AMR organisms are estimated to cause almost 2.8 million infections per year, resulting in more than 35,000 deaths. Infections caused by gram-negative bacteria (GNB), like extended-spectrum β-lactamase–producing Enterobacterales (ESBL-E) or carbapenem-resistant Enterobacterales (CRE), and difficult-to-treat resistance (DTR) nonlactose fermenters, such as Pseudomonas aeruginosa, are therapeutic challenges. Controversies and uncertainties about the roles of older, broad-spectrum agents in the treatment of ESBL-E infections persist, despite the failure of piperacillin-tazobactam to demonstrate noninferiority compared with meropenem in the landmark MERINO trial, which compared the treatments in patients with bacteremia caused by third-generation cephalosporin-resistant Enterobacterales. Since late 2014, 7 novel antibiotics with activity against ESBL-E, CRE, and/or DTR P aeruginosa have been approved by the United States Food and Drug Administration: ceftazidime-avibactam (Avycaz), ceftolozane-tazobactam (Zerbaxa), plazomicin (Zemdri), meropenem-vaborbactam (Vabomere), imipenem-cilastatin-relebactam (Recarbrio), cefiderocol (Fetroja), and eravacycline (Xerava). Others are poised to follow.

Although these agents offer advantages in effectiveness and safety over colistin or polymyxin B, and the long-standing, last-resort antibiotics against CRE or DTR P aeruginosa infections, their uptake into clinical practice has been slow. Moreover, there is considerable confusion among clinicians regarding where specific drugs fit within therapeutic hierarchies.

In parallel with the development of new antibiotics, there have been advances in defining AMR GNB epidemiology. Widespread implementation of rapid and/or molecular diagnostics allows clinicians to identify AMR organisms and characterize resistance mechanisms in real time. Clinical application of molecular platforms and laboratory-based
genomic data (such as those generated in the CRACKLE project) has demonstrated that CRE in the US is not synonymous with *Klebsiella pneumoniae* carbapenemase (KPC) production. Indeed, it is clear that CRE are due to a variety of non-KPC mechanisms, including production of metallo-β-lactamases (such as New Delhi metallo-β-lactamase) or porin mutations combined with noncarbapenem β-lactamase production.

Molecular data are not simply of academic interest, as many new antibiotics are active against strains expressing particular resistance determinants. Therefore, making optimal treatment decisions against CRE and other AMR GNB infections requires clinicians to be familiar with local epidemiology and resistance mechanisms.

The Infectious Diseases Society of America (IDSA) identified the development and dissemination of timely practice recommendations as a top initiative in its 2019 Strategic Plan. The just-released IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections offers practical recommendations for the antimicrobial management of ESBL-E, CRE, and DTR *P. aeruginosa* infections. In the Strategic Plan, IDSA acknowledged that traditional timelines used to generate new or updated clinical practice guidelines limited the ability to address rapidly evolving topics like antimicrobial resistance. IDSA endorsed developing more narrowly focused guidance documents for the treatment of specific, complex infectious processes based on the critical review of published data and expert opinion, rather than formal GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria. A panel of 5 physicians and 1 pharmacist with clinical and research expertise in the treatment of patients with AMR GNB infections was assembled and given the latitude to identify key problem areas that are addressed in the initial document.

The panel held an initial meeting in March 2020, at which time the 3 pathogen groups above were chosen. Other pathogens were discussed, including AmpC-producing *Enterobacterales*, carbapenem-resistant (CR) *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, but left them to subsequent iterations to facilitate timely completion of the initial publication of the first guideline. The panel was split into 3 groups of 2 members each to draft guidance for each of the 3 pathogen groups; recommendations made in the final document were discussed among the entire group over a series of subsequent meetings.

The IDSA panel will review the recommendations at least quarterly for revisions, with updates issued as needed based on new evidence.

As with any guidance document, opinions differed; however, the panel came to a consensus over each recommendation. The final document addresses 18 important clinical questions and includes 4 summary tables, 1 of which includes recommended antimicrobial dosing for each recommended agent. As the guidance was intended to be an easily accessible summary, an extensive review of the evidence and detailed rationale were not included for each recommendation. Rather, the panelists intend to provide this additional information as complementary published reviews.

**GUIDANCE HIGHLIGHTS**

There are several key recommendations in the guidance that should be specifically mentioned. First and foremost, the polymyxins (colistin and polymyxin B) are not recommended for treating any infections by the various pathogens (with one exception) as long as 1 of the novel β-lactam/β-lactamase inhibitor combinations remains active. Simply put, nearly any alternative is preferred. The sole exception to this is DTR *P. aeruginosa* infections in which ceferodol is the only active β-lactam. Results from the recently published CREDIBLE-CR trial (NCT02714595) demonstrated an unexplained mortality imbalance favoring primarily polymyxin-based combination therapy over ceferodol among patients treated for CR GNB infections, including those caused by DTR *P. aeruginosa*. For CRE infections, including those caused by metallo-β-lactamase-producing *Enterobacterales*, other new agents almost invariably are available and preferred over polymyxin-based therapy. Second, carbapenem-based therapy (rather than piperacillin-tazobactam) is recommended for the treatment of most infections caused by ESBL-E, including pyelonephritis. The consensus of the panel was that the mortality benefit for carbapenem observed in the MERINO trial is compelling, even when viewed in the light of contradictory observational data. Although the data are less clear for pyelonephritis, the panel felt that the hypothetical stewardship considerations (eg, less selective pressure for CR organisms) did not outweigh the potential risks of therapeutic failure. Therefore, the panel determined that it could not recommend piperacillin-tazobactam for the treatment of pyelonephritis caused by ESBL-producing organisms.

Lastly, active β-lactam monotherapy is recommended for the treatment of most multidrug-resistant GNB infections. Observational data for CRE and DTR *P. aeruginosa* infections prior to the advent of the novel β-lactam/β-lactamase inhibitors suggested a benefit with combination therapy with several suboptimal and/or inactive antibiotics, but both observational and randomized trial data for the new agents support the use of monotherapy. This recommendation should not be taken to preclude the use of combination therapy in appropriate situations (eg, polymicrobial infections, medically complex infections where prolonged or indefinite therapy may be likely).

**FUTURE DIRECTIONS**

This IDSA guidance is intended to be a living document. The panel will review the recommendations at least quarterly for revisions, with updates issued as needed based on new evidence. When evidence reaches a threshold where GRADE-based recommendations become reasonable, the panel will convert the document to such a framework. Additionally, the panel will expand the scope of the document to address AMR GNB infections not included in the first iteration.

As a final note, the panel also welcomes comments. The panel is fully vested in adapting recommendations (or providing detailed rationales when not adapted) as outside opinions are voiced and evidence is presented. ▲

References are available at ContagionLive.com.
The Role of Antimicrobial Stewardship in the Treatment of C difficile

The significance of biologics in the treatment landscape.

BY HELEN G. BERHANE, PHARMD, AND JENNIFER N. CURELLO, PHARMD, BCIDP

includes oral antibiotics vancomycin and fidaxomicin. However, comprehensive management of CDI cannot be achieved with antibiotics alone, as they disrupt the normal gut flora and do not target Clostridioides difficile spores. Fidaxomicin and fecal microbiota transplant (FMT) have been favored in the management and prevention of recurrent CDI due to their theorized ability to combat microbiota dysbiosis. With mounting evidence of the correlation between antibiotic use, host microbiota dysbiosis, and recurrent CDI, biologics and novel strategies may also play a key role in CDI therapy.

Bezlotoxumab (Zinplava) is a human monoclonal antibody approved by the United States Food and Drug Administration (FDA) in October 2016 as adjunctive therapy for the management of patients at high risk for recurrent CDI. Clostridioides difficile exerts its pathologic effects primarily through the production of enterotoxin (toxin A) and cytotoxin (toxin B). Bezlotoxumab functions by binding to and neutralizing the effects of toxin B. Bezlotoxumab received FDA approval based on the results of the MODIFY I and MODIFY II phase 3 clinical trials. Results of these trials showed significant reduction in the recurrence of CDI up to 12 weeks after initial resolution of symptoms with bezlotoxumab when compared with placebo (MODIFY I: 28% vs 17%, respectively, \( P < .001 \); MODIFY II: 26% vs 16%, \( P < .001 \)). Bezlotoxumab is well tolerated; however, there was an increased incidence of heart failure (HF) found among those with underlying HF compared with placebo. Data support the routine use of bezlotoxumab for the management of recurrent CDI. Although the 2018 Infectious Diseases Society of America and Society for Healthcare Epidemiology of America clinical practice guidelines do not provide guidance for incorporating its use into routine practice, bezlotoxumab may be recommended in combination with fidaxomicin in a subset of patients at high risk for recurrent disease in the next iteration of the guidelines. Results from a post hoc analysis of the MODIFY trials suggested patients at highest risk of recurrence included those who were 65 years and older and had compromised immunity, severe CDI, prior CDI episode(s), and infection with ribotypes 027/078/244. The greatest benefit observed with bezlotoxumab was in patients with 3 or more risk factors. Bezlotoxumab may help address the significant clinical and economic impacts seen by recurrent CDI A 20% to 30% rate of recurrence has been shown...
among patients treated with antibiotics (primarily vancomycin and metronidazole) for CDI. Recurrent infection leads to increased length of hospital stay, prolonged antibiotic exposure, and increased morbidity and mortality. Recurrent CDI also creates significant financial costs. Approximately $8.2 billion was spent on CDI hospital stays in 2009, with a recurrent episode estimated to cost $11,146 more than an initial episode. 

On an institutional level, there is also the associated cost of infection prevention services to mitigate transmission to staff and patients. Bezlotoxumab administered as a single 10-mg/kg intravenous dose has the potential to offset these costs by preventing readmission for recurrent CDI. The average wholesale price of bezlotoxumab is estimated to be $114 per milliliter (1 gram per 40 mL). Not including administrative costs, insurance coverage, and unique drug pricing strategies, the cost for a patient weighing 70 kg would be approximately $3192. To determine the cost-effectiveness of bezlotoxumab compared with placebo, Prabhu et al conducted a computer-based study to assess incremental cost comparisons and impact on quality-adjusted life-years (QALYs). They determined the incremental cost for receiving bezlotoxumab is $2444 per patient. They also found a reduction in CDI recurrence and a 0.12 difference in QALY between the bezlotoxumab (8.45 QALY) and placebo (8.33 QALY) groups. Bezlotoxumab may help offset costs associated with recurrent CDI readmissions as well as enhance patients’ quality of life.

Results from additional post hoc analyses of the MODIFY trials showed no difference in recurrent CDI when bezlotoxumab was administered on days 0 to 2 or 3 to 4, or 5 or more days after the initiation of standard-of-care oral antibiotics (vancomycin, metronidazole, or fidaxomicin). Also, bezlotoxumab did not reduce the duration of diarrhea. Given the cost of the drug, and its use primarily to prevent recurrence, bezlotoxumab is often reserved for outpatient use. To truly carve out a niche for its use in CDI therapy, cost and efficacy comparisons between bezlotoxumab and other antibiotics and biologic strategies, such as FMT, are needed. Data suggest that treatment of CDI with fidaxomicin has a lower risk of second recurrence compared with vancomycin. The impact of using bezlotoxumab in patients treated with fidaxomicin would further help identify a definitive role for bezlotoxumab in CDI therapy.

As with bezlotoxumab, FMT and bacteriophage therapies have been introduced to further combat the microbiota disruption seen with traditional antibiotic treatment. FMT is recommended for patients with second or subsequent CDI who have failed appropriate antibiotic treatments. Guideline recommendations of 2 or more failed antibiotic treatments prior to FMT are largely based on expert opinion. Results from observational and randomized clinical trials showed treatment success rates between 77% and 94%. The highest success rates were observed with the instillation of feces via the colon (80%-100%), and results from other studies suggested increased success with more than 2 FMT administrations. A small, randomized controlled trial comparing FMT with standard vancomycin 14-day treatment, with the primary end point of resolution of diarrhea without relapse after 10 weeks, was terminated early due to significant differences favoring resolution in the FMT arm. FMT is generally safe; however, there is a risk of physical complications with instillation and transmission of infection from donors. Of recent concern is the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 can cause gastrointestinal symptoms, and the virus has been detected in stools. However, the transmission of COVID-19 infection by fecal route is unclear. The primary supplier of FMT, OpenBiome, has indicated it is providing appropriate COVID-19 screening of all FMT donors.

Bacteriophage therapy is the use of viruses to specifically infect bacteria. Many bacteriophages have narrow ranges of host targets, which help prevent the dysbiosis seen with antibiotics. Furthermore, bacteriophages can potentially degrade and penetrate biofilms. Data for bacteriophage use are promising, however, identification of definitive targets for CDI is ongoing.

Antimicrobial stewardship can aid in identifying patients at risk for CDI recurrence, disease progression, and those who may benefit from biologic therapies. Although it is expensive compared with antibiotic treatment options, biologic therapy can provide cost savings in the long term by preventing recurrence leading to hospitalization. Antimicrobial stewardship programs can also help prevent the inappropriate use of agents such as bezlotoxumab by redirecting their use to the outpatient setting. Administration of bezlotoxumab in the outpatient setting ensures the health care system will be reimbursed for the cost of the drug by third-party payers. Biologics are a novel and promising treatment option, particularly for patients with CDI refractory to antibiotic therapy. More data would assist in the incorporation of these agents into the CDI treatment algorithm in a way that is beneficial to the patient and cost effective.

References are available at ContagionLive.com.
New antiretroviral drugs with unique mechanisms of action and delivery provide promising options for treatment and pre-exposure prophylaxis (PrEP) of HIV infection and may improve adherence in certain subgroups of individuals. However, the development of an effective vaccine remains elusive, according to experts who participated in a recent Contagion® Peer Exchange panel.

EMERGING TREATMENT OPTIONS FOR HIV

Fostemsavir (formerly BMS-663068/GSK3684934), a prodrug whose active metabolite (temsavir) is a first-in-class attachment inhibitor that binds directly to the viral envelope glycoprotein 120 near the CD4+ binding site, was approved by the FDA on July 2, 2020, for adults living with HIV who have tried multiple HIV medications and whose infection cannot be treated with other therapies because of resistance, intolerance, or safety reasons. This approval was based largely on results from a phase 3 trial, which showed a virologic response (HIV-1 RNA < 40 copies/mL) at week 48 in 54% of patients with heavily pretreated, multidrug-resistant HIV infection who received fostemsavir plus optimized background therapy.

Session moderator Joseph Eron, MD, said that its oral dosing is advantageous over ibalizumab, which is dosed intravenously, although he said that fostemsavir will probably be limited for patients with few or no treatment options.

Allison Agwu, MD, ScM, added that long-acting injectable and oral agents, capsid inhibitors, and monoclonal antibodies are also being studied in the HIV space, as are alternative delivery approaches, such as subcutaneous injections, pumps, implants, and patches. However, she pointed out that access to and the cost of these novel options will be key issues moving forward, particularly when currently available oral agents are highly effective for suppressing HIV viral load in the majority of cases.

“The discussions we’ll have to have on how and who and where are going to be very important,” said Agwu. “It doesn’t mean we shouldn’t have those discussions because for the people who are living with HIV, these are maybe life-saving, game-changing remedies for them.”

LONG-ACTING INJECTABLE THERAPIES TO TREAT HIV

The panelists discussed potential uses and challenges with the long-acting injectable therapy containing cabotegravir (an HIV-1 integrase strand-transfer inhibitor) and rilpivirine (a non-nucleoside reverse-transcriptase inhibitor), which is injected in 2-mL doses in the gluteus medius every 4 weeks for the maintenance of virologic suppression in patients who are initiating or transitioning therapy. Although the FDA declined to approve the combination in December 2019 due to concerns related to chemistry manufacturing and controls, the drug manufacturer (ViiV Healthcare) stated that no related safety issues have been reported and the safety profile of the products has not changed. ViiV Healthcare submitted another new drug application that was accepted in April 2020.
Colleen Kelley, MD, MPH, said that a benefit of long-acting injectable dosing is that it may help reduce the internalized stigma for many individuals living with HIV who take a daily oral medication. “It’s a constant reminder when you have that pill bottle on your bathroom stand that says, ‘I am HIV positive,’” she noted.

However, the panelists pointed out potential drawbacks with long-acting injectables, such as the risk for drug resistance in patients who miss injections and the possible need to modify the clinic set-up to ensure availability of nursing staff when patients are receiving injections.

“Although there may be some adherence problems that get solved by the injections, I think that there are other adherence risks that get created,” said Ian Frank, MD. “It’ll be more incumbent upon us as providers to ensure that our patients are coming in at the appropriate frequency, and we may need to modify our practices.”

**LONG-ACTING INJECTABLES AS PRE-EXPOSURE PROPHYLAXIS**

Long-acting injectable therapy with cabotegravir may provide a discreet option for PrEP that does not require daily dosing, according to a recent interim analysis of the phase 2b/3 HPTN 083 trial (NCT02720094). The interim results from the trial showed that cabotegravir injection every 8 weeks was superior to daily oral emtricitabine/tenofovir (Truvada) for preventing HIV acquisition in cisgender men who have sex with men and transgender women who have sex with men.

To have population-level effectiveness, long-acting injectable PrEP needs to cater to a population of individuals who are eligible for and interested in receiving it but are not interested in daily oral PrEP, according to Julia Marcus, PhD. “If the only people who are interested in long-acting PrEP are people who are already taking daily PrEP...it’s not going to have any population-level effectiveness,” she said.

Marcus added that identifying individual barriers to receiving oral PrEP is important to assess whether long-acting injectable PrEP is appropriate for them, noting that it would be more likely to benefit an individual who forgets to take daily medications than one who has difficulty with coming into the clinic.

“If their [issue is] that they don’t want to be coming into the clinic every 3 months, long-acting injectables may not help them,” she said. “They may have to come in even more.”

Other individuals who may be good candidates for long-acting injectable PrEP include those for whom having oral medication may put them at risk for bodily or emotional harm, such as people in unequal power relationships, commercial sex work, or homeless living situations, said Eron and Marcus. Individuals who use injectable drugs or are on methadone maintenance may also be good candidates for PrEP if they come in frequently for syringe changes, said Marcus.

Agwu added that long-acting injectable PrEP could also expand the options in the armamentarium for a given patient at different times of their life.

“If a patient has to go abroad for 2 months, maybe that’s the time to get your shot,” she said. “You don’t have to worry about taking your pills to Morocco.”

She said that further work is needed to optimize system and administration issues and improve practices for delivering long-acting injectable therapy in the clinic. Eron concluded that further research to ensure the efficacy and demedicalization of PrEP is important to improve uptake, as the perception that PrEP care is more intensive than HIV care continues to persist among individuals who are eligible for PrEP.

**PREVENTATIVE AND THERAPEUTIC HIV VACCINES**

Although the phase 2b/3 HVTN702 trial (NCT02968849), which studied the RV144 Thai vaccine regimen for the prevention of HIV infection in South Africa, was recently discontinued because of a lack of efficacy, Kelley said that this outcome does not mark the end of the journey for finding an effective vaccine, which will be the key to ending the HIV epidemic.

“There’s still more work to be done and no reason to lose hope,” she said. “We’re thinking about monoclonal antibodies and long-acting antiretrovirals in place of a traditional vaccine.”

Kelley said researchers are getting closer to identifying what the immune system needs to do to protect itself from HIV infection. “If these neutralizing antibodies are the key, how do we make our human immune system create those neutralizing antibodies? …That’s been extremely difficult to do,” she said. “We can make the antibodies outside the person, but we can’t make the person produce the antibodies. This is the biggest barrier right now.”

Frank added that therapeutic vaccines are also being investigated as a strategy for curing HIV, with “cure” defined “in the context of doing something other than requiring people to take regular antiretroviral therapy to control the virus replication.” Specifically, the goal of a therapeutic vaccine is to improve the individual’s immune response against the infection to enable the withdrawal of antiretroviral therapy and promote an improved immune response to control virus replication, said Frank. He concluded that although therapy and prevention continue to improve, the absence of an effective vaccine and a cure are “the real vacuum” in HIV prevention and treatment, respectively.

**ADVICE FOR PHYSICIANS TREATING PATIENTS WITH HIV**

At the conclusion of the exchange, the panelists discussed tips for physicians in the screening, diagnosis, and treatment of patients living with HIV. Agwu stressed the importance of asking patients about risk factors for HIV, including sexual activity, and testing and offering PrEP for patients at high risk. Kelley added that in addition to routine discussions about sexual health, maintaining consistency in the treatment of each patient and identifying other issues that are common to those living with HIV, such as other sexually transmitted infections, is important.

Marcus added that discussing sexual health in an open-ended, nonjudgmental, patient-centered way is important for optimal communication with patients and that communicating the U = U (undetectable = untransmissible) message can be "transformative" for them.

Frank concluded that although undetectable viral load is often the primary focus of antiretroviral therapy, providers should also consider additional factors, such as comorbid conditions, when optimizing HIV therapy and managing overall care for patients.

“It’s important that we remind our patients that they may have other medical conditions, or they may develop other medical conditions, and those medical conditions may pose as great a risk, if not a bigger risk, than their HIV disease,” said Frank. “I have many patients with uncontrolled hypertension and uncontrolled diabetes and lipids that are high. I tell them that they’re going to die of a heart attack or a stroke or be on dialysis long before they ever get a complication of their HIV. Dying of a heart attack with an undetectable viral load isn’t my goal of their treatment. It’s not just about their HIV.”

References are available at ContagionLive.com.
Virtual October 21-25, 2020

STARTING ADDICTION CARE WITH INJECTION DRUG-INFECTED PATIENTS

Sarah Blevins, PharmD, a clinical pharmacist at the University of Kentucky, provides a firsthand look into a regional program that's initiated opioid use disorder care in recurring injection-based infection patients with HIV, hepatitis C, and other chronic conditions.

contagionlive.com/idweek1

COVID-19 CASE STUDIES: HOW FAR SCIENCE HAS COME

Ravina Kullar, PharmD, MPH, founder of duXsana, reflects on rapid advances in treatment understanding during IDWeek 2020.

contagionlive.com/idweek2

PEDIATRIC ANTIBIOTIC PRESCRIBING REMAINS HIGH IN ED, DESPITE TESTING

New data from the team of Suchitra Rao, MBBS, MSCS, associate professor at the University of Colorado School of Medicine, highlight the need for more antimicrobial stewardship adoption in emergency care settings.

contagionlive.com/idweek3
As the name suggests, post-Ebola syndrome occurs in survivors of the infectious disease and can present as a wide range of lingering symptoms, including eye problems sometimes leading to blindness, neurological issues, and muscular and joint pain.

The condition can be quite debilitating to the point where patients are sometimes unable to work.

As such, investigators decided to understand the depth of the syndrome. They identified survivors in East Sierra Leone, and household contacts of survivors were identified by enrolled survivors. Both groups were administered a questionnaire assessing self-reported symptoms. Providers performed a physical exam.

For nearly 3 years from March 2016 and January 2019, 375 Ebola survivors and 1040 contacts were enrolled.

"Symptoms were then compared using hierarchical clustering," the investigators wrote. "Statistical analysis of the correlations between clusters was conducted using conditional logistic regression. Both SPICE and principal component (PCA) analyses were performed to explore the relationships between symptom clusters."

In terms of symptom clusters, 6 were identified representing organ systems. The SPICE analysis revealed 2 general phenotypes: with or without rheumatologic symptoms.

"Clusters including rheumatologic symptoms were correlated with one another, but not with other clusters. Ophthalmologic/auditory symptoms were moderately correlated with the non-rheumatologic clusters," the investigators wrote. "Interestingly, psychologic/neurologic, cardiac/GI and constitutional clusters correlated with one another in all cases. The symptom clusters were then mapped onto a PCA. Each symptom cluster separated from the remainder along PC1, particularly the phenotypes with rheumatologic symptoms."

Sarah Talia Himmelfarb, MD, resident in internal medicine and pediatrics at Tulane University is a presenting author of the study and spoke to Contagion during IDWeek 2020 about the study and offered significant insights into its important findings.

**What was your motivation for doing this study?**

**Himmelfarb:** To date, several studies have been performed to determine if specific markers of inflammation are associated with post-Ebola syndrome. No marker has been identified when looking at survivors as a homogeneous group. The goal of the study was to look for patterns within the wide variety of symptoms that Ebola survivors present with. Our motivation in doing this was to see if any patterns fit known disease processes. In particular, we wanted to investigate the possibility that they fit the pattern of a rheumatologic or autoimmune disease. This would help us better understand this poorly characterized syndrome and might help lead to therapies for those who suffer from it.

**What are the important takeaways from it?**

Using multiple modalities of statistical analysis of reported symptoms and physical exam findings we found clusters of symptoms that occur together. We also found a group of patients that has complaints from the musculoskeletal cluster of symptoms such as joint pain and decreased range of motion, and this group overlaps with a group that has gastroenterological symptoms such as abdominal tenderness.

This suggests that there is a group of survivors which seem to have a rheumatologic pattern of disease, and that this may be related to GI dysfunction in some way. An intriguing possibility is that inflammation stemming from impaired gut barrier, as was detected in a previous study, may be an etiologic cause of this group of symptoms.

**Do you have any plans for follow-up?**

Our next steps will be to try to correlate different symptom patterns with serum and plasma biomarkers and antibody phenotypes. We also hope to explore how these symptom patterns vary over time and with relationship to demographic features such as socioeconomic status and profession.

**Why is this an important topic?**

This work has significance for the thousands of Ebola survivors who emerged from the 2014-2016 epidemic in Western Africa. It also contributes a small but growing body of knowledge of post-viral sequelae. This field has only become more relevant in the age of COVID-19 [coronavirus disease 2019].

Currenly, the only 2 pneumococcal vaccines licensed for use in the United States are a 13-valent pneumococcal conjugate vaccine (PCV13/Prevnar 13) and a 23-valent pneumococcal polysaccharide vaccine (PPSV23/Pneumovax23). In an effort to expand serotype coverage beyond 13, a 20-valent pneumococcal conjugate vaccine, PCV20, is currently in development.

In a presentation at the virtual ID Week 2020, investigators reported on phase 3 safety, tolerability, and immunologic noninferiority data for PCV20 in participants 18 years and older. PCV20 includes the additional conjugates for serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F.

The study grouped adults naïve to pneumococcal vaccination into 3 age cohorts of ≥60, 50-59, and 18-49 years of age in order to assess tolerability, safety, and immunogenicity (opsonophagocytic activity [OPA] responses) of PCV20. Participants in first age group, comprising adults aged ≥60 years, were randomized 1:1 (double-blind) to either PCV20 and saline 1 month later, or PCV13 and PPSV23 1 month later. The remaining 2 age groups, adults aged 50-59 years and 18-39 years, received either a dose of PCV20 or PCV13 (3:1 randomization, double blind). A total of 3889 participants received the vaccine.

Of participants in the older age group, 1507 received PCV20 and 1490 received control. “All 20 vaccine serotypes induced robust responses and OPA geometric mean titers (GMTs) to all 13 matched serotypes were noninferior to PCV13,” investigators reported, adding that OPA GMTs to 6 of the 7 additional serotypes were noninferior compared with the same serotypes in PPSV23 1 month after PCV20. OPA GMT of the remaining serotype, 8, missed noninferiority by a very narrow margin (2-sided 95% lower bound of GMT ratio [20xPnc/PPSV23] was 0.49, with noninferiority criterion of >0.5), the research team noted.

In both the younger cohorts, GMTs after vaccination with PCV20 were noninferior to adults aged 60-64 years, and safety and tolerability of PCV20 was similar to PCV13.

“Based on the robust immune responses and comparability to licensed pneumococcal vaccines, as well as bridging to the younger age group, these data support that PCV20 will be protective against pneumococcal disease due to the 20 serotypes in adults,” investigators concluded.
Brigham and Women’s Provides Blueprint for Hospital COVID-19 Protection

BY KEVIN KUNZMANN

Innovators from Brigham and Women’s Hospital reported new observational data showing coronavirus disease 2019 (COVID-19) infections to originate in the hospital were especially rare during the first wave of the pandemic in the United States.

Over 12 weeks from March to May 2020, the investigators traced just 2 COVID-19 cases to nosocomial origin.

The findings, presented at IDWeek 2020 by Chanu Rhee, MD, MPH, Assistant Professor at Harvard Medical School, provide clinical evidence for a series of rigorous infection control practices applied in the Boston hospital. They may also inform institutions in COVID-19 hotspots or those at continued risk of institution outbreaks.

In an interview with Contagion® during IDWeek, Rhee provided context into his team’s findings, what practices Brigham and Women’s put in place at the beginning of the pandemic, and how such measures can inform both hospitals and other community settings attempting to mitigate COVID-19 spread.

**CONTAGION®: Prior to research, what was our working theory or understanding of nosocomial COVID-19 infection among hospitals in the early days of outbreak?**

**RHEE:** In the early days of the pandemic, there were reports of widespread outbreaks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within skilled nursing facilities and other congregate settings. However, little was known about nosocomial SARS-CoV-2 infection among patients in acute care hospitals. As such, there was a lot of anxiety about whether the infection control measures recommended by the CDC were adequate to prevent spread within the hospital and many patients have foregone essential medical care due to fear of contracting COVID-19.

**What observed measures were put into place to manage COVID-19 hospital spread?**

At our hospital, the core components of our infection control program included the following:

- Screening of all patients for COVID-19 symptoms on admission and daily thereafter
- Requiring all hospital staff to attest to the presence or absence of symptoms prior to starting their shift; staff with symptoms are referred for COVID-19 testing and not allowed to work if symptoms are present
- Liberal use of PCR testing initially for all symptomatic patients on admission or with any new symptoms during hospitalization. In late April we implemented universal testing for all patients at the time of admission, including asymptomatic patients.
- Dedicated COVID-19 units with airborne infection isolation rooms
- Personal protective equipment (PPE) in accordance with CDC recommendations
- PPE donning and doffing monitors
- Universal masking of staff and subsequently patients and visitors
- Restriction of visitors except in extenuating circumstances

We also developed hospital-wide protocols on when clinicians were permitted to discontinue isolation precautions in patients with suspected COVID-19, which generally required 2 negative RT-PCR tests at least 12 hours apart, and used protocols based on CDC-guidance to determine when patients with confirmed COVID-19 could be released from isolation.

**How did this research better inform infection control measures and resourcing?**

COVID-19 presents many infection control challenges since many infected individuals are asymptomatic yet contagious; current diagnostic tests are imperfect, especially if patients are tested too early in the incubation period; and transmission can occur through multiple mechanisms including droplets, fomites, and aerosols. Our analysis, however, demonstrates that a multifaceted infection control program based on US CDC guidance can minimize the risk of nosocomial transmission of SARS-CoV-2.

Over the first 12 weeks of the pandemic, our hospital cared for over 9000 patients including nearly 700 with COVID-19. Despite the high burden of COVID-19 in our hospital, we only identified 2 patients who likely acquired their infection in the hospital, including one who was most likely infected by his spouse prior to visitor restrictions and universal masking.

**Adversely—given the rarity of hospital spread when such measures are applied—what can other community settings at risk of significant spread take away from these findings?**

While our study cannot determine which interventions are most important to prevent spread of COVID-19, my take-away is that a comprehensive program is needed to minimize the risk. In other words, there is no one silver bullet.

One important observation that emerged from our case reviews was that several patients were only tested for the first time three or more days after hospitalization, sometimes because of atypical symptoms that were initially attributed to non-COVID-19 conditions. These cases highlighted the importance of implementing universal testing on admission, and we observed fewer late-onset cases after this intervention. However, universal testing is not infallible as several patients initially tested negative while asymptomatic and then tested positive after symptoms began several days later. This underscores the fact that PCR can miss some infections early in the incubation period.

Another important theme that emerged from our case reviews was the need to conduct serial testing of patients with clinical syndromes highly suspicious for COVID-19. At least three cases with concerning syndromes initially tested negative but were positive on repeat testing. Based on our early experience, we instituted a protocol requiring at least 2 negative RT-PCR tests in symptomatic patients before discontinuing isolation.

**Are there any plans for continued or follow-up research?**

In addition to the analysis presented in the study, which encompassed the period from March 7 to May 30, we have continued to closely monitor our hospital for any new potential cases of nosocomial SARS-CoV-2 infection. We found no additional cases of nosocomial infection over the ensuing months. However, in late September we did have a cluster of SARS-CoV-2 infections that occurred on two units in our hospital that affected both patients and staff.

Our investigation determined that the cluster likely began with a highly contagious patient who initially tested negative twice on admission. With a combination of preemptive precautions, intense contact tracing, and serial testing of all patients and staff associated with the affected units, and numerous other measures, we have been able to fully contain this cluster. We are currently evaluating the lessons learned from the cluster to determine how best to further improve our infection control policies moving forward. ▲
Decreasing Antiretroviral Regimens in an Aging Population

BY JOHN PARKINSON

As people living with HIV (PLWH) age, there is a move to have them taking fewer antiretrovirals, and ones with fewer drug-drug interactions (DDIs), and long-term adverse effects.

Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is an example of one antiretroviral that is a combination therapy looking at this population.

Past clinical trials of B/F/TAF demonstrated favorable efficacy and safety in older adults, however, data from real-world experience are needed to validate results.

Investigators did a retrospective analysis evaluating medical records from PLWH aged 50 years or younger who had switched their regimen to B/F/TAF between February 7, 2018, and May 31, 2019.

The study included 306 PLWH and they identified the primary end point as maintaining HIV-1 RNA < 50 copies/mL and found FMGX to have potent in vitro activity against all study isolates for antifungal susceptibility evaluations reported.

In results from a phase 2 proof-of-concept (POC) study presented virtually at ID Week 2020, investigators with the University of Alabama at Birmingham and Amplyx Pharmaceuticals report favorable safety and efficacy data for fosmanogepix (FMGX) as first-line treatment for patients with candidemia.

FMGX targets more resistant Candida spp, specifically the fungal enzyme Gwt1, and is formulated for both oral and intravenous (IV) administration.

"In this real-world cohort, switching to B/F/TAF was associated with maintenance of virologic control, improvement in lipid parameters, and avoidance of DDIs in a large proportion of patients," investigators concluded. "These data support use of B/F/TAF as a treatment option in older PLWH." ▲

Fosmanogepix Shows Promise as an Effective Novel Antifungal in POC Trial

BY ALEXANDRA WARD, MA

Fungal infections represent a massive health burden in terms of both mortality and cost, as they contribute to an estimated 1.5 million deaths per year globally and were estimated in 2017 to have driven $7.2 billion in direct medical costs, according to the US Centers for Disease Control and Prevention (CDC).

Consider, too, that there are only a handful of classes of antifungals and it is clear why the need for novel agents with unique mechanisms of action is so urgent.

In results from a phase 2 proof-of-concept (POC) study presented virtually at ID Week 2020, investigators with the University of Alabama at Birmingham and Amplyx Pharmaceuticals report favorable safety and efficacy data for fosmanogepix (FMGX) as first-line treatment for patients with candidemia.

FMGX targets more resistant Candida spp, specifically the fungal enzyme Gwt1, and is formulated for both oral and intravenous (IV) administration. The global, multicenter, open-label, non-comparative study enrolled eligible participants who had a recent diagnosis of candidemia as evidenced by a positive blood culture for Candida spp within 96 hours prior to study entry and with 2 or fewer days of prior antifungal treatment.

Exclusion criteria included neutropenia, C krusei infections, and deep-seated Candida infections.

The modified intent-to-treat (mITT) population included patients with candidemia that had been diagnosed within 96 hours of starting the study drug and who received at least 1 dose of FMGX.

Outcome at end of study treatment (EOST) as determined by an independent data review committee (DRC) was the primary efficacy outcome. Success was defined as clearance of Candida from blood cultures with no additional treatment with antifungals and survival at EOST.

The course of treatment was up to 14 days of FMGX, administered at 1000 mg IV twice a day for 1 day, then 600 mg IV 4 times a day for at least 2 days, followed by either 600 mg IV 4 times a day or 700 mg by mouth 4 times a day. If treatment was required beyond 14 days, patients could receive fluconazole (or appropriate alternative).

Those included in the mITT, 20 of 21 subjects, received a median 11 days of FMGX (range 5-14). IV FMGX was administered to all subjects, while 48% (10/21) received FMGX orally. At EOST, the success rate as determined by the DRC was 80% (16/20).

Day 30 survival rate was 85% (17/20), and the 3 deaths were not related to the study drug. There were no serious treatment-related adverse events or discontinuations reported.

Investigators tested all Candida isolates for antifungal susceptibility and found FMGX to have potent in vitro activity against all study Candida spp (EUCAST MIC range 0.001-0.03 µg/ml), including those resistant to other antifungal treatments.

Peter G. Pappas, MD, professor of medicine at the University of Alabama at Birmingham, and presenting author of the study, told Contagion that development of a phase 3 trial is now in progress.

"The compound appears to be safe and well tolerated, [and we observed] excellent efficacy based on a very small sample size," Pappas said. ▲
CASE STUDY

A Case of Pneumonia and Bacteremia in a Trauma Patient Caused by *Bordetella hinzii*

A presentation of bacterium in an immunocompetent patient

BY ELIZABETH NOVICK, MD, AND REBECCA MOON

**FINAL DIAGNOSIS: *B hinzii* PNEUMONIA AND BACTEREMIA**

**HISTORY OF THE PRESENT ILLNESS**

A man, aged 21 years, presented to our emergency department with gunshot wounds to the right upper back and left anterior chest. He required needle decompression of the right chest prior to arrival due to hypotension and concern for pneumothorax. Upon arrival at the trauma bay, the patient was awake and alert. An initial exam was notable for bilateral lower extremity paralysis. A chest X-ray revealed a widened mediastinum, and a CT scan of the chest identified tracheal injury, vertebral body fractures of the fourth and fifth thoracic vertebrae, pneumomediastinum, and pneumopericardium. The patient required emergent surgical stabilization, including median sternotomy, tracheal repair, and innominate vein ligation. The patient was initiated intraoperatively on venovenous extracorporeal membrane oxygenation (VV-ECMO) and was then transferred to the surgical intensive care unit, intubated, and sedated.

**MEDICAL HISTORY**

Notable only for mild, intermittent asthma.

**KEY MEDICATIONS**

At presentation, none.

**EPIDEMIOLOGICAL HISTORY**

The patient was born in the United States and had never lived outside of Philadelphia, Pennsylvania. He reported frequent sightings of rodents on the streets near his home, but not inside his residence. Three pet cats lived in his residence and were without signs of illness prior to the patient’s presentation. He reported an isolated incident of handling live chickens 2 months prior to presentation. He denied recent travel. He had no significant family history, except that his grandmother had died from lung cancer. He smoked 1 pack of cigarettes daily.

**PHYSICAL EXAMINATION**

On presentation to our hospital, the patient was awake and alert, saturating well with a nonrebreather mask delivering 15 L of oxygen per minute. His heart rate was 105 beats per minute. Other vital signs were within normal limits. He was noted to have a small abrasion over the right eye. Breath sounds were auscultated bilaterally. He had no sensation and had 0 of 5 strength in his lower extremities bilaterally. The rest of his exam was without obvious abnormalities.

**STUDIES**

Initial labs were notable for mild anemia with a hemoglobin level of 13.5 g/dL (14.0-17.5 g/dL) with a decrease to 8.9 g/dL within several hours of presentation. His basic metabolic panel was unremarkable. His initial lactic acid level was elevated at 8.1 mmol/L (0.5-0.2 mmol/L) with a decrease to 4.2 mmol/L within several hours of presentation. A nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 was negative.

An X-ray of the chest revealed large-volume pneumomediastinum. A CT scan of the chest revealed highly comminuted fractures of T4 and T5 vertebral bodies, as well as mediastinal hematoma, extensive pneumomediastinum, pneumopericardium, and suspected tracheal injury.

**CLINICAL COURSE**

The patient remained hemodynamically stable and did not require further surgical intervention after hospital day 1 (HD1). The patient tolerated the removal of his endotracheal tube on HD2 and removal of VV-ECMO on HD3. After the removal of VV-ECMO, the patient became febrile with a temperature of 102.6 °F and developed a productive cough. On HD4, blood and sputum cultures were collected and he was initiated on empiric piperacillin/tazobactam and vancomycin. On HD6, piperacillin/tazobactam was changed to meropenem due to persistent fevers. On HD7, a sputum culture that was collected on HD5 was noted to have grown *Bordetella hinzii* and *Acinetobacter*.
**Bordetella hinzii** treatment for mero-

Serial blood cultures were collected for approximately showed susceptibility to meropenem was continued in order to target **B hinzii**, and susceptibility testing was requested. Vancomycin was discontinued given that the patient’s cultures were without growth of a gram-positive organism. A **B hinzii** susceptibility testing ultimately showed susceptibility to meropenem, so this was continued as targeted treatment for **A baumanii** and empiric treatment of **B hinzii**.

**DISCUSSION**

**Bordetella** species are small, gram-negative coccobacilli. There are 10 known species of **Bordetella**, although many species are seldom encountered in clinical settings.

The most common species to cause disease in humans is **B pertussis**, which is a highly transmissible organism that causes prolonged respiratory illness. With improved molecular testing, however, identification of new species in clinical centers is occurring with increasing frequency.

**B hinzii** was first identified as a cause of respiratory infection in poultry and more rarely has been isolated from rodents. The species was first reported in humans in 1994 as a cause of bacteremia in a patient with AIDS. Most reports of infection have occurred in immunocompromised patients and have presented as respiratory infection, cholangitis, bacteremia, and endocarditis. The organism’s pathogenic role, particularly in immunocompetent patients, remains poorly understood. To our knowledge, only 3 reports have described cases of symptomatic **B hinzii** infection in patients without underlying disease or immunocompromise. These cases presented as fatal bacteremia, respiratory infection, and cervical subcutaneous abscess.

In this case, the exact route of transmission of **B hinzii** was unclear, but the patient did describe regular indirect exposure to rodents as well as recent direct handling of poultry, both of which are known bacteria reservoirs. The pathogenicity of **B hinzii** in this case was also uncertain. An additional organism, **A baumanii**, was isolated from the patient’s sputum and could have been the primary pathogen responsible for his respiratory symptoms. Isolation of **B hinzii** from the blood in addition to the sputum, however, suggests systemic illness. Additionally, the patient’s fevers persisted for several days despite appropriate antimicrobial therapy based on later susceptibility testing. This suggests that his fevers were likely multifactorial in etiology given his preceding trauma and extensive surgical intervention, and not entirely attributable to **B hinzii** infection.

**B hinzii** is frequently resistant to many antibiotics. Prior reports have identified resistance to β-lactams, cephalosporins, macrolides, and fluoroquinolones. In this case, **B hinzii** was noted to be resistant to aztreonam, ciprofloxacin, and tobramycin, with intermediate susceptibility to gentamicin. The patient recovered well with a 14-day course of empiric meropenem, susceptibility to which was noted after completing treatment. This case, in addition to the in vitro sensitivity data reported in the literature, suggest that piperacillin/tazobactam and meropenem are reasonable empiric antibiotics in the treatment of **B hinzii** infection.

In summary, manifestations and outcomes of **B hinzii** infection are variable and further reports are needed to illustrate its pathogenicity and optimal treatment. Our case serves as one of few reports of **B hinzii** in an immunocompetent patient. Although rare, **B hinzii** will likely be identified more frequently in clinical settings due to increasing access to microbial identification technology such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, and it should be considered as a potential pathogen in immunocompetent patients.

**TREATMENT AND FOLLOW-UP**

The patient completed a 14-day course of meropenem at the recommendation of the infectious disease specialists. His fevers persisted for the first 5 days of antibiotic treatment, although with a progressive downtrend in his temperature curve. His fevers had completely resolved after 6 days of antibiotic treatment. Numerous subsequent blood cultures were without growth. He was discharged to a rehabilitation facility after a 19-day hospitalization.

**DIAGNOSTIC PROCEDURES AND RESULTS**

Serial blood cultures were collected for several days after the initial growth of **B hinzii**, but subsequent blood cultures remained without growth.

A repeat CT scan of the chest was obtained due to the patient’s persistent fevers, cough, and sputum culture results; it was notable for consolidative and ground glass opacities in the right lung apex and right lower lobe. These findings were felt to represent sequelae of pulmonary contusion.

Due to unclear pathogenicity of the **B hinzii** noted in the patient’s blood cultures, a transthoracic echocardiogram was obtained; it did not demonstrate valvular vegetations or other evidence of endocarditis. Additionally, an HIV fourth-generation assay was nonreactive, and an HIV RNA level was below the level of detection.

Susceptibility testing for **B hinzii** was requested and sent to an outside laboratory. Results were not available during the patient’s hospitalization, but ultimately demonstrated susceptibility to meropenem, which the patient had received empirically throughout his hospitalization (Table). 

### Table. Antimicrobial Susceptibility Testing

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC (mcg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam</td>
<td>16/4</td>
<td>S</td>
</tr>
<tr>
<td>Cefepime</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.12</td>
<td>S</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;2</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.8</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8</td>
<td>I</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;8</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>0.5/9.5</td>
<td>S</td>
</tr>
</tbody>
</table>

I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible.

**References are available at ContagionLive.com.**
What is the power of the microbiome?

...and how can it be unlocked to treat disease?

Ferring is committed to exploring the crucial link between the gut microbiome and the threat of recurrent *Clostridioides difficile* infections. With the 2018 acquisition of Rebiotix and several other alliances, Ferring is rapidly advancing its microbiome research, developing novel therapies to address significant unmet needs in deadly and debilitating diseases, and helping people live better lives.

©2020 Ferring B.V. US-MBIO-2000020