The first case of coronavirus disease 2019 (COVID-19) in Philadelphia, Pennsylvania, was identified on March 10, 2020.1 Prior to this, Temple University Health System was preparing for the inevitable influx of patients suffering from COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Temple University Hospital is a 700-plus–bed urban, level 1 trauma center on Temple University’s Health Sciences Campus. Temple provides care to many of the city’s most vulnerable populations—those disproportionately affected by the coronavirus pandemic.2 Temple is also a center of excellence for lung diseases, making the hospital suited to care for patients with a deadly pulmonary disease. As of early May, Temple University Hospital had provided care to the largest number of patients with COVID-19 among hospitals in Philadelphia. Through multidisciplinary planning, thoughtful triage, follow-up of mild cases, and anticipation of future needs, Temple has been able to cope with a significant burden of disease while maintaining a high level of care for its patients. This article outlines the hospital’s response to the pandemic.

HIV/AIDS
How Close Are We to a Cure for HIV?
By Della Xu, PharmD; and David E. Koren, PharmD, BCPS, AAHIVP

WORLDWIDE, APPROXIMATELY 37.9 MILLION individuals live with HIV, with approximately 1.1 million such individuals in the United States alone.1,2 Despite the widespread implementation of highly effective antiretroviral therapy (ART) and subsequent validation of the “undetectable equals untransmittable,” or U=U, concept,1,7 million new cases occur annually alongside nearly 770,000 AIDS-related deaths.1,3 Although the cure for HIV has been a priority since the virus’ discovery, it remains elusive.
local practices and consisted of 1 to 3 antibacterial drugs with activity cUTI were included in the trial. BAT regimens varied according to with nosocomial pneumonia, bloodstream infections, sepsis, or

Resistant Gram-Negative Bacterial Infections

Fetroja is contraindicated in patients with a known history of severe

of complicated urinary tract infections (cUTIs), including pyelonephritis who have limited or no alternative treatment options for the treatment

IMPORTANT SAFETY INFORMATION

INDICATION

Fetroja® (cefiderocol) is indicated in patients 18 years of age or older who have limited or no alternative treatment options 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.

Approval of this indication is based on limited clinical safety and efficacy data for Fetroja.

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.

Fetroja—the world’s only siderophore cephalosporin—overcomes Gram-negative antibacterial resistance

OUTSMART RESISTANCE

Fetroja outsmarts pathogens by using iron to gain cell entry, like a Trojan horse.1,2

Stable in vitro against all known classes of β-lactamases, including serine-carbapenemases (such as KPC and OXA) and metallo-β-lactamases (such as VIM and NDM)1

Active against some pathogens with porin channel deletions1

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, 26.7%].] Generally, deaths were in patients with infections caused by Gram-negative organisms, including nonfermenters such as Acinetobacter baumannii, 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.

The safety and efficacy of Fetroja has not been established for the treatment of nosocomial pneumonia, bloodstream infections, or sepsis.

Reserve Fetroja for use in patients who have limited or no alternative treatment options for the treatment of cUTI. Closely monitor the clinical response to therapy in patients with cUTI.

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 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.

INCREASE IN ALL-CAUSE MORTALITY IN PATIENTS WITH CARBAPENEM-RESISTANT GRAM-NEGATIVE 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.
Fetroja is highly active in vitro vs Gram-negative carbapenem-NS pathogens

In vitro activity does not necessarily correlate with clinical efficacy.

**Fetroja in vitro susceptibility (US isolates)**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptibility rates using FDA-approved breakpoints for pathogens in which Fetroja demonstrated both in vitro and clinical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae overall</td>
<td>99% (n=10,186)</td>
</tr>
<tr>
<td>Enterobacteriaceae carbapenem non-susceptible</td>
<td>91% (n=142)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> overall</td>
<td>98% (n=2445)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> carbapenem non-susceptible</td>
<td>97% (n=468)</td>
</tr>
<tr>
<td>Susceptibility rates using CLSI investigational breakpoints for pathogens in which Fetroja demonstrated in vitro activity</td>
<td>99% (n=536)</td>
</tr>
<tr>
<td><em>A. baumannii</em> overall</td>
<td>98% (n=1849)</td>
</tr>
<tr>
<td><em>A. baumannii</em> carbapenem non-susceptible</td>
<td>96% (n=568)</td>
</tr>
<tr>
<td><em>S. maltophilia</em> overall</td>
<td>99% (n=536)</td>
</tr>
<tr>
<td><em>S. maltophilia</em> carbapenem non-susceptible</td>
<td>99% (n=536)</td>
</tr>
</tbody>
</table>

**Additional Comments for Sizing**

**WARNINGS AND PRECAUTIONS (continued)**

**Hypersensitivity Reactions (continued)**

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. 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.

**Clostridiodes difficile-Associated Diarrhea (CDAD)**

Clostridiodes 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.

**IMPORTANT SAFETY INFORMATION (continued)**

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

Cephalosporins, including Fetroja, have been implicated in triggering seizures. Convulsive status epilepticus (NCSE), encephalopathy, coma, astersixis, neuromuscular excitability, and myoclonia have been reported with cephalosporins in particular 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 a prophylactic indication is unlikely to provide benefit to the patient and may increase the risk for development of drug-resistant bacteria.

**ADVERSE REACTIONS**

The most common adverse reactions occurring in ≥2% of patients receiving Fetroja compared to imipenem/cilastatin in clinical trials were: diarrhea (4% vs 6%), infusion site reactions (4% vs 5%), constipation (3% vs 4%), rash (3% vs 1%), candidiasis (2% vs 3%), cough (2% vs 1%), elevations in liver tests (2% vs <1%), headache (2% vs 5%), hypokalemia (2% vs 3%), nausea (2% vs 4%), and vomiting (2% vs 1%).

Please see a Brief Summary of Prescribing Information on following page.
hyper-sensitivity and/or a history of sensitivity to multiple allergens. These reactions are more likely to occur in individuals with a history of beta-lactam protein intake, monitor antibacterial treatment of C. difficile, and institute surgical evaluation as clinically indicated.

4 CONTRAINDICATIONS

FETROJA is contraindicated in patients with a known history of severe hypersensitivity to cephalosporins or any 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 Gram-Negative 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 (NCT02714365). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or sepsis syndrome 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 (24.6%) vs. 9/84 (10.7%), treatment difference 13.9%, 95% CI (-2.3, 26.9)). All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 (31/101 (30.7%) vs. 10/49 (20.4%), treatment difference 10.3%, 95% CI (-2.5, 23.0)). Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as Acinetobacter baumannii, Stenotrophomonas maltophilia, and Pseudomonas aeruginosa, and were the result of worsening or complications of infection, or underlying conditions. The cause of the increase in mortality has not been established. The safety and efficacy of FETROJA has not been established for the treatment of nosocomial pneumonia, bloodstream infections, or sepsis.

Reserve FETROJA for use in patients who have limited or no alternative treatment options for the treatment of cUTI [see Indications and Usage (1.1)]. Closely monitor the clinical response to therapy with patients with cUTI.

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 clinical trials [see Adverse Reactions (6.1)]. These reactions are more likely to occur in individuals with a history of beta-lactam allergy 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. Before therapy with FETROJA is initiated, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibacterial drugs. Discontinue FETROJA if an allergic reaction occurs.

5.3 Clostridium difficile-Associated Diarrhea (CDAD)

Clostridium 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 bowel 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 compared to non-hypertoxigenic strains. There have been reports of fatal CDAD associated with C. difficile treatment. 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 (NCSO), encephalopathy, coma, ataxia, neuromuscular excitability, and myclorea 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 seizure 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 in a prophylactic indication is unlikely to benefit the patient and may increase the risk for development of drug-resistant bacteria [see Indications and Usage (1.2)].

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)]

• Clostridium 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. Clinical Trial Experience in cUTI, Including Pseudomonas aeruginosa

FETROJA was evaluated in an active-controlled clinical trial in patients with cUTI, including Pseudomonas aeruginosa (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 gram7, gram every 8 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 99 years), with approximately 53% of patients aged greater than or equal to 65. Approximately 98% 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%) patients treated with FETROJA and 10/148 (6.8%) of patients treated with imipenem/cilastatin experienced serious adverse reactions. One death (0.3%) occurred in 305 patients treated with FETROJA as compared to one death in 300 patients treated with imipenem/cilastatin. Discontinuation of treatment due to any adverse reaction occurred in 10/300 (3.3%) of patients treated with FETROJA and 10/148 (6.9%) of patients treated with imipenem/cilastatin. Specific adverse reactions leading to treatment discontinuation in patients who received FETROJA included urticaria (1.3%), drug hypersensitivity (0.3%), and increased hepatic enzymes (0.3%).

Common Adverse Reactions

The most common selected adverse reactions occurring in ≥ 2% of patients receiving FETROJA in the cUTI trial are listed in Table 3.

Table 3 Selected Adverse Reactions Occurring in ≥2% of Patients Receiving FETROJA in the cUTI Trial

<table>
<thead>
<tr>
<th>Reaction</th>
<th>FETROJA (N = 300)</th>
<th>Imipenem/Cilastatin (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Infusion site reactions</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Rash</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Eruptions in liver tests</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hepatomegalia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

cUTI = complicated urinary tract infections

7 Gram 7/IV over 1 hour every 8 hours (with dosing adjustment based on renal function)
General system disorders: pyrexia, peripheral edema
Hepatobiliary disorders: cholestasis, cholestatics, gallbladder pain
Immune system disorders: drug hypersensitivity
Infections and infestations: Clostridial difficile infection
Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), red blood cells urine positive, creatine phosphokininase increase
Metabolism and nutrition disorders: decreased appetite, hypocalcemia, fluid overload
Nervous system disorders: dysgeusia, seizure, respiratory, thoracic, and mediastinal disorders: dyspnea, pleural effusion
Skin and subcutaneous tissue disorders: pruritus
Psychiatric disorders: insomnia, restlessness

7 DRUG-INTERACTIONS
7.1 Drug/Laboratory Test Interactions
Cefiderocol may result in false-positive results in dipstick tests (urine 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 with cephalosporin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data).

Developmental toxicity studies with cefiderocol administered during organogenesis to rats and mice showed no evidence of embryofetal toxicity, including drug-induced fetal malformations, at doses providing exposure levels 1.4 times (rats) or 2 times (mice) higher than the average observed in cUTI 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 15% to 20%, respectively.

Data

Animal 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 identified an association with cephalosporin use during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

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 identified an association with cephalosporin use during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

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 1.4 times (rats) and 2 times (mice) the daily mean plasma exposure in cUTI 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 rats that received the drug intravenously. When a drug is present in animal 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.

Data

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 efficacy of FETROJA is pediatric patients younger than 18 years of age have not been established.

8.5 Geriatric Use
Of the 300 subjects treated with FETROJA in the cUTI trial, 158 (52.7%) were 65 years of age and older. 57 (22.3%) were 75 years of age and older. No overall differences in safety or efficacy were observed between these subjects and younger subjects.

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
Dose adjustment is required in patients with CLcr 15 to 59 mL/min, and in patients with end-stage renal disease or who are receiving hemodialysis (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 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. Dose 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/secretion 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
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Questions related to editorial content and submissions should be sent to Managing Editor Alexandra Ward, MA: AWARD@CONTAGIONLIVE.COM.
COVID-19 Preprints: Reader, Beware

CORONAVIRUS DISEASE 2019 (COVID-19) is taxing us in so many ways. In some parts of the country, our health system has been pushed to the brink of capacity or beyond. Our economy has been descimated as a result of the widespread closures enacted to decrease the spread of the severe acute respiratory syndrome coronavirus 2 and prevent health-system collapse. Misinformation about COVID-19 has circulated faster and faster than the actual infection, confusing individuals and forcing health care practitioners to constantly counter myths mentioned by patients, friends, and family. Finally, the flow of literature about COVID-19 has been unending, tiring those of us who look to it for guidance to improve patient outcomes. I want to focus on this last point for this month’s column.

The saga of 2020 will have many subtitles. One of them could be “The rise of the preprint.” Keeping up with newly available literature on COVID-19 feels like drinking from a firehouse, except that only a portion of the contents is actually clean water. Preprints have moved from a mostly unused venue for scientists to gather feedback on studies they are finalizing to a primary method for sharing “breaking data” as fast as possible. When these data are in the basic sciences and largely remain within a self-policing circle of scientists, they are probably fine. However, now there are millions of clinicians desperately looking for ways to more effectively treat patients with COVID-19. The media are reporting on unreviewed preprints that are often flawed, pushing catchy narratives that miss major points and the nuances that need emphasis. Reacting to preprints of clinical and translational science without critique is potentially dangerous. It is also understandable.

Many professional schools in the health sciences have curricula that include literature interpretation. We all know better than to “just read the abstract,” accept results at face value, or accept conclusions of papers without vetting the methods. Remaining steadfast to sound practice is much harder when we are constantly reacting to a continuous influx of new information. We are all looking for that golden paper that will help us improve our standard of care to something more satisfying than the largely watch-and-wait approach that we are stuck with now.

Peer review has flaws, but its absence has highlighted its utility. Ironically, it has become harder to find peer reviewers recently, as clinical scientists face long hours on busy clinical services. This column is a reminder that when you read a preprint, remember that you serve as your own reviewer and possibly the only reviewer that paper will see before you. I wrote about seeking notes for the sake of posterity during the COVID-19 pandemic. Examining the influence of preprints will be well, and you thank you for reading Contagion.

Jason C. Gallagher, PHARMD, FCCP, FIDP, FIDSA, BCPS

The Future of Health Care After COVID-19

MY HOPE is that years from now, when we look back on the coronavirus disease 2019 (COVID-19) pandemic, it will have served a few purposes. First and foremost, COVID-19 highlights the unimaginable bravery and heroism of our frontline health care workers, for whom we are eternally grateful.

Second, it inspires a renewed appreciation and gratitude for infection prevention and control professionals, as well as infectious disease clinicians. These specialists are likely to be in high demand as health care facilities, ranging from acute-care hospitals to long-term care, navigate a new normal and reevaluate their standards of disinfection, sterile processing, and hand hygiene protocols.

Lastly, COVID-19 will have long-lasting and perhaps permanent effects on the health care system as a whole: no more crowded physician office waiting rooms, an increased emphasis and reliance on telemedicine, and perhaps a change in the way we consume scientific literature, to name a few.

Our cover story this month on page 14, by Carly Sedlock, MD, and Contagion® Editor-in-Chief Jason C. Gallagher, PHARMD, FCCP, FIDP, FIDSA, BCPS, details Temple University Hospital’s response to the COVID-19 pandemic, a model that other health care systems may be able to adapt and follow for future outbreaks of infectious diseases.

Also in this issue you’ll find a recap of our recent Contagion® webinar titled, “What Clinicians Need to Know About COVID-19,” featuring Tufts Medical Center’s Helen Boucher, MD, FACP, FIDSA; Emory University’s Carlos del Rio, MD; and Stanford University’s Stanley Deresinski, MD. It is through educational offerings such as this that we remain committed to serving as a resource for our audience of infectious disease clinicians.

Please contact Editorial Director Alexandra Ward, MA, at award@mjlifesciences.com if you have any questions or comments.

Stay informed, stay well, and thank you for reading.

Mike Hennessy Sr
Chairman and founder
Hospital Logistics Are Key to Managing COVID-19 Cases

Temple University Hospital’s pandemic planning and navigation may be a model for other institutions facing high numbers of patients with COVID-19.

BY CARLY SEDLOCK, MD; AND JASON C. GALLAGHER, PHARMD, FCCP, FIDP, FIDSA, BCPS

IN THE LITERATURE

Improving Vaccine Uptake in a Cohort of Patients With Asplenia
BY SEAN BULLIS, MD; AND ANDREW J. HALE, MD

Finding the Sweet Spot for Treating AmpC β-Lactamase–Producing Organisms: Noncarbapenem β-Lactams
BY ADRIENNE TERICO, PHARMD, BCPS, BCIDP

MEDICAL WORLD NEWS

Learn more about important and trending infectious disease news from around the world.

NEWS & BREAKTHROUGHS

Lefamulin: An Overview of a Lonely Soldier
Lefamulin, a recently approved pleuromutilin, adds to the current antibiotic armamentarium although its place in therapy remains to be seen.
BY ALEXANDRA HANRETTE, PHARMD; AND LUCIA ROSE, PHARMD, BCIDP

EMERGING & RE-EMERGING INFECTIONS

COVID-19: A Primer
This virus has multiple facets and highlights a need for real-time learning.
BY AMESH A. ADALJA, MD

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BY DELLA XU, PHARMD; AND DAVID E. KOREN, PHARMD, BCPS, AAHIVP

MULTIDRUG-RESISTANT INFECTIONS

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BY JEFFREY M. RYBAK, PHARMD, PHD

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BY TONI CAMPANELLA, PHARMD

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Impaired splenic function is common and may result from splenectomy, pathologies such as sickle cell disease that result in hyposplenism, and disorders causing splenic engorgement or infiltration. Given the spleen’s pivotal role in preventing infection from encapsulated bacteria and intraerythrocytic parasites, impaired splenic function predisposes patients to overwhelming postsplenectomy infection (OPSI). Specifically, diminished opsonization and phagocytic capacity lead to excessive microbial proliferation relative to clearance, and low-level bacteremia has the potential to rapidly progress. The prevalence of an OPSI episode has been estimated at 3%, with greater than one-third of these patients suffering 2 or more recurrences. The trajectory is often that of rapid decline, with death observed in greater than 50% of cases. Thus, prevention of OPSI is critical.

Vaccination remains the cornerstone of OPSI prevention. Clinicians should vaccinate patients with asplenia against the most common bacterial causes of OPSI, including Streptococcus pneumoniae, Haemophilus influenzae type b (HiB), and Neisseria meningitidis. However, despite published guidelines, completion of the full postsplenectomy vaccine series remains low. Possible explanations include provider perception of a complicated vaccine schedule, lack of clarity on who exactly is responsible for giving vaccines, patient vaccine hesitancy, and patients lost to follow-up post splenectomy.

Rieg et al recently examined this issue and the effect of a dedicated outpatient service on vaccine uptake. In a prospective cohort study from Germany, the authors recruited and referred patients with asplenia from January 2009 to December 2016 to a comprehensive outpatient clinic. The aims were (1) to evaluate the impact on vaccination uptake and (2) to evaluate the incidence and microbiological features of postsplenectomy infections among patients referred to the study clinic. Patients who had undergone splenectomy during the study period, as confirmed by examination of blood smears, were included in the trial. Exclusion criteria included an estimated life expectancy of 3 months or less.

Eligible patients were invited to an outpatient clinic where they were counseled on the risk of infection, prescribed pill-in-pocket preventive antibiotics, and vaccinated according to guideline-based recommendations. During this visit, clinicians recorded demographic variables, comorbidities, vaccination status, and hospitalizations for postsplenectomy infections. Additional follow-up occurred at 3 and 12 months, as well as at the conclusion of the study.

The study enrolled 459 patients, with the most common indications for splenectomy being malignancy, trauma, therapeutic splenectomy, benign abdominal tumors, and functional hyposplenism. Among study participants, 71% received at least a single dose of a pneumococcal vaccine, 52% received at least a single dose of a meningococcal vaccine, and 69% received HiB vaccination within 3 months of splenectomy. Only 17% of patients who underwent elective splenectomy had been vaccinated within 2 weeks of surgery. Vaccination uptake increased during the study, with cumulative pneumococcal vaccination uptake reaching 90%.

Ninety-three percent of the cohort had a minimum of 3 months of follow-up, and the median duration of follow-up was 2.9 years. Twenty-three percent of the cohort required hospitalization for postsplenectomy infection, and 4% met criteria for OPSI. Twenty percent of study participants died after a median of 1.5 years, with the cause of death being infection related in 10% and related to comorbid illness (59%) or unknown factors (32%) in the remainder.

The most common sites of severe sepsis/septic shock were the lower respiratory tract (32%) and the urinary tract (23%), with primary bacteremia representing 5%. The median time to first infection from splenectomy was 3.1 years. A microbiologic diagnosis was established in 43% of patients during follow-up, with the most common pathogens being Escherichia coli and Klebsiella spp. The authors observed only 1 episode of sepsis due to S pneumoniae, in a patient who had been vaccinated with pneumococcal polysaccharide vaccine 14 months prior. This was in contrast with 22 episodes of OPSI in the cohort prior to study entry, in which primary bacteremia represented the majority of infections, at 32%. S pneumoniae was the causative pathogen among 36% of episodes, with 87% of these patients never having received pneumococcal vaccination prior to study enrollment.

This is one of the first studies examining the effect of a dedicated postsplenectomy comprehensive clinic. It also provides updated data regarding the microbiology and clinical features of postsplenectomy sepsis in the era of the 13-valent pneumococcal conjugate vaccine. Prior to study entry, the authors found poor baseline rates of vaccination against pneumococcus (27%), meningococcus (17%), and HiB (18%). The authors significantly increased pneumococcal vaccination by creating a dedicated clinic that provided specialized postsplenectomy care, with a cumulative pneumococcal vaccination rate of 90% and comparable rates for meningococcus and HiB. The authors observed that the microbiology of postsplenectomy sepsis largely mirrored that of the general public, with significantly fewer episodes due to pneumococcal disease. This study underscores the critical importance of improving vaccination rates in this vulnerable population. Similar asplenic-focused clinics elsewhere may further decrease morbidity and mortality in this population.

References are available at ContagionLive.com.
Finding the Sweet Spot for Treating AmpC β-Lactamase–Producing Organisms: Noncarbapenem β-Lactams

BY ADRIENNE TERICO, PHARMD, BCPs, BCIDP

In an era of increasing antimicrobial resistance, clinicians are hard-pressed to use narrow-spectrum agents to preserve antibiotic activity. Mortality rates for patients with bacteremia secondary to AmpC β-lactamase–producing organisms have been reported to be between 10.9% and 25.6%. Clinicians commonly employ carbapenem antibiotics to treat AmpC-producing organisms, but because of increasing gram-negative resistance, alternative strategies are needed. Although the general consensus avoids third-generation cephalosporins such as ceftriaxone because of the potential for emergence of resistance, the data supporting use of cefepime or piperacillin-tazobactam are less clear.

Tan and colleagues explored the potential for noncarbapenem β-lactam treatment of AmpC harboring gram-negative bacteria such as Enterobacter, Serratia, and Providencia spp as well as Citrobacter freundii and Morganella morganii. Of particular interest were cefepime, a poor inducer of chromosomal AmpC that also evades enzyme inactivation, and piperacillin-tazobactam, a weak inducer of AmpC. Because clinicians frequently use these agents empirically to treat gram-negative infections, both empiric and definitive treatment could be assessed.

This retrospective cohort study was conducted at 2 academic hospitals in Singapore and included patients with bacteremia secondary to the aforementioned organisms. Genetic detection of AmpC was not performed but presumed based on organism. Investigators classified patients into 2 cohorts: carbapenem treatment and noncarbapenem β-lactam treatment with a primary outcome of 30-day mortality. Investigators performed a multivariate logistic regression model to identify risk factors associated with the primary outcome.

Overall, 241 patients were included. The most common sources of infection were urinary (22.8%), vascular line (22.0%), unknown (14.5%), respiratory (12.5%), and hepatobiliary (11.6%), and most patients achieved source control (81.3%). Fifty-two patients were treated in an intensive care unit at the time of bacteremia, and the median Pitt bacteremia score was 1 (interquartile range [IQR], 0-2). Enterobacter spp comprised 58.1% of isolates, followed by Serratia spp (22.4%), M morganii (16.6%), C freundii (2.1%), and Providencia spp (0.8%). The primary outcome of 30-day mortality was met in 12.9% of patients.

Investigators did not conduct an analysis for empiric cefepime compared with carbapenems because only 2 patients received cefepime empirically. More than half of the patients were empirically treated with piperacillin-tazobactam or carbapenems (69 patients each), with a median empiric duration of 3 (IQR, 2-3) days in each group. The primary outcome was met in 11.6% of patients treated with piperacillin-tazobactam and 23.2% treated with carbapenem (P = .07). Empiric use of piperacillin-tazobactam did not influence 30-day mortality in multivariate analysis (adjusted odds ratio [aOR], 0.29; 95% CI, 0.07-1.27). Propensity score–adjusted independent risk factors for mortality were male sex (aOR, 0.29; 95% CI, 0.10-0.79), age (aOR, 1.04; 95% CI, 1.01-1.08), and Pitt bacteremia score (aOR, 1.21; 95% CI, 1.01-1.45).

Piperacillin-tazobactam was infrequently selected as definitive therapy (5.4%); therefore, investigators compared only definitive cefepime therapy with carbapenems. More than twice as many patients were treated with definitive carbapenems (n = 132) as those with cefepime (n = 57). The median definitive duration was 7 (IQR, 4-12) days for carbapenems and 7 (IQR, 4-11) days for cefepime. The primary outcome was met in 5.3% of patients treated with cefepime and 18.9% treated with carbapenem (P = .02). Use of cefepime for definitive therapy did not influence 30-day mortality on multivariate analysis (aOR, 0.65; 95% CI, 0.12-3.55). The only independent risk factor for mortality was Pitt bacteremia score (aOR, 1.33; 95% CI, 1.06-1.69). Using carbapenems for the duration of treatment (empiric and definitive) did not influence the risk of mortality (aOR, 2.25; 95% CI, 0.86-5.91).

Although a higher Pitt bacteremia score was associated with mortality, the median scores were relatively low, which may explain the lower overall mortality rate compared with previous studies. Additionally, the definitive cefepime cohort included a higher incidence of infections in which cefepime would achieve higher concentrations or would be less susceptible to inoculum effect (eg, urinary tract or vascular access devices). On the contrary, more patients in the cefepime cohort did not achieve source control.

Of note, although interpretation of susceptibility results was available at both institutions, minimum inhibitory concentration (MIC) data were available for isolates at only 1 hospital (n = 132). This hospital uses European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, whereas the other uses Clinical & Laboratory Standards Institute (CLSI) breakpoints. The EUCAST susceptibility breakpoints for cefepime and piperacillin-tazobactam are lower than those implemented by CLSI (1 mg/L and 8/2 mg/L vs 8 mg/L and 16/4 mg/L, respectively); therefore, concordance would be expected when evaluating this hospital’s MIC data using either society’s breakpoints. However, the MIC distribution is unknown for the remaining 109 isolates interpreted according to CLSI criteria. This is noteworthy because treatment with cefepime for Enterobacter bacteremia when MICs were 4 or 8 mg/L was associated with mortality in a previous study. Such an elevation in cefepime MICs can be indicative of coproduction of extended-spectrum β-lactamases in the absence of genotypic testing.

Overall, this study supports empiric use of piperacillin-tazobactam for bacteremia secondary to presumed AmpC-harboring organisms and definitive therapy with cefepime, especially in infections for which lower inoculums or higher drug concentrations are expected. Definitive treatment with piperacillin-tazobactam cannot be established based on this study. The results are consistent with those of previous studies that have evaluated these noncarbapenem β-lactams for treatment of AmpC-producing organisms. The ongoing prospective, randomized, controlled MERINO II trial (NCT02437045) seeks to establish the utility of piperacillin-tazobactam compared with meropenem in low-risk patients with bacteremia caused by AmpC-producing organisms.

References are available at ContagionLive.com.
The world should prepare for waves and hot spots of coronavirus disease 2019 (COVID-19) to continue for the next 2 years. Yet similarities between the current pandemic and past influenza pandemics can help alter the future of the disease’s progression, according to a Center for Infectious Disease Research and Policy (CIDRAP) viewpoint.

The CIDRAP Viewpoint working group outlined pandemic scenarios to add information and address viewpoints and thus shed more light on these topics. The authors explained that they wanted to help planners “envision some of the situations that might present themselves later this year or next year, so that they can take key steps now, while there’s still time.” They also discussed topics such as crisis communication, testing, contact tracing, surveillance, supply chains, epidemiology issues, and areas for further research.

The most direct comparison with the current COVID-19 crisis is pandemic influenza, which has happened 4 times since 1900: 1918-1919, 1957, 1968, and 2009-2010. Learning from those past pandemics can help shape the future of the COVID-19 pandemic, the authors wrote.

Epidemiologically, pandemic influenza and COVID-19 both had little preexisting immunity when introduced into the community, which led to worldwide susceptibility, the authors wrote. They spread similarly, as well, through the respiratory system via large droplets and smaller aerosols.

However, significant differences exist, such as incubation period (approximately 2 days for influenza, 5 days for COVID-19) and the evidence that up to a quarter of COVID-19 cases may be asymptomatic (much more than influenza).

The authors presented 3 scenarios to illustrate possible futures of COVID-19 in the world. In the first scenario, smaller waves would occur through summer and then consistently over a 1- to 2-year period, they said. The virus may diminish sometime in 2021, they said, but the hot spots may vary geographically and depend on what mitigation steps the population adheres to.

In the second scenario, which is the worst-case scenario, larger waves of COVID-19 activity would hit in the fall or winter of 2021, with subsequent, smaller waves through 2022. This would require more significant mitigation measures in the fall to flatten the curve of infection and prevent health care systems from being overwhelmed.

In the third scenario, a “slow burn” of ongoing transmission and case occurrence would play out but without a clear wave pattern. This could be geographically influenced or dictated by mitigation measures in various areas. This was not observed for prior flu pandemics but remains a possibility for COVID-19, the authors wrote.

No matter what happens, the authors suggested planning for the worst-case scenario, which would include no vaccine or herd immunity. Government agencies and health care delivery organizations should create plans and strategies to protect health care workers and identify triggers for stay-at-home measures when peaks occur.

### Twenty Drugs Are Evaluated for Repurposing Against COVID-19 in Preclinical Testing

BY KENNETH BENDER, PHARMD

Virologists have taken approved, marketed drugs from in vitro screening for potential repurposing against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through in vivo testing in an animal model surrogate of coronavirus disease 2019 (COVID-19), according to a new preprint report in bioRxiv.

Matthew B. Frieman, PhD, associate professor at the University of Maryland School of Medicine in Baltimore, and colleagues identified 20 drugs as priority candidates from previous screening for in vitro testing of their capacity to inhibit SARS-CoV-2 cell entry at concentrations that were not themselves cytotoxic.

“We prioritized testing these for antiviral activity against SARS-CoV-2 [because] they displayed broad-spectrum antiviral activity,” Frieman and colleagues explained.

The team found 17 of the 20 to be viable candidates and further tested 7 to confirm their capability to inhibit infectious SARS-CoV-2 production. These included hydroxychloroquine and chloroquine and the related amodiaquine dihydrochloride, amodiaquine dihydrochloride dihydrate, and mefloquine. They were chosen, investigators commented, “because chloroquine has garnered much interest as a potential treatment for COVID-19, and the others are similarly used as [antimalarial] compounds.”

The 2 other agents subjected to the additional screening were imatinib and chlorpromazine. Frieman and colleagues explained that imatinib has demonstrated the capacity to inhibit both SARS-CoV and Middle East respiratory syndrome coronavirus, as well as infectious bronchitis virus entry into cells. Chlorpromazine has been found to inhibit clathrin function in cells.

Frieman and colleagues then selected 2 of the 7 agents, chloroquine and chlorpromazine, to test for efficacy in vivo.

“There is currently a lack of an established mouse model for SARS-CoV-2,” investigators wrote, “so we used the mouse adapted SARS-CoV strain (cause of 2003 epidemic) as a surrogate to assess the in-vivo efficacy of these drugs against a closely related coronavirus.”

Frieman and colleagues used a well-established mouse adapted system for SARS-CoV (MA15 in BALB/c mice). They administered each drug prior to introduction of the virus, to ascertain whether it offered any prophylactic effect.

Investigators rationalized the “repurposing” of the animal model from the SARS-CoV strain as a test of whether a drug might be repurposed against the novel coronavirus, as both viruses use angiotensin-converting enzyme 2 as a receptor and therefore have similar cellular tropism that could be susceptible to inhibition.

In contrast with the in vitro results, however, neither chloroquine nor chlorpromazine was found to inhibit viral replication in mouse lungs; the viral titer was equivalent. A clinical benefit did appear to exist, however, as both drugs were associated with a reduction in the weight loss that occurs in untreated, infected mice. Mice infected with MA15 without drug treatment lost approximately 15% of their baseline body weight over 4 days and had other clinical signs of disease, including ruffled fur and labored breathing. Subsequent examination demonstrated significant inflammation and denuding bronchiolitis, suggesting severe disease. Mice receiving the higher test doses of either chloroquine or chlorpromazine showed markedly reduced weight loss and less inflammation in the lungs.

“Future research will be aimed at testing these compounds in SARS-CoV-2 animal models to further assess their potential utility for human treatment,” Frieman and colleagues concluded.
The HIV Outpatient Study: What 25 Years Has Shown

BY LAURIE SALOMAN

HIV has gone from a virtual death sentence in the 1980s and early 1990s to a chronic condition that patients and physicians can control well with antiretroviral therapy (ART). No better catalog of the improvements in management of the disease may exist than the multidecade HIV Outpatient Study (HOPS), which has profiled and tracked individuals living with HIV in the United States since 1993.

Funded by the US Centers for Disease Control and Prevention (CDC), it has enrolled thousands of patients with HIV in multiple locations. It provides a rare look at a cohort of individuals across time, highlighting shifts in disease metrics, comorbidities, death rates, demographics, and treatment protocols.

A team of investigators in the Division of HIV/AIDS Prevention at the CDC, along with colleagues at medical schools across the country, undertook a fresh analysis of the HOPS to shed light on HIV’s changes.

“The rich data in our large prospective cohort enable investigation of new risk factors for HIV-related complications and monitoring progress along the HIV care continuum,” Kate Buchacz, PhD, a senior epidemiologist at the CDC and an author of the study, told Contagion®.

Some of the key findings include the characterization of new conditions in individuals with HIV, such as lipodystrophy and immune reconstitution inflammatory syndrome, reduced mortality due to earlier administration of ART, and the revelation that certain ART medications carry a risk of damage to the cardiovascular and renal systems. The study results also showed that the state of patients’ immune systems has gotten a big boost over the years. In the early to mid-1990s, the median CD4 T-cell count was 244 cells/mm³ vs 640 cells/mm³ in 2017.

Death rates also dropped sharply during that period, from 121 per 1000 person-years to just 16. The median age at death in 1994 was 39 years compared with 54 years in 2017. The median age at death in 1994 was 39 years compared with 54 years in 2017.

“Today, [the] majority of HOPS patients are successfully treated with ART and have suppressed HIV viral load [92% in 2017],” said Buchacz. However, her report notes that race- and ethnicity-based disparities in virologic suppression remain, with African American men and women less likely to be virologically suppressed than others.

How Physician “Burnout” Gets the Real Problem Wrong

BY CHRIS MAZZOLINI

Wendy Dean, MD, cofounder of Fix Moral Injury, discusses why the term burnout does not encompass the full scope of the problem and what can be done to address physician career dissatisfaction.

**Medical Economics**: Do we have a burnout crisis in medicine today?

**Wendy Dean, MD**: We have a crisis of distress. Clinicians across the board have told us that they are struggling with their jobs. They love their patients. They love medicine in general, but they’re struggling with the day-to-day challenges that they face as they try to do those jobs and take care of the patients. Whether it’s burnout is debatable.

**Medical Economics**: Can you expand on that a little? Many may think burnout is sort of the catchall that a lot of physicians use to describe how they’re feeling. If it’s not burnout, what is it?

**Dean**: Several years ago, I started noticing that a lot of my friends were struggling more. And they said to me, “I love my job; I love medicine. I love what I’m trying to do. But all these other things get in the way and challenge me.” I would ask them, “OK, so you’re burned out?” And they’d say, “That does not strike me as really what my experience is.”

So I started thinking about it more and more with a coauthor, a colleague of mine whom I’d worked with for several years. And we started thinking about it in a different way. We realized that every physician takes an oath to put their patient first as a priority. It comes before lunch; it comes before sleep. We found that the challenge is when there’s some barrier keeping us from taking care of our patients according to that oath we took to put them first. That’s where we struggle.

We framed it as moral injury, which means transgressing a deeply held belief. And in health care, that belief is the oath that you take to make your patient the priority.

**Medical Economics**: Can you talk a little about what you see as the difference between the term burnout and this term moral injury? A lot of physicians may be still thinking in the burnout mentality. So what is actual burnout, and what is actual moral injury?

**Dean**: Right. We’re not trying to say that burnout doesn’t exist, because there are some physicians who truly struggle and really do meet the criteria for burnout. We think that burnout is a constellation of symptoms, which are emotional exhaustion, feeling ineffective, and depersonalizing. That can come from several places. But as we talked to physicians across the country, we found that moral injury may be the primary cause of those symptoms. And we believe that when we’re trying to get our patients that care and routinely struggle to make that happen, it’s exhausting. It makes you feel very ineffective. And eventually, as you do that time after time and you sort of anticipate that it’s going to happen again, you start to separate yourself from your patients because it’s painful to watch them go through the difficulty of not getting the care they need. That’s the depersonalization point.

**Medical Economics**: A lot of these problems are systemic. And I’m wondering what individual physicians can do to make their own career more satisfying and healthier and also to chip in to try to help the system change for the better.

**Dean**: Every one of these problems can be mitigated to some degree at the local level. And for every problem, you can find a local, personal immediate solution. They may not fix everything. But if you know there’s a particular issue that you find most problematic, the best thing to do is to educate yourself about it, to follow how the incentives drive that process, and then work with other people who also have the same problem and who may be driving that pattern because of their incentives, and all can work together to try to change that pattern of decision making.

It does mean partnering with people whom we may not typically partner with. It may be that we need to be much more in contact with the coders or the billing department or the safety officer, and asking that they engage with us and think through a different way to approach a problem.

To read the complete Q&A and watch the video interview, visit www.contagionlive.com/link/2535.
Lefamulin: An Overview of a Lonely Soldier

Lefamulin, a recently approved pleuromutilin, adds to the current antibiotic armamentarium, although its place in therapy remains to be seen.

BY ALEXANDRA HANRETTY, PHARMD; AND LUCIA ROSE, PHARMD, BCIDP

The pleuromutilin class of antibiotics has been a veterinary medicine staple for decades. These antibiotics have a unique mechanism of action that provides a high barrier to resistance. Lefamulin (Xenleta) is the first systemic pleuromutilin antibiotic available for human use. The FDA approved it in August 2019 for the treatment of community-acquired bacterial pneumonia (CABP). Lefamulin is available for intravenous and oral administration dosed at 150 mg intravenously every 12 hours or 600 mg by mouth every 12 hours for a minimum of 5 days.

MECHANISM OF ACTION

Lefamulin inhibits bacterial protein synthesis by binding to the 50S subunit at the peptidyl transferase center, thereby preventing peptide bond formation. Its novel mechanism includes binding to the target site through an induced-fit mechanism in which the binding pocket closes around itself, giving it a tight bind to the ribosome. Because of this unique mechanism, the probability of cross-resistance with other antibiotic classes is low, and it has a higher barrier of resistance by overcoming bacterial ribosomal mutations. The C14 side chain is responsible for the optimal properties of the drug, including solubility, broad spectrum of activity, and pharmacokinetics.

SPECTRUM OF ACTIVITY

Lefamulin demonstrates potent in vitro activity against many common respiratory and skin pathogens, including gram-positive (except Enterococcus faecalis), fastidious (ie, Chlamydia spp), and atypical gram-negative organisms. It is active against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-intermediate S aureus, vancomycin-resistant S aureus, and Enterococcus faecium, including vancomycin-resistant isolates. Compared with other common CABP antibiotics, lefamulin was the most potent against Streptococcus pneumoniae. It has reliable Haemophilus influenzae and Moraxella catarrhalis activity, including β-lactamase-positive strains. Lastly, it is active against Neisseria gonorrhoeae, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) species. Notably, it has no reliable activity against other gram-negative organisms because of the presence of AcrAB-ToI efflux pumps.

COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

Lefamulin has excellent penetration into epithelial lining fluid and reaches high intracellular concentrations. The efficacy and safety of lefamulin for CABP were established by 2 phase 3 studies, both of which were multicenter,
multinational, randomized, and double-blind with a noninferior design. The LEAP trial (NCT02559310) evaluated lefamulin versus moxifloxacin with and without linezolid (if evidence of MRSA) in adults with moderate to severe CABP for 7 days.13 Investigators randomized 551 patients 1:1 (276, lefamulin; 275, moxifloxacin). Patients started both agents as intravenous therapy, with the ability to switch to oral by day 3. Investigators found lefamulin to be noninferior to moxifloxacin for early clinical response, which was the primary outcome (87.3% vs 90.2%, respectively), as well as assessment of clinical response (81.7% vs 84.2%). Diarrhea was more common in the moxifloxacin group compared with the lefamulin group (7.7% vs 0.7%, respectively; P < .001). Rates of study drug discontinuation due to treatment-emergent adverse events (AEs) were 2.9% for lefamulin and 4.4% for moxifloxacin.13

The LEAP2 trial (NCT02813694) evaluated oral lefamulin for 5 days versus oral moxifloxacin for 7 days for CABP.14 Investigators randomized 738 patients 1:1 (370, lefamulin; 368, moxifloxacin), and 707 completed the trial. In the microbiologically evaluable patients, the most commonly isolated pathogen was S pneumoniae. Although about half of patients had microbiologic data, investigators used nonculture methods, which limited the ability to obtain minimum inhibitory concentration data. The early clinical response rate at 96 hours in the intention-to-treat population (primary end point) was 90.8% with lefamulin versus 90.8% with moxifloxacin. This demonstrated noninferiority of 5 days of lefamulin to 7 days of moxifloxacin. Treatment-emergent AEs occurred in 32.6% of patients taking lefamulin and 25.0% of those taking moxifloxacin. More patients in the lefamulin arm experienced gastrointestinal (GI) intolerances (17.9% vs 7.6%, respectively), particularly diarrhea. Drug discontinuation occurred in 12 (3.3%) patients taking lefamulin and 9 (2.4%) taking moxifloxacin.14

**ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS**

Lefamulin’s activity against common skin pathogens, availability of oral administration, and high concentration in adipose and skeletal muscle tissue make it an appealing option for acute bacterial skin and skin structure infections (ABSSSIs). In a phase 2 double-blind, parallel-group study, investigators randomized 210 hospitalized adult patients with an ABSSSI to receive lefamulin 100 mg, lefamulin 150 mg, or vancomycin via intravenous infusion for 5 to 14 days.15 Of the 186 patients who completed the study, clinical success at the test-of-cure visit was similar among those receiving lefamulin 100 mg, lefamulin 150 mg, and vancomycin (90.0%, 88.9%, and 92.2%, respectively). In the presence of Panton-Valentine leucocidin–positive S aureus, lefamulin showed success rates similar to those of vancomycin. Lefamulin was well tolerated at both doses, with the most frequently reported AEs being GI in nature.15 No ongoing phase 3 studies are evaluating lefamulin for this indication, but it has a promising role for ABSSSI.

**SEXUALLY TRANSMITTED INFECTIONS**

Lefamulin has excellent genitourinary penetration, including into prostate and pelvic tissues. In vitro data suggest activity against common sexually transmitted infection (STI) pathogens, including drug-resistant strains of *Mycobacterium genitalium* and *N gonorrhoeae*, with no evidence of cross-resistance.7,13 It demonstrated a 5-fold greater potency compared with azithromycin in *Chlamydia trachomatis*.16 In 117 gonococcal isolates that were MDR or XDR, lefamulin showed reliable activity.10 Of note, the presence of the mtrCDE efflux pump, which is responsible for enhancing *N gonorrhoeae* survival through a variety of factors including drug efflux, did influence lefamulin susceptibility.13 This warrants further exploration.

**ADVERSE REACTIONS, WARNINGS, AND PRECAUTIONS**

Although lefamulin was generally well tolerated in clinical studies, GI AEs including nausea and diarrhea were frequently reported. Diarrhea was less common than with moxifloxacin in LEAP, but the opposite held true in LEAP2.12,14 GI AEs are most notable when initiating oral lefamulin, and clinicians should counsel patients accordingly. Lefamulin has the potential to prolong the QT interval and therefore should be avoided in patients at risk for arrhythmias. In addition, those with renal or hepatic impairment are at increased risk of QT prolongation.2

**COST**

The average wholesale price of lefamulin is $246 per day for intravenous therapy and $330 per day for oral therapy. This may be cost prohibitive in an era when alternative agents cost less than $5 per day. Although lefamulin may have some benefits, cost has been a major barrier to its widespread use.

**ONGOING RESEARCH**

Lefamulin is currently in phase 1 trials for various indications, including prostatic joint infections, STIs, and osteomyelitis, as well as pediatric infections (specifics unknown).

**PLACE IN THERAPY**

Lefamulin enriches the current antimicrobial armamentarium, although CABP is not short of treatment options. Even though lefamulin has a novel mechanism of action, a high barrier to resistance, and a low likelihood of cross-resistance with other antibiotic classes, currently available therapies for CABP are quite effective. Because of its high cost and prevalence of GI AEs, its widespread use in CABP is unlikely. However, a dire need exists for safe and effective oral options to treat bone and joint infections, particularly in the outpatient setting. The pharmacokinetic properties and spectrum of activity of lefamulin may fill this gap, but more data are needed. Lastly, as the prevalence of resistant *N gonorrhoeae* rises globally, agents to treat this common STI are necessary. We are hopeful that larger trials evaluating its use for STIs will be completed.

References are available at ContagionLive.com.
Hospital Logistics Are Key to Managing COVID-19 Cases

Temple University Hospital’s pandemic planning and navigation may be a model for other institutions facing high numbers of patients with COVID-19.

BY CARLY SEDLOCK, MD; AND JASON C. GALLAGHER, PHARMD, FCCP, FIDP, FIDSA, BCPS

LEADERSHIP

The keys to an effective response to a crisis are leadership and organization. Voices from internal medicine, nursing, pulmonary/thoracic medicine, infectious diseases, emergency medicine, pharmacy, respiratory therapy, ventilator management, and those involved in infection control/procuring personal protective equipment (PPE) were all present in task forces and planning groups.

Clinical leadership for the COVID-19 response has come from Gerard J. Criner, MD, FACP, FACCP, director of the Temple Lung Center and chair of the Department of Thoracic Medicine and Surgery. His relationship with scientists in Wuhan, China, has helped inform Temple’s COVID-19 response by enabling frontline practitioners with experience to guide those who lacked it before our first patient was admitted. Criner has also been holding interdisciplinary systemwide daily video calls 6 days a week to allow clinicians, infection control, laboratory management, informatics personnel, and supply management to weigh in on evolving outcomes, policies, and treatment protocols.

Multiple groups have become leaders in the Temple COVID-19 response. The Section of Infectious Diseases has guided policy for infection control, PPE, and testing. An infectious disease attending is on call as the “COVID czar” 24 hours a day to answer clinical questions about testing and other policy questions. A designated hospitalist administrator handles questions about transfers, bed management, and patient disposition. Kathleen Reeves, MD, director of the Center for Urban Bioethics and senior associate dean of Health Equity, Diversity and Inclusion, has also been working to meet the needs of Temple’s underserved patient population in the face of the pandemic. She has been leading efforts to deliver food to city residents, connect individuals to social services, and maintain utilities for residents.

HOSPITAL ORGANIZATION

To allow essential services to continue and to decrease the risk of nosocomial COVID-19 acquisition, hospital leadership took advantage of Temple University Hospital’s facility to create functional COVID-19 and non–COVID-19 hospitals. Temple University Hospital’s physical layout proved fortuitous for our response; Temple comprises 2 separate hospital buildings connected by a covered bridge. The main hospital building (the Rock Pavilion) has operated with normal services at reduced volumes. Meanwhile, Temple transformed the Boyer Pavilion, which usually houses several outpatient offices as well as a few inpatient floors and intensive care units (ICUs), into a separate 250-bed COVID-19 hospital. Physicians first admit patients with suspected COVID-19 to a service in Boyer as their status is determined. If they are polymerase chain reaction (PCR) negative and clinical suspicion subsides with an alternative diagnosis, for instance, staff transfer patients from Boyer to Rock (COVID-19 to non–COVID-19). If Rock patients are suspected of having COVID-19, as with an atypical or delayed presentation, staff transfer them to Boyer. With the cancellation of elective procedures and decreased patient volumes in Rock, Temple has scaled up staffing in Boyer to accommodate patient volume. Boyer also houses a designated CT scanner.

TRIAGE

One of the keys to Temple’s approach has been triage, which starts with emergency department personnel. Clinical leadership created triage algorithms to facilitate consistency in patient care and bed management using clinical, radiological, and needs-based criteria (Figure). As the need for beds increased, administration quickly facilitated conversion of office spaces and lobbies in the building into patient wards and postanesthesia care units into ICUs.

Patients who present with mild disease and are treated with outpatient care are offered monitoring with the HGE COVID symptom tracking application, a website where patients can log symptoms daily. This allows occupational health and primary care clinicians to assess outpatients based on patient-reported symptoms and act to redirect them to inpatient care if necessary.

STAFFING CHALLENGES

Shortly before patients with COVID-19 were admitted to Temple, hospital administration instructed nonessential and off-duty personnel to work from home, and experienced training for health sciences students ended. To maintain a viable, healthy workforce, medical residents had elective rotations canceled, and services included essential personnel only. Remote support using the electronic health record (EHR) has allowed clinical services to continue, even for essential services. Temple also enacted a universal masking policy and temperature checks for anyone entering.

As the crisis has progressed, Temple has had to adapt its staffing needs. For example, an unanticipated increase in patients requiring renal replacement led to around-the-clock shifts for dialysis personnel.

To allow our emergency department providers to effectively triage and manage cases of patients presenting with symptoms of COVID-19, the hospital has created various “pods” staffed by other specialties to triage and see patients without COVID-19. Triage staff funnel patients presenting with chest pain and acute coronary syndrome to a cardiology pod staffed directly by cardiologists; a surgeon sees patients presenting with abdominal pain. This team approach extends to inpatient services as well. As inpatient volume has increased, Temple has created more COVID-19 care teams, and specialists have staffed these teams in several day blocks to relieve hospitalists. Behind
the scenes, outpatient providers have embraced the use of telemedicine for the vast majority of patient needs.

**TESTING**

Temple has been subject to the nationwide shortage of testing supplies for COVID-19. As in many institutions, Temple’s lab took advantage of Emergency Use Authorization to create and quickly validate in-house PCR-based testing. The lab increased testing capacity through technican training and by running multiple testing shifts per day. Shortages of testing supplies have created challenges intermittently, and Temple has responded in several ways. When the ability to run assays became limited, send-out testing was used for situations in which turnaround time was less urgent, as in which situations,

**CLINICAL MANAGEMENT AND TREATMENT**

Temple’s pulmonary and critical care physicians have been the frontline managers in the treatment of patients with COVID-19. Temple has employed early strategies for noninvasive ventilation, including use of high-flow oxygen and prone positioning to decrease rates of intubation. Temple developed its treatment algorithm for COVID-19 with input from many disciplines, and it has evolved continuously. To preserve PPE, principles of the algorithm are to preferentially use less frequently dosed regimens (eg, enoxaparin over heparin) and those that do not require specific laboratory blood draws (eg, linezolid over vancomycin). Informatics created a panel in our EHR specifically for monitoring patients with COVID-19, including vitals, laboratory values, and pertinent biomarkers.

With a lack of therapies for COVID-19, early enrollment in clinical trials has been a primary therapeutic modality for our patients. We facilitate this through several means, including placement of available clinical trials in treatment pathways, prioritization of COVID-19 protocols by the Temple institutional review board, and the use of multiple personnel for consent.

Given the cytokine storm often seen in patients with COVID-19, Temple has used immunomodulatory therapies inside and outside clinical trials, including those that inhibit IL-1, IL-6, and granulocyte-macrophage colony-stimulating factor. Because both therapies are associated with increased risk of infection and blunt diagnostic markers of infection, infectious diseases physicians follow all patients who are prescribed or enrolled to receive one.

**WORKFORCE SUPPORT**

A healthy workforce is necessary to adequately care for the surge of patients with COVID-19, and Temple has created policies and procedures with employee health in mind. Physicians on the COVID-19 services work 8-hour shifts to decrease provider fatigue, which can compromise patient and provider safety. Temple created an in-hospital testing site, which now primarily provides testing for symptomatic employees and has also offered several services focusing on wellness, including provision of dorms at the undergraduate campus where health care workers can stay, free shuttle service in the city, and free mental health resources.

**CONCLUSIONS**

Despite many challenges, Temple has succeeded in providing high-quality care to those most in need. Although the differences between hospitals in the United States are considerable, we believe that aspects of Temple’s approach can offer our medical peers examples to follow and adapt for their own institutions. ▲

References are available at ContagionLive.com.

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**FIGURE. Triage Algorithm for Patients With Suspected COVID-19**

<table>
<thead>
<tr>
<th>Unknown COVID-19 status Patient presents to ED with lower respiratory tract symptoms (eg, dyspnea, cough) and meets observation/inpatient criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Other HPI risk factors • ≥ 5-day prodrome • Subjective fevers • History of present illness; HR, heart rate; ICU, intensive care unit; NC, nasal cannula; O₂, oxygen; PAPP, powered air-purifying respirator; PPE, personal protective equipment; RR, respiratory rate; RVP, respiratory viral panel; sat, oxygen saturation; SOB, shortness of breath.</td>
</tr>
<tr>
<td>• Lymphopenia • Fever • Tachycardia • Imaging findings (CXR or CT) • Supplemental oxygen requirement</td>
</tr>
<tr>
<td>0-1 Clinical criteria ED discharge guidance • Mild illness severity: low risk for decompensating, temperature &lt;101 ° F, HR &lt; 110 BPM, no extra O₂ requirement (&lt;92% O₂ sat), normal imaging results</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>&gt;2 Clinical criteria Do they require mechanical ventilation, 40% FIO₂, or SL NC, HFNC, or BIPAP?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>For low illness severity, consider alternative diagnosis, ED orders. • RVP, COVID-19 test • Text ANC level to admit to COVID-19 hospitalist/medicine team • Green isolation: enhanced droplet (contact/droplet/eye) • Location: medicine Boyer areas Hospitalist COVID-19 admitting team: • Use COVID-19 order set. • Can use a CT to look for GGO to help determine risk profile • Can discharge to home isolation with precautions with pending testing</td>
</tr>
<tr>
<td>Moderate illness ED orders • Clinical guidance: SOB, RR &gt;20-25 BPM, HR &gt;110 BPM, temperature &gt;101 ° F, imaging with GGO or peripheral consolidation at lobal level, respiratory support O₂ sat ≤ 92%, 2-4 L O₂ required • RVP, COVID-19 test • Discuss case with pulmonary Boyer attending/fellow, who will designate the appropriate admission team (medicine vs pulmonary). • Green isolation order: enhanced droplet (contact/droplet/eye) • Location: pulmonary or medicine Boyer areas COVID-19 admitting team • Use the Epic COVID-19 admission order set. • Order “CT COVID-19” for further information on risk stratification if needed • PPE required: surgical face mask with eye protection, gown, gloves, N95 mask for aerosolizing procedures • If patient is on medication for COVID-19 infection, consider transfer to pulmonary COVID-19 service.</td>
</tr>
<tr>
<td>ED orders for high illness severity • RVP, COVID-19 • Other clinical considerations: temperature &gt;101 ° F, RR &gt;25 BPM, HR &gt;110 BPM, GGO or multilobar consolidation, with more than 6L O₂ requirement • Discuss case with pulmonary Boyer X attending/fellow (under pulmonary attending in Amion) • Location: Boyer ICU or high-risk Boyer designated areas Pulmonary team orders • Use COVID-19 admission order set. • Blue enhanced isolation: Ensure airborne/contact isolation (negative pressure room) if patient is not intubated. • If patient is intubated, can de-escalate to enhanced droplet isolation appropriate • Blue isolation PPE required: N95 mask with eye protection or PAPR, gown, gloves</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; BIPAP, bilevel positive airway pressure; BPM, beats per minute; COVID-19, coronavirus disease 2019; CXR, chest x-ray; ED, emergency department; FIO₂, fraction of inspired oxygen; GGO, ground-glass opacity; HFNC, high-flow nasal cannula; HPI, history of present illness; HR, heart rate; ICU, intensive care unit; NC, nasal cannula; O₂, oxygen; PAPP, powered air-purifying respirator; PPE, personal protective equipment; RR, respiratory rate; RVP, respiratory viral panel; sat, oxygen saturation; SOB, shortness of breath.
COVID-19: A Primer
This virus has multiple facets and highlights a need for real-time learning.

BY AMESH A. ADALJA, MD

(continued from cover page)
Below I will discuss the transmission, mortality, and clinical characteristics of the novel virus and compare and contrast it with SARS, Middle Eastern respiratory syndrome (MERS), and influenza.

THE VIRUS
SARS-CoV-2 was initially identified in a cluster of 41 individuals who developed pneumonia in Wuhan, China. The virus is the seventh human coronavirus identified. Coronaviruses are a large group of enveloped RNA viruses named for their characteristic appearance on an electron micrograph. The others include 4 viruses—229E, OC43, NL63, and HKU1—that generally cause mild symptoms of the common cold. Of these, HKU1 does appear to have the capacity to cause more severe disease.2 SARS-CoV and MERS-CoV are the other 2 and, by contrast, tend to cause severe disease and are closely linked to animal spillover events from palm civet cats and bats, respectively. Within the coronavirus family, SARS-CoV-2 is classified as a betacoronavirus, a cluster that also includes SARS-CoV and MERS-CoV, as well as HKU1 and OC43. The virus uses its spike protein to bind to its requisite receptor, which for SARS-CoV and SARS-CoV-2 is the angiotensin-converting enzyme 2, found on various cell types. This protein is also the focus of vaccine development efforts.2

TRANSMISSION
The virus appears to transmit primarily through the respiratory route in large droplets from the mouth and nose. Such droplets fall to the ground within about 6 feet of their point of emanation. They may land on surfaces and remain viable for some time depending on environmental conditions. As an enveloped virus, SARS-CoV-2 is...
not hardy. Concerns exist regarding airborne or aerosol transmission, but this appears to be more of an issue for health care facilities performing aerosol-generating procedures, such as the use of bilevel positive airway pressure (BiPAP), aerosol drug treatments, intubation, and bronchoscopy. Some concern also exists over fecal-oral transmission, but the frequency and circumstances of that form of transmission are not well characterized.3

Currently, the degree of seasonality that this virus may exhibit is unclear. The 4 community-acquired coronaviruses do exhibit seasonality; however, the novel virus, despite poor weather conditions for its surface viability, may be less seasonal given the lack of population immunity. Such low levels of immunity may be sufficient to overcome the diminished environmental viability and natural social distancing that occurs in warmer months in temperate climates.

CLINICAL CHARACTERISTICS

COVID-19, the disease caused by SARS-CoV-2, has a wide spectrum of illness, ranging from asymptomatic infection to fulminant respiratory disease leading to acute respiratory distress syndrome (ARDS). According to case series, the most common signs and symptoms can include fever, chills, myalgias, and sore throat. Some individuals, in contrast with others with many other respiratory viral infections, may experience gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Loss of smell and taste has also been reported.4,5

Although most patients have a mild course that does not require hospitalization, those with advanced age or other comorbid conditions may fare worse. Risk factors such as diabetes, hypertension, obesity, lung disease, immunosuppression, and cardiovascular disease can portend a worse prognosis.6

The presence of dyspnea, which can signify the presence of pneumonia, may signal more severe symptoms. Pneumonia, which radiologists may not detect on an ordinary chest x-ray but only on a chest CT scan, is often described as having a ground-glass appearance.7

ARDS can ensue, and emerging data suggest the possibility of 2 phenotypes with different treatment implications: one form, known as L, with preserved lung compliance, and another, H, with diminished lung compliance. Those with near-normal lung compliance (L form) may benefit from noninvasive ventilation options such as BiPAP and continuous positive airway pressure and when intubated may tolerate higher tidal volumes. Those with the H form, in which classic ARDS is present with bilateral infiltrates on chest radiography, should be treated with standard ARDS low-tidal volume protocols and may require prone-position ventilation.8

Another serious clinical manifestation is cardiomyopathy (acute cardiac injury), which clinicians can diagnose via electrocardiogram, echocardiography, and troponin measurement.9 The novel virus has also been hypothesized to cause a thrombophilia-like condition characterized by a prothrombotic predisposition leading to microthrombi in digits as well as in the pulmonary vasculature. This is evidenced by elevated D-dimer levels as well as the development of antiphospholipid antibodies.5,10 Neurologic manifestations, including stroke and neuropathy, have also been reported in some patients.11

Laboratory abnormalities that may be present include leukopenia, lymphopenia, and elevated C-reactive protein, low procalcitonin, elevated lactate dehydrogenase, and elevated D-dimer levels. Elevated ferritin and IL-6 levels have also been observed and may be a signal of a hyperinflammatory state; patients with these laboratory abnormalities might be study candidates for anti–IL-6 (tocilizumab, sarilumab), anti–IL-1 (anakinra), and cytokine apheresis therapies.12

No recommended treatments for this virus exist, although clinical trials are ongoing, and the use of the antiviral remdesivir has shown the ability to hasten clinical improvement in severe cases, which led to an emergency use authorization.13

MORTALITY

The mortality risk from COVID-19 is not currently known because the denominator of infection is unclear. This uncertainty stems largely from variance in testing policies and availability, which has introduced a severity bias in the data. The best estimates for infection fatality ratios all fall under 1.0%, with some as low as 0.66% and 0.37%.

The relative risk of mortality increases substantially with each decade of life. The same is true for hospitalization ratios, which have been significantly influential in hospital capacity planning.

SARS, MERS, AND SEASONAL INFLuenza COMparisons

A comparison of the novel virus with fellow coronaviruses SARS and MERS highlights some major differences. Although all are respiratory viruses with overlapping clinical syndromes, both SARS and MERS have considerably higher mortality risks. Approximately 10% of patients with SARS and over 30% of those with MERS succumbed to their illness. SARS and MERS, however, do not exhibit the efficient human-to-human transmissibility of the novel virus and are better characterized as zoonotic viruses with poor efficiency in transmission between humans. Seasonal influenza also has clinical symptoms similar to those of the novel virus and exhibits efficient human-to-human transmission. However, because of population-level immunity to influenza, it has a lower attack rate season to season. Its mortality ratio is likely 0.1%, although it can be significantly higher in older populations.

As the novel coronavirus pandemic continues, the clinical and scientific knowledge base will increase dramatically. Critically, clinicians will need to keep abreast of all new developments to optimize patient care. ▲

References are available at ContagionLive.com.
How Close Are We to a Cure for HIV?

Evolving research has led the infectious diseases community to redefine its definition of cure.

BY DELLA XU, PHARM.D.; AND DAVID E. KOREN, PHARM.D., BCPS, AAHIVP

THE TYPES OF “CURE”

The FDA defines HIV cure research as “any investigation that evaluates (1) a therapeutic intervention or approach that controls or eliminates HIV infection to the point where no further medical interventions are needed to maintain health, and (2) preliminary scientific concepts that might ultimately lead to such a therapeutic intervention.” Thus, the medical community is pursuing 2 types of HIV cure: eradicative and functional, also called HIV remission. Eradication, also known as sterilization, implies that HIV has been removed completely from the human host. A functional cure differs significantly because the goal is not to clear the viral reservoir from the human host but rather to reach sustainable infection control in the absence of ART.

CHALLENGES IN CREATING A CURE FOR HIV-1

ART targets only viral replication in activated cells. It cannot touch latent virus, meaning the vast amount of virus hidden in memory or otherwise inactive T cells. This reservoir poses the biggest challenge to HIV elimination, as viral latency is a reversible process in the absence of effective ART. While patients are on ART, this latent pool of cells declines slowly but may take an estimated 7 decades to fall to 0; recent research has also described a decline of only 4 years followed by a plateau. A unique hypothesis of this persistence centers on the ability of the infected cells to expand via clonal proliferation rather than active HIV replication to sustain the viral reservoir. Complicating viral latency further, a latent reservoir may form in compartments of the human body that are spared from immune recognition and ART.
because of both physical and cellular barriers (also called viral escape). Some examples of these barriers include the blood-brain barrier, the Sertoli cell layer of the testes, and the B-cell follicles within the lymph nodes.

**CURE SUCCESS**

Despite these challenges, 2, and possibly 3, eradicative cures exist. In addition to the CD4 receptor, HIV requires a second coreceptor to infect a cell. One such receptor, the CCR5, is congenitally absent in 0% to 2.3% of individuals.12

The “Berlin Patient” (Timothy Ray Brown), as part of treatment for acute myeloid leukemia (AML), received full-intensity conditioning chemotherapy, whole body radiation, and 2 transplants from an HLA antigen–matched donor with CCR5 coreceptor Δ32 deletion. However, he did not receive radiation but instead received reduced intensity conditioning chemotherapy.13,14 Both Brown and Castillejo have been deemed cured (no HIV viremia off ART). A third patient, known as the Düsseldorf patient, remains under evaluation; the 49-year-old man received a bone marrow transplant from a donor with the CCR5Δ coreceptor Δ32 deletion. However, he did not receive radiation but instead received reduced intensity conditioning chemotherapy.15,16

The “London Patient” (Adam Castillejo), as part of treatment for Hodgkin lymphoma, also received a stem cell transplant from a donor with the CCR5Δ coreceptor Δ32 deletion. However, he did not receive radiation but instead received reduced intensity conditioning chemotherapy.15,16

Both Brown and Castillejo have been deemed cured (no HIV viremia off ART). A third patient, known as the Düsseldorf patient, remains under evaluation; the 49-year-old man received a bone marrow transplant from a donor with the CCR5Δ coreceptor Δ32 deletion. However, he did not receive radiation but instead received reduced intensity conditioning chemotherapy.15,16

**REMISSION APPROACHES**

No single approach has achieved long-term viral remission. Described here are several approaches that investigators are evaluating for a functional cure that may be used in combination: early initiation, shock and kill (including several potential components), clustered regularly interspaced short palindromic repeats (CRISPR), and chimeric antigen receptor (CAR) T-cell technology.

Early initiation of ART upon diagnosis of HIV has been correlated with varying degrees of posttreatment control, reducing residual viral replication, decreasing viral reservoir, preserving innate immunity, and enhancing immune response.16,17 Several cohorts evaluating treatment interruption (CHAMP/SPARTAC/VISCONTI) concluded that initiation of ART during the early acute phase of HIV infection can preserve CD4+ cell counts and delay viral rebound after ART interruption.17-19 Nevertheless, treatment interruption studies have fallen out of favor given multiple increased risks with ART interruption, as seen in the SMART trial (NCT00027352) (eg, clinical progression, cardiovascular risk, or malignancies).20 New consensus recommendations for analytical ART interruptions in HIV research trials now exist to guide future study designs.21

The shock-and-kill method combines (1) latency reversal agents such as histone deacetylase inhibitors and toll-like receptor (TLR) agonists to induce HIV-1 transcription followed by (2) ART, therapeutic vaccines, and/or broadly neutralizing antibodies (bNAbs) to decrease the latent reservoir. Major histone deacetylase inhibitors romidepsin and vorinostat induce HIV gene transcription by suppressing histone deacetylases enzymes that enzymatically remove the acetyl group from histones.22,23 TLR agonists such as vesatolimod induce the secretion of tumor necrosis factor α and thus promote viral reactivation.24 This process of reactivation is then followed by immunomodulation with agents such as therapeutic vaccines and/or bNAbs. The aim of therapeutic vaccines (such as the modified vaccinia Ankara B and the recombinant canarypox virus) is to elicit an antigenic immune response to suppress viral replication in the absence of ART. Broadly neutralizing antibodies (such as VRC01 and 3BNC117) induce host immunity by targeting specific epitopes of HIV.22,25

Combined approaches using these methods were presented at the 2020 virtual Conference on Retroviruses and Opportunistic Infections. Notable studies included (1) a 20-patient cohort given romidepsin and bNAb 3BNC117, resulting in neither delay of viral rebound nor reduction in reservoir size, and (2) the safety and efficacy of a combination TLR7 agonist/therapeutic vaccine approach to induce CD8+ T cell–mediated control of the simian immunodeficiency virus (a commonly used nonhuman primate model), finding no statistically significant differences between treatment and placebo. The authors did report a modest increase in time to viral rebound with this strategy.26-27 Of note, these novel drug mechanisms are only limited examples of the vast array of immunoregulatory agents under development. Agents such as immune checkpoint inhibitors, PD-1 and CTLA-4 agents, may possibly be used in combination to enhance the response of HIV-specific T cells and improve viral control.28-29

Emerging strategies and evolving science regarding genetic modification have unlocked new approaches for HIV cure research. These approaches include using CRISPR and CAR T-cell technology. CRISPR enables DNA cleavage to occur prior to proviral integration (resulting in proviral destruction) or after proviral integration (resulting in small insertions and deletions in the HIV genome).30-32 CAR T-cell technology uses cytotoxic T cells engineered with extracellular components to recognize both HIV epitopes and intracellular components with accompanying signal inductions.34

**CONCLUSIONS**

Although current research has not yet elucidated the path to either “cure” approach, research remains highly prioritized and active, with promising novel drug mechanisms and emerging science. Evolving methods have redefined the concept of HIV cure, with the eventual goal of bringing the story of HIV to its completion. ▲

References are available at ContagionLive.com.
Candida auris is Changing the Paradigm of Antifungal-Resistant Candida

Candida auris is an emerging health care–associated multidrug-resistant fungal pathogen with public health concerns more similar to those of extensively drug-resistant bacterial pathogens than other species of Candida.

BY JEFFREY M. RYBAK, PHARMD, PHD

Jeffery M. Rybak is a postdoctoral research associate at the University of Tennessee College of Pharmacy in Memphis. His research focuses on the identification and characterization of antifungal resistance mechanisms in fungal pathogens such as Aspergillus fumigatus and Candida auris.

(continued from cover page)

Therapeutic options for the treatment of candidemia and other forms of invasive candidiasis are unfortunately limited, with only 3 classes of antifungal agents currently available to clinicians. Thus, antifungal resistance against clinical isolates, estimated to include 35,000 infections each year and 7% of all cases of candidemia in the United States, is a threat to public health.3 Unlike drug-resistant bacterial pathogens such as methicillin-resistant Staphylococcus aureus and carbapenem-resistant Enterobacteriaceae, infections caused by antifungal drug-resistant Candida are most often reported as individual cases among at-risk patients following previous antifungal exposure, and they are generally not associated with transmission in health care settings. The discovery and emergence of Candida auris, however, have significantly changed the way clinicians need to consider antifungal-resistant Candida, and it represents new challenges not previously associated with this genus of fungi.

Shortly after the initial identification of C auris was described in 2009, clinical outbreaks of infections caused by this organism occurred in South Africa, Venezuela, India, and Pakistan.4 Less than a decade later, invasive infections caused by C auris have been reported in 40 countries, with approximately 1000 infections and more than 2000 patients colonized in the United States alone.5 Furthermore, nearly all clinical C auris isolates are found to be resistant to at least 1 antifungal agent, and a large proportion of isolates are multidrug resistant (defined as resistance to agents from more than 1 class of antifungal agents).6 As a result, C auris has become a fungal pathogen of great clinical concern and is now considered a pathogen of urgent threat level by the US Centers for Disease Control and Prevention (CDC).7 Although considerable research efforts continue to expand the epidemiology and pathogenesis of C auris, 3 factors define its threat to public health: the organism’s ability to rapidly spread among patients and health care environments, challenges in the detection of C auris in the clinical microbiology laboratory, and the prevalence of antifungal resistance among clinical isolates.

RAPID SPREAD AMONG PATIENTS AND WITHIN HEALTH CARE

The first clinical specimens of C auris were isolated from patients with ear infections in Japan and South Korea, and this is how the species acquired its name (auris is Latin for “ear”).8 Within a few years, C auris was identified as the cause of unrelated outbreaks of invasive infections on 3 continents.4 In India and South Africa, where C auris appeared earliest and before widespread recognition, C auris quickly became a leading cause of candidemia in some institutions.9 In fact, the most recently available data from South Africa show that C auris was isolated from 14% of nearly 6000 cases of candidemia in private sector hospitals.9 In health care settings outside these regions, introduction of a single clinical isolate has been reported to cause prolonged outbreaks as a result of the unique ability of C auris to resist commonly employed disinfectants, persist on surfaces for weeks, and colonize...
patients for months. In the Chicago, Illinois, metropolitan area, where it was first clinically identified in 2016, C. auris has now spread across health care facilities, most notably long-term post-acute care facilities with large populations of patients at high risk for infections due to multidrug-resistant organisms. A point prevalence study at one institution reported that 71% of screened patients were colonized with C. auris, and 49% of patients were positive for both C. auris and carbapenemase-producing bacterial pathogens. This high rate of colonization among high-risk patients is particularly concerning considering no established methods exist to effectively decolonize patients; an estimated 5% to 10% of colonized patients develop invasive C. auris infections. Thus, excellent infection control practices are essential to controlling the spread of C. auris colonization and infection. As with other, similar bacterial multidrug-resistant threats, clinicians should report cases of C. auris colonization or infections to local and state departments of public health, and they should be aware if C. auris has been identified in their region. Clinicians must also evaluate patients for recent travel or direct personal contacts who may have exposed them to C. auris, and those who are positive for C. auris should be placed under contact precautions. Health care workers should be reminded to employ good hand hygiene, and facilities and equipment should be cleaned and sanitized with agents carrying Environmental Protection Agency claims for C. auris or Clostridiodes difficile (list K). Further detailed recommendations for the prevention and control of C. auris in health care settings are available on the CDC’s C. auris website.

DIFFICULT IDENTIFICATION IN THE CLINICAL MICROBIOLOGY LABORATORY

Reliable and timely identification of C. auris in the clinical setting is imperative to the prevention of its spread in health care environments. Unfortunately, many clinical microbiology laboratories are unable to provide definitive species-level identification of Candida isolates in-house. Among those that can, standard phenotypic methods often misidentify C. auris (platform-specific examples are available on the CDC’s C. auris website), and in some cases, misidentification occurs even after implementing updated testing panels. Taken together, the most reliable methods of identifying C. auris from clinical specimens are matrix-assisted laser desorption ionization–time of flight platforms with C. auris spectral libraries, the T2 magnetic resonance platform with the updated T2Cauris panel, and molecular techniques such as sequencing of ribosomal DNA markers. However, these methods require costly equipment or advanced technical skills that may not be feasible in every clinical setting. Thus, clinicians must be aware of resources available at their own institutions for the identification of C. auris, and if limitations exist, clinicians should also carefully consider them when caring for patients in whom C. auris is suspected. Clinical isolates exhibiting multidrug antifungal resistance should also be carefully identified to the species level by methods capable of identifying C. auris. Clinicians can send clinical isolates in question to the CDC’s Antibiotic Resistance Laboratory Network for confirmatory identification and susceptibility testing.

HIGH RESISTANCE TO ANTIFUNGALS

Further contributing to the clinical significance of this emerging fungal pathogen, C. auris demonstrates higher-level resistance to most antifungal drug classes than do other Candida species. Although clinical experience and epidemiologic data relating to C. auris are currently insufficient to support the establishment of true clinical breakpoints at this time, in an effort to provide provisional guidance for clinicians, the CDC has put forth tentative antifungal breakpoints for the treatment of C. auris infections. These breakpoints are based on available in vitro susceptibility data, limited in vivo pharmacodynamics studies, and the distribution of mutations in genes associated with antifungal resistance in other species of Candida. The specific breakpoints and comments relating to their appropriate application are available on the CDC’s C. auris website. Approximately 90%, 30%, and 5% of clinical C. auris isolates from the United States are resistant to fluconazole, amphotericin B, and the echinocandins, respectively, when applying these tentative breakpoints. Moreover, one-third of isolates are resistant to agents from more than 1 class of antifungals, and isolates resistant to all available therapies have repeatedly been identified. The CDC currently recommends empiric therapy with echinocandins (using labeled dosing) for the treatment of infections in which C. auris is suspected in patients at least 2 months of age. Furthermore, fungal cultures with species-level identification and antifungal susceptibility testing are recommended, as is the consultation of an infectious disease specialist. Clinicians should obtain repeat cultures and antifungal susceptibilities and monitor patients carefully for signs of clinical response, as cases of patients developing antifungal-resistant C. auris infections on therapy have been reported. Most of these instances of acquired antifungal resistance have occurred following prolonged courses of treatment with echinocandins. However, the rate at which C. auris may develop resistance to echinocandins or other classes of antifungals is unknown. In the event of insufficient patient response or the development of echinocandin-resistant disease, clinicians should consider switching to liposomal amphotericin B. However, clinicians need to consider specific patient-, pathogen-, and infection-related factors on a case-by-case basis in collaboration with infectious disease specialists.

CONCLUSIONS

Although much research is needed on C. auris and its long-term impact on invasive candidiasis as a whole, ultimately the best strategies to overcome the challenges posed by C. auris focus on not only therapeutics but also infection control and mitigation. Clinicians must be aware of any cases of C. auris focus on not only therapeutics but also infection control and mitigation. Clinicians must be aware of any cases of C. auris in their local area, monitor new patients for travel or contacts with risk of C. auris exposure, and practice good antimicrobial stewardship and infection control when C. auris is suspected or identified. Finally, clinicians should regularly check the CDC’s C. auris website for the latest information and recommendations.

References are available at ContagionLive.com.
Antimicrobial stewards and infection preventionists have worked in harmony for decades. The benefits of this collaboration are evident in several facets, including several models of multidisciplinary efforts to reduce hospital onset of *Clostridioides difficile* infections (CDIs).1,2 Both new and established antimicrobial stewardship programs (ASPs) likely have something to gain from careful examination of the design of infection prevention strategies. For years, infection preventionists have labored over whether horizontal or vertical strategies are more effective in reducing nosocomial transmission of infectious pathogens. Horizontal methods have historically focused on attempts at reducing broad acquisition of health care–acquired infections through application of practices across wide varieties of patients and settings (eg, hand hygiene, universal precautions, reduction in unnecessary lines or catheters). Vertical infection prevention methods attempt a more targeted intervention aimed at reducing infections due to a specific pathogen or in a specific patient population (eg, neutropenic precautions, environmental sterilization efforts in *C difficile*, and active pathogen surveillance with associated isolation).2 When applied to antimicrobial stewardship, horizontal efforts would refer to interventions aimed at reducing or optimizing antimicrobial use on a broader scale, whereas vertical efforts would focus on specific drugs and disease states that reflect key opportunities for improvement.3 A combination of these 2 methodologies, rather than purely vertical or horizontal efforts, will likely produce optimal outcomes.

An institution beginning ASP development will most likely focus on horizontal strategies. This early focus was reflected in the first version of the antimicrobial stewardship guidelines from the Infectious Diseases Society of America (IDSA), which placed emphasis on programs implementing the primary strategies of prospective audit with intervention and feedback and formulary restriction. Additionally, many of the recommended secondary strategies (eg, education, dose optimization, intravenous to oral conversion, and de-escalation) represent horizontal efforts. This early focus on horizontal methods is profoundly important when designing a new ASP, and the efficacy...
Vertical ASP efforts focused on CDI reduction have demonstrated significant value. Various intervention types have been proposed and/or evaluated, with the most reliably successful aimed at targeted reductions in antibiotics accompanied by the highest risk for development of CDI (eg, targeted prospective audit or formulary restriction) and CDI-specific provider education. One recent abstract described a unique, focused effort to reduce antibiotic use in a specific population known to be asymptomatically colonized with C difficile admitted to a single institution. In this study, the authors screened patients admitted to 1 of the 5 targeted units over a 7-month period for C difficile colonization using a nucleic acid amplification test collected at the time of admission. An ASP pharmacist then evaluated on a daily basis patients found to be colonized for systemic antimicrobial optimization and acid suppressive therapy (AST) de-escalation. A total of 265 patients were included, of whom 73% received antimicrobial therapy and 72% received AST. Investigators made antimicrobial and AST interventions in 17% and 26% of cases, respectively. Thirty-seven (14%) patients developed colitis, and of these, 6 (16%) and 10 (27%) had received recommendations for antimicrobial or acid suppressive therapy optimization, respectively. The feasibility, potential cost of testing, and lack of control group in this study may limit its overall reproducibility and impact; however, this demonstrates a creative approach to designing a vertical antimicrobial stewardship intervention in patients at risk for CDI.

Another potential application for vertical stewardship methodologies is in patients reporting penicillin allergies. Penicillin allergy is one of the most commonly reported drug allergies, with reported incidences in the population ranging from 6% to 25%. However, studies have shown that up to 98% of these patients may have their penicillin allergy delabeled after undergoing skin testing. A reported penicillin allergy has known adverse impacts on both clinical and financial outcomes, including longer lengths of hospital stays, increased mortality, higher antimicrobial costs, and increased risk of C difficile, methicillin-sensitive Staphylococcus aureus, and vancomycin-resistant Enterococcus faecium infections. The implementation of penicillin allergy testing as an antimicrobial stewardship strategy continues to gain momentum given the demonstration of significant impacts on antimicrobial use and outcomes.

One excellent demonstration of a vertical intervention addressing penicillin allergy and associated antimicrobial prescribing was performed at The University of Texas MD Anderson Cancer Center in Houston. This study incorporated both drug- and population-specific vertical considerations as investigators evaluated the impact of penicillin allergy testing on aztreonam use in immunocompromised patients with cancer. They performed penicillin skin testing in 49 patients, 46 of whom tested negative. Of the patients who tested negative, 33 were subsequently switched to a β-lactam antibiotic. This was associated with a significant reduction in overall aztreonam use (10 vs 8 days of therapy per 1000 patient days; \( P = .005 \)) and a projected savings of $63,192.61.

Vertical antimicrobial stewardship strategies may also be designed to reduce inappropriately long durations of therapy in specific clinical syndromes. Interventions focusing on this target may include education, development of local guidelines emphasizing appropriate durations of therapy, and/or incorporation of a specific clinical syndrome, with a focus on duration of therapy, into a program’s prospective audit. One such study, including 62 patients with community-acquired pneumonia (CAP), demonstrated significant reduction in duration of therapy for CAP (10 vs 7 days; \( P < .001 \)) after a 3-tiered intervention comprising a preimplementation survey of providers, an educational offering, and incorporation of CAP durations into the program’s prospective audit and feedback. Another study also demonstrated reductions in antimicrobial use (10 vs 8 days; \( P = .001 \)) after implementation of both a prospective audit service including patients with CAP and development/dissemination of a local clinical pathway including recommendations for duration of therapy. Investigators also found a shift from the use of fluoroquinolones to more β-lactam- and macrolide-based regimens, as well as a reduction in inpatient length of stay during the study period (7.24 vs 5.71 days; \( P = .011 \)). These studies demonstrate that a horizontal stewardship method, such as prospective audit with intervention and feedback, can be further tailored into a highly effective vertical method when redirected through a single syndrome.

As the landscape of antimicrobial stewardship, both in the United States and globally, continues to change, programs will need to remain both curious and nimble to innovate and advance practice. Using the existing data within an institution to craft new and creative interventions across the continuum of care is sure to catalyze ongoing programmatic development. The addition of vertical stewardship methods to preexisting horizontal methodologies represents one manner by which a program may further expand and/or enhance its impact on patient outcomes, antimicrobial use, and health care costs.

References are available at ContagionLive.com.
What Clinicians Need to Know About COVID-19

BY GINA BATTAGLIA, PHD

To address the urgent need for knowledge about coronavirus disease 2019 (COVID-19) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes it, infectious disease experts participated in a continuing medical education–certified webinar hosted by Contagion® and Physicians’ Education Resource® on Wednesday, March 25, 2020, to discuss the clinical presentation and course of infection, mitigation of transmission, and promising options for treatment.

COVID-19 CLINICAL PRESENTATION AND COURSE

In her presentation, Helen W. Boucher, MD, FACP, FIDSA, said that although the incubation period ranges from 2 to 14 days, individuals generally start showing signs of illness 4 to 5 days after exposure. Dry cough and fever are common symptoms, according to guidance from the Centers for Disease Control and Prevention Health Alert Network,1 but Boucher cautioned that clinicians should not rule out COVID-19 in afebrile patients, who accounted for up to half of the patients in some series, and should strongly consider it in patients reporting “really profound myalgias,” particularly in the upper body.

Gastrointestinal symptoms and changes in smell and taste were also noted in a recent study, with approximately half of patients reporting a digestive symptom (lack of appetite, diarrhea, vomiting, and/or abdominal pain) and a small proportion of patients presenting with gastrointestinal symptoms alone.2 Although the majority of patients have mild illness that does not require medical intervention, Boucher stated that the severity of illness ranges widely, with potential for clinical deterioration in the second week of illness. She added that results of early studies show that 23% to 32% of hospitalized patients required intensive care, with acute respiratory distress syndrome (ARDS) developing in up to 29% of hospitalized patients and invasive mechanical ventilation needed in approximately 10% of patients.1

Boucher noted that Chinese colleagues rely heavily on CT for diagnosis and treatment, although she said that she and her colleagues at Tufts Medical Center have used mostly chest x-rays and clinical criteria for diagnosis because CT scanners are difficult to disinfect after use. She added that both imaging modalities often show bilateral patchy infiltrates consistent with viral infection.

Factors associated with severe disease and mortality

Patients greater than 55 years of age and those with underlying lung disease or current smoking habit, cardiovascular disease, diabetes, and immunocompromised status are at higher risk for severe disease, said Boucher. Clinical and laboratory findings associated with severe disease include elevations in respiratory or heart rate; oxygen saturation less than 90%; elevations in D-dimer, creatine phosphokinase, C-reactive protein, lactate dehydrogenase, troponin, and ferritin levels; and low lymphocyte and platelet counts.

Results of a study of patients in Wuhan, China, showed that using multivariate analysis, older age, higher Sequential Organ Failure Assessment (SOFA) score (ie, more severe illness), and D-dimer greater than 1 μg/mL was associated with increased risk for mortality.2 Results also showed that the median duration of viral shedding was 20 days and that 50% of the patients who died had a secondary bacterial infection.

“This [high rate of bacterial infection] is something for us to keep our eyes on in this disease,” said Boucher. “I worry that we’re going to see resistant bacterial infections here in the United States among these patients.”

EXPONENTIAL GROWTH IN COVID-19 INFECTIONS AND MITIGATING TRANSMISSION

The next presenter, Carlos del Rio, MD, noted that the exponential pattern of growth in the number and geographical spread of COVID-19 cases reflects the high transmissibility of the virus and that the lack of testing in the United States...
has hampered the ability to respond effectively in the early phases and see the “full picture” of identifying infected individuals.

“One of the main lessons for us as clinicians and public health experts is that we really need to push for more testing,” said del Rio. “Scaling up the testing is going to be critical for us to identify...and isolate those [who] are infected.”

COVID-19 is thought to be transmitted primarily through respiratory secretions, namely respiratory droplets from coughs and sneezes that travel 4 to 5 ft (hence, the rationale for the 6 or more feet of distance between individuals, said del Rio) and can land on high-contact surfaces such as doorknobs, elevator buttons, and tables, which become a source of virus transmission. Social distancing, which involves interventions designed to maintain physical distance between individuals and minimize the number of times they come into close contact, has been the primary mitigation strategy in the United States and primarily aims to prevent overwhelming health care services, according to del Rio.

“We may still see the same number of infections, but we’re going to see it over a longer period,” del Rio said. “It keeps [the impact on] health care and economy more manageable, and it slows the progression of the epidemic to, hopefully, allow for the development of vaccine and other treatment options.”

Del Rio added that social distancing can have a particularly profound effect on reducing the transmissibility of a virus with a high basic reproductive number (R0, the expected number of cases directly generated by 1 case in a population in which all individuals are susceptible to infection). He provided a hypothetical example in which an individual infected with a virus with an R0 of 2.5 could infect an average of 2.5 other individuals over 5 days (a typical incubation period for SARS-CoV-2) and more than 400 in a 30-day period if no social distancing measures were implemented. Decreasing the infected individual’s exposure by 50% in this example would lead to only 15 infected individuals over a 30-day period, del Rio explained.

COVID-19 TREATMENT CONSIDERATIONS

In his presentation, Stanley Deresinski, MD, reviewed proposed molecular mechanisms of SARS-CoV-2 infection and the most promising options for treatment of COVID-19 currently in clinical trials.

**Mechanism of Infection**

SARS-CoV-2 is an enveloped, single-stranded RNA betacoronavirus with a genetic homology of 96% to SARS-CoV-1 at the RNA polymerase, a potential target for treatment, said Deresinski. Entry into and infection of human cells occur when the attachment glycoprotein “spike” binds to the angiotensin-converting enzyme 2 receptors, which are located in the lungs, heart, and gastrointestinal tract and likely contribute to the pneumonia, cardiac disease, and diarrhea often observed with COVID-19, said Deresinski.

CD147, a member of the immunoglobulin G superfamily, has also been identified as a receptor that increases production of mixed metalloproteinase and proinflammatory cytokines and may be important for the pathophysiology of COVID-19, he added.

**Remdesivir**

With COVID-19 straining health care systems worldwide, “the number of drugs that are being proposed is growing almost as rapidly as the [pandemic] itself,” said Deresinski. He noted that remdesivir (Gilead), a nucleoside analogue that inhibits RNA-directed RNA polymerase after intracellular phosphorylation, has demonstrated activity in animal models of Middle East respiratory syndrome and SARS-CoV-1, as well as in vitro models of COVID-19, and is the drug experts “have the most hope in.” At least 6 registered clinical trials are ongoing, with 4 located in the United States and 2 in China. The Gilead moderate COVID-19 trial (NCT04292730) is randomizing patients with moderate disease to standard of care, 5 days of remdesivir, or 10 days of remdesivir, and the Gilead severe COVID-19 trial (NCT04292899) is randomizing patients with severe disease to 5 or 10 days of remdesivir. The National Institute of Allergy and Infectious Diseases’ ACTT trial (NCT04280705) will compare 10 days of remdesivir with placebo in patients with laboratory-confirmed infection and an indication of lung involvement, although remdesivir will be substituted for another drug if it is found to be inactive, said Deresinski.

**Chloroquine and Hydroxychloroquine**

Chloroquine and hydroxychloroquine, which have received widespread attention in the media, have nonspecific antiviral effects by increasing endosomal pH and interfering with glycosylation of the SARS-CoV-2 cellular receptors. A news brief from China reported that chloroquine had efficacy in reducing exacerbation of pneumonia, promoting negative conversion, and shortening duration of disease in “over 100 patients,” although Deresinski cautioned that specific data from this report have not been published.

Additionally, the results of a study from France increased the public spotlight on hydroxychloroquine, although Deresinski noted several limitations of the findings. The treatment group included hospitalized patients (age >12 years) with confirmed COVID-19 infection at the Méditerranée Infection University Hospital Institute in Marseille who agreed to participate, but Deresinski pointed out the selection of the control group—which included patients who had received treatment at a different hospital, were ineligible for hydroxychloroquine, or had declined the experimental treatment—was flawed. He added that 6 of the 22 patients in the hydroxychloroquine arm, but none of the 16 patients in the control arm, were excluded from the analysis because of transfer to the intensive care unit (n = 3), death (n = 1), leaving against medical advice (n = 1), and nausea (n = 1).

“Four [patients] were withdrawn from the study because of significant adverse effects and were not included in the analysis at all,” Deresinski said.

Although the primary end point of virological clearance at day 6 was higher in patients who received hydroxychloroquine with or without azithromycin (100% and 57.1% of patients, respectively, vs 12.5% with standard treatment), Deresinski noted that data from their secondary end points (virological clearance over time, clinical follow-up, and occurrence of adverse effects) were not reported at all.

Deresinski also said that results from a randomized study from China showed that the proportion of patients with negative viral polymerase chain reaction at day 7 was similar between the hydroxychloroquine and standard-of-care arms. Although the study also had limitations and included patients with milder disease than those in the French study, it “nonetheless raises doubts about the Marseille results,” said Deresinski. Nevertheless, clinical trials, such as a phase 3 trial in China (NCT04261517), are currently studying the use of hydroxychloroquine for COVID-19–related pneumonia and will aim to provide more information on the drug’s efficacy.

**Immunomodulator Therapy**

Deresinski noted that tocilizumab and other IL-6 antibodies for patients with ARDS and elevated IL-6 levels, convalescent serum, and monoclonal antibodies are of interest to investigators and are undergoing trials. He ended his presentation by cautioning that although a study from China suggested a benefit of methylprednisolone, most organizations have recommended against the use of adjunctive corticosteroids for treatment of COVID-19 because adverse effects ranging from delayed viral clearance to comorbid complications have been demonstrated in other coronaviruses.

“The general recommendation is to not use corticosteroids unless they have an indication separate from SARS-CoV-2 infection,” said Deresinski. ▲

**References are available at ContagionLive.com.**
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GS-9722 Proves Generally Safe, Well Tolerated in 2 Studies

BY MICHAELA FLEMING

Results of 2 studies favor continued evaluation of GS-9722, which Gilead Sciences is developing for use in an HIV cure regimen. The broadly neutralizing antibody (bNAb) is effector enhanced and targets a V3-glycan motif of the HIV envelope protein.

The agent is derived from the bNAb PGT121, which previously demonstrated success in vitro in immune cell–mediated killing of HIV-infected cells and has shown efficacy in monkeys infected with simian HIV.

In a virtual oral abstract presentation at the Conference on Retroviruses and Opportunistic Infections (CROI 2020), investigators discussed data on safety, tolerability, and efficacy from randomized, blinded, placebo-controlled, staggered dose-escalation studies featuring GS-9722. The investigators conducted 2 studies on intravenously administered GS-9722, 1 in HIV-negative and 1 in virally suppressed individuals with HIV.

In the first study, HIV-negative participants were assigned to receive a single dose (150, 500, or 1500 mg) or multiple doses (150, 500, or 1000 mg every other week for 3 doses) or placebo. For the second study, virally suppressed individuals living with HIV received either a single dose or multiple doses (every other week for 5 doses) of GS-9722 150 or 500 mg. The authors noted that they are assessing safety and pharmacokinetics (PK) throughout this ongoing study.

According to the investigators, in studies 1 and 2, 45 of 49, and 32 of 32 participants completed treatment, respectively.

“Dose-proportional increases in GS-9722 AUC [area under the curve] and Cmax [maximum concentration] were observed,” the investigators wrote regarding study 1. “GS-9722 t1/2 [half-life] was ~26 days, supportive of at least [every-other-week] dosing.”

The study team indicated that based on preliminary PK data, single-dose GS-9722 data are similar in the virally suppressed population and HIV-negative participants.

Overall, most adverse events (AEs) were considered grade 1 or 2. However in study 1, 2 participants who received multiple doses of 1000 mg discontinued the study drug because of drug-related AEs. One individual had thrombocytopenia, considered a grade 3 serious AE, and the other had a grade 2 AE of infusion-related reaction.

In study 2, 1 individual who received a 150-mg single dose had an unrelated grade 2 serious AE of small intestinal obstruction. Thus far, the investigators have reported no other serious AEs or AEs related to study drug discontinuation.

“These studies demonstrate that GS-9722 is generally safe and well tolerated in HIV-negative participants and VS-PWH [virally suppressed people living with HIV], with similar single-dose PK in the 2 populations,” the investigators wrote. The team concluded that based on these data, GS-9722 should continue to be evaluated as part of a combination therapy for HIV cure.

The abstract, “Safety & Pharmacokinetics of GS-9722 in HIV-Negative Participants and People With HIV,” was presented on March 9, 2020, in a virtual session at CROI 2020.

Reference is available at ContagionLive.com.

LONG-ACTING CABOTEGRAVIR/RILPIVIRINE GIVEN EVERY 2 MONTHS WORKS AS WELL AS MONTHLY DOSING

BY ALEXANDRA WARD, MA

At last year’s Annual Conference on Retroviruses and Opportunistic Infections (CROI), investigators presented 48-week results of the ATLAS study showing that a regimen of monthly injectable cabotegravir/rilpivirine was noninferior to continued 3-drug oral antiretroviral (ART) therapy in adults with virologically suppressed HIV-1 infections (NCT02951052). More recently, at the virtual CROI 2020, an international team of investigators shared 48-week results from ATLAS-2M, which tested every-other-month dosing of the intramuscular injection compared with monthly dosing (NCT03299049).

E. Turner Overton, MD, associate professor in the Division of Infectious Diseases at The University of Alabama at Birmingham and presenting author of the ATLAS-2M study, explained why long-acting treatment options are so important for individuals living with HIV. “Despite effective oral HIV therapy, we still face challenges achieving viral suppression in some individuals and maintaining durable viral suppression in others,” he told Contagion®.

“There are numerous reasons for these issues, from socioeconomic factors, logistical issues, chaotic factors, drug-drug interactions, pill fatigue and pill burden, and the stigma related to both HIV and HIV therapies.”

The multicenter, open-label, phase 3b noninferiority study evaluated the efficacy and tolerability of every-other-month dosing of 6000-mg cabotegravir (CAB) plus 900-mg rilpivirine (RPV) long-acting maintenance therapy compared with monthly dosing of 400-mg CAB plus 600-mg RPV in treatment-experienced adults living with HIV-1 infection.

The primary end point at 48 weeks was the proportion with plasma HIV-1 RNA at least 50 copies/mL with a noninferiority margin of 4%, with a key secondary end point of the proportion with HIV-1 RNA less than 50 copies/mL with a noninferiority margin of ~10%.

A total of 1045 participants were randomized 1:1 to receive long-acting CAB plus RPV either every other month (n = 522) or monthly (n = 523). The median age of participants was 42 years (range, 19-83), 27% were women, and 73% were white. A total of 63% of individuals were naive to long-acting CAB plus RPV, and 37% transitioned from monthly long-acting CAB plus RPV in ATLAS.

Investigators found that every-other-month dosing was noninferior to monthly dosing at the 48-week mark for both of the key virologic outcomes, viral suppression (94.3% vs 93.5%) and viral load at least 50 copies/mL (1.7% vs 1.0%).

The safety profiles of both dosing regimens were similar, with just mild or moderate injection site reactions reported. Two percent of patients withdrew because of an adverse event. Of the ATLAS-2M participants who were treated every other month and received at least 48 weeks of monthly treatment in ATLAS, 93% (115 of 124) reported a preference for every-other-month dosing.

The ATLAS-2M results support the therapeutic potential of every-other-month long-acting CAB plus RPV, the investigators concluded. “Having more options for HIV treatment is wonderful,” Turner told Contagion®. “This study demonstrates that [every-other-month intramuscular] therapy can be highly effective for virologic suppression. As we add more options for virologic suppression for our patients, we can achieve the goals of 95-95-95 or even better.”


Reference is available at ContagionLive.com.
Comparing Sensitivities: RT-PCR Versus Rapid Influenza Diagnostic Test

BY GRANT M. GALLAGHER

Compared with reverse transcription polymerase chain reaction (RT-PCR) tests, rapid influenza diagnostic tests (RIDTs) detecting viral antigens have only a low to moderate degree of sensitivity. The type of respiratory specimen, sampling environmental factors, and the time from symptom onset are all known to affect their sensitivity.

A team of investigators from the University of Helsinki and HUS Helsinki University Hospital in Finland assessed whether prior influenza vaccine administration also plays a role in rapid influenza diagnostic test sensitivity. The investigators were slated to present the research at the 2020 European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), but ECCMID’s in-person and virtual components were canceled because of coronavirus disease 2019 (COVID-19). The congress organizers, however, released a book of abstracts that were accepted for the conference.

In the 2018–2019 influenza season, a prospective test-negative design influenza vaccine effectiveness study was conducted at HUS Jorvi Hospital. Adult inpatients who fulfilled severe acute respiratory infection criteria were recruited. Investigators swabbed participants for influenza and tested respiratory samples first via RIDT and then confirmed negative results by RT-PCR.

Of the 69 severe acute respiratory infection cases that were tested for influenza with both RIDT and RT-PCR, 21 (30.4%) tested positive, 46 (66.7%) tested negative, and 2 (2.9%) were ambiguous with RIDT. The sensitivity of the RIDTs in detecting influenza was ultimately only 31.3%.

Prior influenza vaccination during the ongoing influenza season appeared to be associated with decreased sensitivity for the antigen test (odds ratio, 0.374; 95% CI, 0.124-1.068; P = .066). Among those vaccinated more than 14 days before sampling, 28 (77.8%) had false-negative RIDT results compared with 17 (56.7%) of those not vaccinated.

Patient age, genetic clade, and influenza A subtype did not have significant associations with the sensitivity of the RIDT. The team’s data suggest an association between influenza vaccination within a given season and decreased sensitivity of RIDT.

False-negative RIDT results may lead to undertreatment of influenza and thus to insufficient application of infection control and antiviral treatments. The issue could also lead to unnecessary antibiotic use. The research suggests that caution is needed when interpreting negative RIDT results.

The abstract, “Decreased Sensitivity of Rapid Influenza Diagnostic Test Among Vaccinated Adults in Influenza Season 2018-19,” was released on May 5, 2020, as part of the ECCMID Abstract Book 2020.

Reference is available at ContagionLive.com.

Study Finds Variability in Cefiderocol Pharmacokinetics

BY CONTAGION® EDITORIAL STAFF

Cefiderocol was one of the most notable FDA-approved drugs of 2019. The agency approved the agent, a novel cephalosporine that shows efficacy against various gram-negative bacteria, for the treatment of complicated urinary tract infections.

Pharmacokinetic characteristics of cefiderocol in patients are not fully understood. French investigators were scheduled to present at the 2020 European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) new research they conducted to explore the pharmacokinetics of cefiderocol after multiple administrations in patients hospitalized in intensive care unit. ECCMID’s in-person and virtual components were canceled because of coronavirus disease 2019 (COVID-19), but the congress organizers released a book of abstracts that were accepted for the conference.

The study included patients treated with 3-hour intravenous infusions of cefiderocol in the intensive care unit. Nine blood samples were drawn from each patient over the course of the infusion.

Investigators determined cefiderocol plasma concentration by an ultra-performance liquid chromatography system coupled with mass tandem spectrometry, developed and validated in the team’s laboratory.

Seven patients were included in the study. They were treated for Pseudomonas aeruginosa, Achromobacter xylooxidans, Klebsiella pneumoniae, or Acinetobacter baumannii infection susceptible to only cefiderocol.

Ventilator-associated pneumonia was the type of infection in 6 of 7 patients. The median age of patients was 53 years (range, 23-73). Four patients were women, and 3 were men.

“Our results suggest that there is significant [interindividual] pharmacokinetic variability in this patient population; this [argues] to consider cefiderocol a candidate for therapeutic drug monitoring,” abstract authors wrote. This is the first prospective pharmacokinetic study of cefiderocol in patients in an intensive care unit.

The abstract, “Pharmacokinetics Study of Cefiderocol in Intensive Care Unit Patients,” was released May 5, 2020, as part of the ECCMID Abstract Book 2020.

Reference is available at ContagionLive.com.
COVID-19 Complicates an Already Difficult Presentation of Infective Endocarditis

Final Diagnosis: Infective Endocarditis Due to Granulicatella adiacens and Streptococcus mitis

BY TONI CAMPANELLA, PHARMD

Granulicatella adiacens is a type of nutritionally variant streptococci (NVS) first described in 1961. NVS are gram-positive cocci that form satellite colonies and require a medium with pyridoxine and cysteine for growth. They are classified into 2 genera, Abiotrophia and Granulicatella, comprising 4 species: Abiotrophia defectiva, G adiacens, Granulicatella elegans, and Granulicatella balaenopterarum. These bacteria are part of the normal oropharyngeal, gastrointestinal, and urogenital flora. NVS are an important cause of bacteremia and infective endocarditis (IE). NVS are responsible for about 5% of cases IE caused by streptococci. Few case reports are described in the literature. This article describes a case of IE due to G adiacens and Streptococcus mitis.

THE CASE

A 49-year-old woman presented to the hospital from her hemodialysis appointment with a fever and a cough. Three days prior, she had begun feeling symptoms of myalgias, fatigue, and worsening cough, causing her to miss her initial hemodialysis appointment. Upon presentation to the following hemodialysis appointment, the patient was febrile to 101 °F and complained of a productive cough, prompting admission.

The patient had a medical history of end-stage renal disease on hemodialysis, type 2 diabetes mellitus, posterior uveitis, peripheral artery disease status post below-knee amputation, pulmonary embolism 10 years prior, cerebrovascular accident, and epilepsy. She has been receiving hemodialysis for 6 years via an arteriovenous graft. The patient had documented allergies to penicillin and amoxicillin, with multiple skin abscesses noted as a reaction with amoxicillin use. She also had a listed ciprofloxacin allergy with an unknown reaction.

At presentation, the patient was taking aspirin, calcium acetate, lanthanum, cyanocobalamin, folic acid, insulin glargine, lamotrigine, levetiracetam, omeprazole, and tamsulosin. Additionally, the patient took difluprednate and neomycin-polymyxin-hydrocortisone eye drops.

CLINICAL COURSE

On the patient’s initial presentation, the physical exam was unremarkable and vital signs were within normal limits. However, the patient was intermittently febrile throughout the first 3 days of her admission, with a maximum temperature of 103.2 °F on day 2. Initial laboratory data revealed an elevated C-reactive protein level of 3.4 mg/dL, a decreased absolute lymphocyte count of 0.9 × 10^9 cells/L, an elevated IL-6 level of 47.83 pg/mL, an elevated D-dimer level of 0.774 ug/mL, and an elevated ferritin level of 848 ng/mL. Initial blood cultures were obtained and ultimately resulted in no growth. A CT scan of the thorax revealed scattered nodular and patchy ground-glass opacities within the right upper and left upper lobes. Given the current pandemic and the patient’s clinical presentation, the patient was tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the nasopharyngeal polymerase chain reaction assay was positive.

On day 3, the patient received a diagnosis of cytokine storm, most likely the result of her current SARS-CoV-2 infection. Her C-reactive protein level increased to 15.5 mg/dL, a decreased absolute lymphocyte count of 0.9 × 10^9 cells/L, an elevated IL-6 level of 47.83 pg/mL, an elevated D-dimer level of 0.774 ug/mL, and an elevated ferritin level of 848 ng/mL. Initial blood cultures were obtained and ultimately resulted in no growth. A CT scan of the thorax revealed scattered nodular and patchy ground-glass opacities within the right upper and left upper lobes. Given the current pandemic and the patient’s clinical presentation, the patient was tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the nasopharyngeal polymerase chain reaction assay was positive.

On day 3, the patient received a diagnosis of cytokine storm, most likely the result of her current SARS-CoV-2 infection. Her C-reactive protein level increased to 15.5 mg/dL, and her ferritin level to 1945 ng/mL. The patient was given tocilizumab on day 3 and intravenous immunoglobulin on days 5 to 7. Her IL-6 level on day 5 was 4829.01 pg/mL. On day 6, the patient required intubation because of increasing oxygen requirements.
Two sets of blood cultures were obtained on day 8 because of no improvement in inflammatory markers and a low threshold for suspicion of infection, as the patient had received immunomodulatory therapy. She was started empirically on cefepime and vancomycin. One set of blood cultures grew *G adiacens*, and the second set grew *S mitis*. The patient was started empirically on cefepime and gentamicin, and a transthoracic echocardiogram (TTE) was obtained. Ceftaroline was selected because of the variable data of *G adiacens* susceptibility to other β-lactams, such as penicillin and ceftriaxone. Additionally, there were challenges with appropriately administering vancomycin. The TTE revealed a small, mobile mass on the mitral valve, confirming a diagnosis of infective endocarditis.

The *G adiacens* was susceptible to penicillin, meropenem, vancomycin, and levofloxacin, and the *S mitis* was susceptible to penicillin G, ceftriaxone, cefepime, and vancomycin. Upon receipt of susceptibilities, the patient was switched from ceftaroline back to vancomycin for ease of dosing with hemodialysis. Concerns also existed regarding alternative antimicrobial therapy options because of documented allergies. Gentamicin was continued. Subsequent blood cultures were negative. The patient’s central venous catheter and arterial lines, which had been placed on day 6, were removed on day 19.

As of this writing, the patient is clinically improving. She has continued to be afebrile, and her white blood cell count is within normal limits at 6.1 × 10⁹ cells/L. Her oxygen requirements have significantly decreased, as she was extubated on day 15 and is on 3 L of oxygen via nasal cannula, saturating at 100%. The patient is anticipated to receive a total of 4 weeks of antimicrobial therapy with vancomycin and gentamicin with hemodialysis sessions. The gentamicin is to be discontinued upon discharge.

**DISCUSSION**

Endocarditis due to NVS typically follows a slow and indolent course, which is concerning for significant destruction of the heart valves.⁶ This destruction is thought to be due to the cha gene present in *A defectiva* and *G adiacens*, which produces a protein that binds to fibronectin of the host cell.¹¹ This relationship with fibronectin-binding capacity is an important step in the pathogenesis of IE.

Current guidelines recommend that IE caused by *Granulicatella* species should be treated with penicillin or ampicillin in combination with gentamicin for 4 to 6 weeks, similar to treatment for IE due to enterococci.¹²,¹³ In patients with penicillin or ceftriaxone allergies, vancomycin is recommended without gentamicin. Previous literature suggests variable susceptibility of NVS, with 30% to 70% of *G adiacens* isolates susceptible to penicillin, 40% to 80% susceptible to ceftriaxone, and 100% susceptible to vancomycin.²,¹⁴,¹⁵ Half of the *G adiacens* isolates that were resistant to ceftriaxone were susceptible to ceftaroline, and the minimum inhibitory concentration (MIC₉₀) was lower for ceftaroline than for ceftriaxone and cefotaxime.² Despite effective antimicrobial therapy, NVS is associated with a 17% mortality rate, a 17% relapse rate, a 30% embolization rate, and a 41% bacteriologic failure rate.⁵,¹⁶

This case is unique given the patient’s initial presentation, administration of immunomodulatory therapy, and documented allergies. It is also an example of how other infections may occur concomitantly in patients with coronavirus disease 2019 and serves as a reminder to remain suspicious for them. IE due to NVS is hard to treat. Identifying these pathogens can be difficult because of their fastidious nature, which may delay treatment and lead to further complications such as valvular destruction. ▲

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