Despite advances in culture and molecular diagnostic methods and availability of transesophageal echocardiography at most centers, diagnosis of infective endocarditis (IE) remains challenging. Complications and mortality associated with IE have (continued on page 16)

HIV/AIDS
Impact of SARS-CoV-2 Infection and the COVID-19 Pandemic
By Eric A. Meyerowitz, MD

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there has been enormous interest in understanding the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on people with HIV (PWH). Given the higher risk of severe outcomes from other respiratory infections such as influenza and (continued on page 20)

Stewardship & Prevention
N95 Respirator Decontamination Strategies
By Christina Yen, MD; Ahmed Abdul Azim, MD; and Preeti Mehrotra, MD, MPH

Personal protective equipment (PPE) remains in short supply across the United States during the coronavirus disease 2019 (COVID-19) pandemic. The N95 respirator has emerged as a critical piece of PPE to protect health care workers during aerosol-generating procedures. What (continued on page 24)

MULTIDRUG-RESISTANT INFECTIONS
Bacterial Coinfections in US Patients With Coronavirus Disease 2019
By Deanna J. Buehrle, PharmD

Nearly half of hospitalized patients in the United States receive antibiotics during their stay, but 20% to 30% of those antibiotic days of therapy (DOT) have been found to be inappropriate. Moreover, 20% of patients who receive an antibiotic experience an adverse drug event. The main objectives of antimicrobial stewardship programs (ASPs) are to optimize antibiotic use and minimize harm associated with antibiotics. The coronavirus disease 2019 (COVID-19) pandemic has presented new challenges for ASPs to streamline antibiotic therapy. To accomplish this, data on the prevalence of bacterial coinfections and secondary infections and rates of antimicrobial-resistant (AMR) infections in patients with COVID-19 are needed to inform optimal antimicrobial use. (continued on page 22)
In HABP/VABP and cUTI caused by susceptible Gram-negative microorganisms

OUTSMART RESISTANCE

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

Fetroja—the world’s only siderophore cephalosporin—overcomes Gram-negative antibacterial resistance\(^1\)

INDICATIONS

Fetroja® (cefiderocol) is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Enterobacter cloacae complex.

Fetroja is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens.

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.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.

WARNINGS AND PRECAUTIONS

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.

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 through Day 49 (34/101 [33.7%] vs 10/49 [20.4%], treatment difference 13.3%, 95% CI [-2.5, 26.9]). Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as Acinetobacter baumannii complex, Stenotrophomonas maltophilia, and Pseudomonas aeruginosa, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

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

Hypersensitivity Reactions

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

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

Active against pathogens with porin channel deletions and efflux pump up-regulation\(^1,3,4\)

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

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Fetroja has an extensive Gram-negative spectrum that includes hard-to-treat pathogens1

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

*Also included in CUTI indication.

Fetroja is highly active in vitro vs Gram-negative carbapenem-NS pathogens3

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

In vitro activity does not necessarily correlate with clinical efficacy.

### Enterobacteriaceae

<table>
<thead>
<tr>
<th>Species</th>
<th>Overall Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td>Carbapenem-sensitive</td>
<td>97%</td>
</tr>
<tr>
<td>Carbapenem-resistant</td>
<td>90%</td>
</tr>
</tbody>
</table>

### Pseudomonas aeruginosa

<table>
<thead>
<tr>
<th>Overall Success Rate (%)</th>
<th>Carbapenem-sensitive</th>
<th>Carbapenem-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>90%</td>
<td>85%</td>
</tr>
</tbody>
</table>

### A baumannii complex

<table>
<thead>
<tr>
<th>Overall Success Rate (%)</th>
<th>Carbapenem-sensitive</th>
<th>Carbapenem-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>93%</td>
<td>85%</td>
</tr>
</tbody>
</table>

### S maltophilia

<table>
<thead>
<tr>
<th>Overall Success Rate (%)</th>
<th>Carbapenem-sensitive</th>
<th>Carbapenem-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

In a phylogenetic reclassification performed in 2016, the nomenclature of Enterobacteriaceae family and other genera such as Photorhabdus, Providencia spp., Pseudomonas stutzeri, and Serratia spp.

### In vitro susceptibility study design

Clinical isolates of Gram-negative bacteria were collected from 4 global surveillance studies (SIDERO-WTO-2014, SIDERO-WTO-2015, SIDERO-WTO-2016, and SIDERO-WTO-2017) that included Enterobacteriaceae and non-fermenter strains. The global surveillance study (Proteus*) collected clinical isolates from 2013-2014, and were tested centrally (HIMA Inc., Schaumburg, IL, USA). Fetroja MICs were determined by microbroth dilution using inoculated, depletor-crafted Mueller-Hinton broth (ID-CAMHB) as approved by the Clinical and Laboratory Standards Institute (CLSI) subcommittee on antimicrobial susceptibility testing in January 2016. FDA breakpoints were used for Enterobacteriaceae MIC ≤ 4 μg/mL, P aeruginosa MIC ≤ 1 μg/mL, and A baumannii complex MIC ≤ 1 μg/mL, whereas CLSI investigational breakpoint was used for S maltophilia MIC ≤ 4 μg/mL. Carbapenem-non-susceptible strain was defined as meropenem MIC ≥ 2 μg/mL for Enterobacteriaceae strains (including Proteae) and MIC ≥ 2 μg/mL for P aeruginosa and A baumannii complex.

FDA breakpoints used for Enterobacteriaceae MIC ≤ 4 μg/mL, P aeruginosa MIC ≤ 1 μg/mL, and A baumannii complex MIC ≤ 1 μg/mL.

### Clinical trials

Overall, n=1416 patients with a multidrug-resistant Gram-negative infection in the ICU with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were enrolled in the study. An increase in all-cause mortality was observed in patients treated with Fetroja compared with placebo (HABP, VABP, and HCABP) and Acute Physiology And Chronic Health Evaluation II (APACHE II) score (C15 and ≥16) as allocation factors. Linezolid was administered for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant Staphylococcus aureus (MRSA), and to maintain the study blind.

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

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

### Development of Drug-Resistant Bacteria

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

### ADVANCE REACTIONS

The most common adverse reactions occurring in ≥2% of patients receiving Fetroja compared to meropenem in the CUTI trial 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 1%), hypokalemia (2% vs 1%), nausea (2% vs 1%), and vomiting (2% vs 1%). The most common adverse reactions occurring in ≥3% of patients receiving Fetroja compared to meropenem in the HABP/VABP trial were:

- Elevations in liver tests (16% vs 16%), hypokalemia (11% vs 15%), diarrhea (9% vs 9%), hypomagnesemia (5% vs 1%), and atrial fibrillation (5% vs 3%).

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

References:

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FOR MORE INFORMATION, VISIT Fetroja.com
FETROJA (ceftolozane) for injection, for intravenous use

Initial U.S. Approval: 2019

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

1 INDICATIONS AND USAGE

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

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

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Increase in All-Cause Mortality in Patients with Carbapenem-Resistant 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 (NCCTD1754956). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality observed in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with FETROJA than in patients treated with BAT (25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)). All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, patients treated with FETROJA than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)].

5.2 Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed in FETROJA-treated patients in clinical trials [see Adverse Reactions (6.1)]. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.

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

5.3 Clostridioides difficile-associated Diarrhea (CDAD)
Clostridioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including FETROJA. CDAD may range in severity from mild diarrhea to toxic megacolon. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. C. difficile 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.

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 (NCSE), encephalopathy, coma, asterixis, neuro muscular excitability, and myoclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust FETROJA dosing based on creatinine clearance [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 a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Indications and Usage (1)].

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)]
- Clostridioides difficile-associated Diarrhea (CDAD) [see Warnings and Precautions (5.3)]
- Seizures and Other Central Nervous System Adverse Reactions [see Warnings and Precautions (5.5)]

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

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

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FETROJAa (N = 300)</th>
<th>Imipenem/Cilastatina (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4% (12)</td>
<td>5% (7)</td>
</tr>
<tr>
<td>Infusion site reactionsb</td>
<td>4% (5)</td>
<td>5% (7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3% (9)</td>
<td>4% (6)</td>
</tr>
<tr>
<td>Rashc</td>
<td>3% (9)</td>
<td>&lt; 1% (0)</td>
</tr>
<tr>
<td>Candidiasisc</td>
<td>3% (9)</td>
<td>3% (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>2% (6)</td>
<td>&lt; 1% (0)</td>
</tr>
<tr>
<td>Elevations in liver testsd</td>
<td>2% (4)</td>
<td>&lt; 1% (0)</td>
</tr>
<tr>
<td>Headachec</td>
<td>2% (6)</td>
<td>5% (8)</td>
</tr>
<tr>
<td>Hyperkalemiae</td>
<td>2% (6)</td>
<td>3% (5)</td>
</tr>
</tbody>
</table>

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

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

1 cUTI = complicated urinary tract infection.
2 2 grams IV every 1 hour every 8 hours (with dosage adjustment based on renal function).
3 1 gram IV every 1 hour every 8 hours (with dosage adjustment based on renal function and body weight).
4 Infusion site reactions include infusion site erythema, inflammation, pain, pruritus, injection site pain, and phlebitis.
5 Rash includes rash macular, rash maculopapular, erythema, skin irritation.
6 Candidiasis includes oral and vulvar-genital candidiasis.
7 Elevations in liver tests include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, blood alkaline phosphatase, hepatic enzyme increased.
8 Hypokalemia includes blood potassium decreased.

Other Adverse Reactions of FETROJA in the cUTI Patients (Trial 1)
The following selected adverse reactions were reported in FETROJA-treated cUTI patients at a rate of less than 2% in Trial 1:

- Blood and lymphatic disorders: thrombocytopenia
- Cardiac disorders: congestive heart failure, Bradycardia, atrial fibrillation
- Gastrointestinal disorders: abdominal pain, dry mouth, stomatitis
- General system disorders: pyrexia, peripheral edema
- Hepatobiliary disorders: cholestasis, cholecystitis, gallbladder pain
- Immune system disorders: drug hypersensitivity
- Infections and infestations: C. difficile infection
- Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), red blood cells urine positive, creatinine phosphokinase 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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FETROJAa (N = 148)</th>
<th>Meropenemb (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevations in liver tests2</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Hypokalemiaa</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypomagnesaemiaa</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
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<td>3%</td>
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</tbody>
</table>

3 HABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.
4 2 grams IV over 1 hour every 6 hours (with dosage adjustment based on renal function).
5 2 grams IV over 1 hour every 6 hours (with dosage adjustment based on renal function).
6 Elevations in liver tests include alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased.
7 Hypokalemia includes blood potassium decreased.

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

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

7 DRUG INTERACTIONS

7.1 Drug/Laboratory Test Interactions
Cefiderocol may result in false-positive results in dipstick tests (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 have not identified an association with cephalosporin use during pregnancy and major birth defects, miscarriage, or 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 1000 mg/kg/day or mice at subcutaneous doses of up to 2000 mg/kg/day given during the period of organogenesis (gestation days 6-17 in rats and 6-15 in mice). No treatment-related malformations or reductions in fetal viability were observed. Mean plasma exposure (AUC) at these doses was approximately 0.9 times (rats) and 1.3 times (mice) the daily mean plasma exposure in patients that received 2 grams of cefiderocol infused intravenously every 8 hours.

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

8.5 Geriatric Use
cUTI
Of the 300 patients treated with FETROJA in the cUTI trial, 158 (52.7%) were 65 years of age and older, and 87 (22.3%) were 75 years of age and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

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

Clinical cure rates at the Test-of-Cure visit (TOC) in FETROJA-treated adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age and 75 years of age and older were 60%, 77.5%, and 60%, respectively. In comparison, the clinical cure rates at the TOC visit in the meropenem-treated patients for each of these subgroups were 65.5%, 64.4%, and 70.5%, respectively. The observed all-cause mortality rates at Day 14 in the FETROJA-treated patients for each of these subgroups were 12.3%, 7.5%, and 17.5%, respectively. In comparison, in the meropenem-treated patients for each of these subgroups, they were 10.3%, 17.8%, and 9.1%, respectively.

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

8.6 Renal Impairment
Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD
No dosage adjustment of FETROJA is recommended in patients with CLcr less than 60 mL/min, who are receiving HD. In patients requiring HD, complete HD at the latest possible time before the start of cefiderocol dosing [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]. Monitor renal function regularly and adjust the dosage of FETROJA accordingly as renal function may change during the course of therapy.

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

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

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

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

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Bacterial Coinfections in US Patients With Coronavirus Disease 2019

A discussion on the implications for antimicrobial use and antimicrobial resistance.

BY DEANNA J. BUEHRLE, PHARMD
PHARMACEUTICAL INNOVATION IS SAVING THE WORLD

NINE MONTHS.

In March 2020, the United States was in the early stages of the coronavirus disease 2019 (COVID-19) pandemic. The entire country was shut down, and the economy grinded to a halt, to slow the spread of the virus.

In just nine months, the US Food and Drug Administration (FDA) authorized a pair of COVID-19 vaccines: BNT162b2, from Pfizer and BioNTech, and mRNA-1273, from Moderna.

By New Year’s Day, millions of Americans had received the vaccine, including frontline physicians and health care providers and nursing home patients, our most vulnerable citizens.

Nine months. Take a moment to let that sink in.

A narrative crafted around the COVID-19 pandemic has depicted a situation that is completely negative. Mainstream media has described the US response to the pandemic as nothing more than a series of blunders, from one mistake to the next.

There is another way to tell the story of the past 9 months. It is a story of heroism, innovation, and precise science, performed under unbelievable pressure.

Let’s not mince words: The US and the world must appreciate the role of the pharmaceutical industry—the investigators, physicians and business leaders—who are rescuing the world from COVID-19. It’s the medical breakthrough of our lifetime.

The next step of the process—distribution of the vaccine—will be as challenging as the development phase, if not more so. But we are again witnessing the pharmaceutical industry rising to the occasion. Factories worldwide are working overtime to produce hundreds of millions of vaccine doses.

Every day, more people will be vaccinated. After health care workers and our most vulnerable citizens, other frontline workers will be next. Teachers will be vaccinated so our children can return to school. And soon, all Americans will be able to receive the vaccine at their doctor’s office or a pharmacy.

With the help, dedication, and expertise of pharmaceutical industry heroes, the unprecedented was accomplished in 9 months. Next time you turn on the TV and see negativity, turn it off and imagine instead where we will be in nine months.

Mike Hennessy Sr
Chairman and founder

COVID-19: Grading the Year in Review

WE HAVE CROSSED the 1-year mark from when the US had its first case of coronavirus 2019 (COVID-19). In my first column addressing the pandemic, I wrote that we needed to evaluate our response as it progressed. Now seems as if like an opportunity to assign grades to our response.

Messaging: Poor messages abound at the beginning. Statements came from officials about the relative lack of importance of COVID-19. The need to preserve masks for health care professionals led to confusing messages against masks for the public, before changing to recommending cloth masks. The willingness to correct this misstep when science dictated is commendable, but some damage already had been done. Grade: F

Testing: The US failed early into testing for severe acute respiratory coronavirus 2 (SARS-CoV-2) when a CDC-developed test was found to be error-prone. Testing capacity expanded over the course of the pandemic but in some places has still not attained feasible systems. Antigen assays that could be used in schools and other in-person group settings have not been prioritized, and a national testing strategy is only starting to materialize. Grade: F

Therapeutics: Examinations of the repurposing of older drugs were worthy efforts when conducted rigorously. The early positive results with remdesivir were tempered after SOLIDARITY findings, though shorter durations of illness are still important outcomes. RECOVERY identified dexamethasone as our first lifesaving therapy for COVID-19 patients. IL-6 inhibitors and convalescent plasma have been studied with equivocal overall results, though they may have roles in the right patients.

Monoclonal antibodies have shown promise. The fact that these therapies were derived from patients who recovered from COVID-19 to being synthesized and given to patients with COVID-19 in under a year is impressive.

An effective, oral medication to prevent progression of mild to moderate cases in outpatients is still needed. Grade: B-

Vaccines: First and foremost, the availability of multiple vaccines in about a year from the discovery of a new pathogen is a truly amazing feat. No matter what else becomes of COVID-19, this point needs emphasis. We are very fortunate that these vaccine platforms had already been developed prior to the emergence of SARS-CoV-2 and that the sequence of the virus was shared early. The acceleration of vaccine development has also been an enormous success and, after initially harboring concerns about political interference, I feel FDA’s review process has remained sound and trustworthy. It remains to be seen how guaranteed federal purchases have benefited dose availability.

Vaccination plans have been disappointing. Some organizations and governments have had detailed plans created well in advance of vaccine availability, whereas others seem to have wasted that planning time. Vaccinators are still being recruited and have not yet been maximized, though recent signals from the new administration are promising. Grade: B

Finally, thank you for all that you have done over the past year. The efforts of health care practitioners in the face of personal danger, limited support, shortages, and exhausting schedules have been remarkable. Grade: A+

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

Active member of the Society of Infectious Diseases Pharmacists (SIDP)
Oral Step-Down Therapy for Uncomplicated Streptococcal Bloodstream Infections: β-Lactams or Fluoroquinolones?

BY YU TING HE, MD; AND ANDREW J. HALE, MD

Bacterial bloodstream infection (BSI) remains a common source of morbidity and mortality in the United States, accounting for approximately 500,000 to 600,000 cases and 70,000 to 80,000 deaths per year. Streptococci rank in the top 10 bacterial pathogens causing BSI, and the ideal treatment for streptococcal BSI remains an important clinical question.

Traditionally, BSIs are treated with parenteral (intravenous [IV]) antibiotics to achieve the fastest and most reliable therapeutic levels. For decades, the natural clinical course of uncomplicated BSI has generally started with empiric antimicrobial treatment until the pathogen is identified, with the targeted narrowing of antimicrobials. This is followed by a prolonged hospital stay or outpatient parenteral antibiotic therapy course with medications typically administered via a peripherally inserted central catheter. However, this treatment modality is accompanied by an increased risk of nosocomial infections, procedural complications, and thrombosis, and a higher cost of care. Therefore, there has been a recent trend toward exploring oral antibiotics after the patient has reached a clinically stable state, so-called oral step-down therapy.

A growing body of literature supports this approach in appropriate patients. An 8-year multicenter cohort study in Taiwan showed no significant difference in 30-day clinical failure rates between a short IV course with switch to oral antibiotics compared with IV antibiotics alone in noncritically ill patients with community-onset, uncomplicated BSI. Data from the POET trial (NCT01375257) suggested that patients with stabilized infective endocarditis fared no worse with oral-step down therapy than patients who completed a full parenteral course.

A few studies have assessed oral step-down therapy specifically in streptococcal BSI, though mostly in the context of bacteremic pneumococcal pneumonia. In one study, the authors found no significant difference in clinical failures between nonstaphylococcal gram-positive BSI (of which 75% were streptococcal) in patients treated with oral step-down therapy with low versus high bioavailability oral antibiotics; however, this study was also underpowered. Although it is premature to say that all BSIs should be treated with oral step-down therapy, increasing literature supports its use. But more research is needed to elucidate when clinicians should offer the therapy.

Arensman et al have helped clarify what to do in treating patients with streptococcal BSI. They conducted a retrospective, multicenter cohort study between January 2014 and June 2019 assessing outcome differences between patients who received oral step-down therapy with either a fluoroquinolone (FQ) or β-lactam (βL) antibiotic. The primary outcome was clinical success, defined as lack of all-cause mortality, recurrent BSI, or infection-related readmission within 90 days. Secondary outcomes included incidence of 90-day Clostridioides difficile infection or an antibiotic-related adverse effect within 30 days.

The investigators conducted the study at 7 sites in Chicago, Illinois. Eligible patients were 18 years or older and had at least 1 blood culture positive for Strep-tococcus species during the study period, with completion of treatment with oral step-down to an FQ or βL antibiotic. Exclusion criteria included polymicrobial blood cultures, BSI complicated by endocarditis or central nervous system infection, or transition to hospice before completion of BSI therapy.

Two hundred twenty patients of similar demographics participated in the study, with 87 (40%) receiving an FQ and 133 (60%) a βL for step-down therapy. The most common Strep-tococcus species was Strep-tococcus pneumoniae (34.1%) followed by Strep-tococcus pyogenes (17.3%) and Strep-tococcus agalactiae (16.4%). Patients in the FQ group were most likely to have a respiratory infection (62%), whereas patients in the βL group were most likely to have a skin and soft tissue infection (45%). The most common antibiotic regimens included amoxicillin-clavulanate potassium 875 mg/125 mg every 12 hours (22.3%), moxifloxacin 400 mg every 24 hours (16.4%), and levofloxacin 750 mg every 24 hours (12.7%). The median duration of total antimicrobial treatment was 14 (interquartile range, 13-16) days.

One hundred twenty-two (92.0%) patients of the FQ group and 81 (93.2%) of the βL group achieved the primary outcome, with no statistically significant difference (90% CI, -5.2 to 7.8). There was also no statistically significant difference in the secondary outcomes. In a regression analysis, the authors identified that starting oral step-down therapy earlier than day 3 (odds ratio [OR], 5.18; 95% CI, 1.21-22.16) and low-dose oral antibiotics (OR, 2.74; 95% CI, 0.95-7.90) were factors predicting clinical failure (though the latter was not statistically significant).

This study is among the first adequately powered studies to dive into the relative efficacies of oral step-down therapy of FQs and βLs for streptococcal BSI, showing no significant differences between them. This study gives clinicians treating uncomplicated streptococcal BSI confidence that higher-dose oral βLs are a safe and efficacious option. Further prospective, randomized trials are needed to solidify the role of oral step-down therapy for BSI. Given the risks of complications, cost, and inconvenience of parenteral antibiotic treatment, steps toward a safe transition to oral regimens are welcomed by clinicians and patients alike.

References are available at ContagionLive.com.

Highlighted Study
Getting Help From HAL: Applying Machine Learning to Predict Antibiotic Resistance

BY ZACHARY HITCHCOCK, PHARM D CANDIDATE; AND J. DREW ZIMMER, PHARM D, BCPS

Appropriate empirical antimicrobial therapy is paramount for ensuring the best outcomes for patients. The literature shows that inappropriate antimicrobial therapy for infections caused by resistant pathogens leads to worse outcomes.\(^3\)\(^5\) Additionally, increased use of broad-spectrum antibiotics in patients without resistant pathogens can lead to unintended consequences.\(^3\)\(^5\) As technology advances, it may enable clinicians to better prescribe empiric antimicrobials. Lewin-Epstein et al studied the potential for machine learning to optimize the use of empiric antibiotics in patients who may be harboring resistant bacteria.

As machine learning and artificial intelligence technology improves, investigators are examining new ways to implement it in practice. Lewin-Epstein et al studied the potential for machine learning to predict antibiotic resistance in hospitalized patients.\(^7\) This study specifically targeted the use of empiric antibiotics, attempting to reduce their use in patients who may be harboring resistant bacteria.

The single-center retrospective study was conducted in Israel from May 2013 through December 2015 using electronic medical records of patients who had positive bacterial culture results and resistance profiles for the antibiotics of interest. The investigators studied 5 antibiotics from commonly prescribed antibiotic classes: cefazidime, gentamicin, imipenem, ofloxacin, and sulfamethoxazole-trimethoprim. The data set included 16,198 samples for patients who had positive bacterial culture results and sensitivities for these 5 antibiotics. The most common bacterial species were Escherichia coli, Klebsiella pneumoniae, coagulase-negative Staphylococcus, and Pseudomonas aeruginosa. The investigators also collected patient demographics, comorbidities, hospitalization records, and information on previous inpatient antibiotic use.

Employing a supervised machine learning approach, they created a model comprising 3 submodels to predict antibiotic resistance. The first 85% of data were used to train the model, whereas the remainder were used to test it. During training, the investigators identified the variable with the highest effect on prediction—the rate of previous antibiotic-resistant infections, regardless of whether the bacterial species was included in the analysis. Other important variables included previous hospitalizations, nosocomial infections, previous antibiotic usage, and patient functioning and independence levels. The model was trained in multiple ways to identify which manner of use would be the most accurate. In one analysis, the model was trained and evaluated on each antibiotic individually. In another, it was trained and evaluated on all 5 antibiotics. The model was also evaluated when the bacterial species was included and excluded. The model’s success was defined by the area under the receiver-operating characteristic (auROC) curve and balanced accuracy, which is the unweighted average of the sensitivity and specificity rates.

The ensemble model, which was made up of the 3 submodels, was effective at predicting bacterial resistance, especially when the bacteria causing the infection were identified for the model. When the bacterial species was identified, the auROC score ranged from 0.8 to 0.88 versus 0.73 to 0.79 when the species was not identified. These results are more promising than previous studies on the use of machine learning in identifying resistant infections, despite this study incorporating heterogenous data and multiple antibiotics. Previous studies that only included 1 species or 1 type of infection yielded auROC scores of 0.7 to 0.83. This shows that using the composite result of multiple models may be more successful at predicting antibiotic resistance.

One limitation of this study is that it did not compare the model with providers’ abilities to recognize potentially resistant organisms and adjust therapy accordingly. Although this study did not directly make a comparison, a previous study involving machine learning showed that a similar model performed better than physicians when predicting resistance. The model in this study performed better than the one in the previous study, which suggests that this model may perform better than providers when predicting resistance. Another limitation of this study is that it did not evaluate causal effects of antibiotic resistance. The authors believe that further research should be conducted in this area to evaluate whether machine learning could be employed to determine further causes of antimicrobial resistance. A third limitation is that this study only evaluated the 5 antibiotics included, which are the 5 antibiotics most commonly tested for resistance at that facility. Additional research and machine learning would likely need to be incorporated to apply this model to other antibiotics.

The authors concluded that the model used in this study could be used as a template for other health systems. Because resistance patterns vary by region, this seems to be an appropriate conclusion. A model would have to be trained at each facility that was interested in employing machine learning in antimicrobial stewardship, and additional training would have to occur periodically to keep up with evolving resistance patterns. Additionally, if a facility would like to incorporate this type of model, they might want to also incorporate rapid polymerase chain reaction testing to provide the model with a bacterial species for optimal predictions. Overall, the results of this study indicate that great potential exists for machine learning in antimicrobial stewardship programs.

References are available at ContagionLive.com.

Highlighted Study

Sporadic Pediatric Norovirus Cases May Predict Broader Outbreaks

BY JONNA LORENZ

Seasonal increases in sporadic pediatric cases of norovirus gastroenteritis correlate with norovirus outbreaks among older populations, a study found.

The study, published in the November issue of Clinical Infectious Diseases, analyzed seasonal patterns and genotypic characteristics of norovirus cases between December 2012 and June 2016 in middle Tennessee.

“Sporadic case surveillance and outbreaks followed very similar patterns geographically and temporally,” John R. Dunn, DVM, PhD, deputy state epidemiologist with the Tennessee Department of Health Policy, told Contagion®. “These commonalities in the different surveillance systems indicate that opportunities may exist to slow or prevent outbreaks when sporadic cases start to increase in the community.”

During the study period, 755 pediatric sporadic norovirus cases and 45 outbreaks involving 1924 individuals were reported.

The mean age of sporadic pediatric cases was 2.9 years, 81.3% of cases were among children younger than 5, and 30% reported attending child care facilities.

Among 740 outbreak cases with reported ages, 61.6% were in individuals older than 50 years, and 42% of outbreaks occurred in long-term care facilities. Child care facilities and restaurants each accounted for 8.9% of outbreaks. Person-to-person transmission was reported in 80% of outbreaks, and 8.9% of cases were reported as foodborne transmission.

“Predominant genotypes explained the majority of both surveillance cases and outbreaks,” Dunn said.

Most cases were attributed to GII genogroup noroviruses, including 90.1% of sporadic cases and 83.3% of reported outbreaks, with GII.4 being the most prevalent genotype. It was reported among 39.1% of sporadic cases and 52.8% of outbreaks.

The proportion of cases infected with GII noroviruses was significantly higher in the winter than in the summer.

Seasonality wasn’t reported among cases involving GI noroviruses, which are more strongly associated with foodborne and waterborne transmission.

The study found that most norovirus infections occurred between November and April, including 74.9% of sporadic cases and 86.8% of reported outbreaks.

“During the winter months, providers and clinicians should consider norovirus in patients with acute gastroenteritis and counsel patients regarding preventing transmission in settings where vulnerable populations reside, eg, long-term care facilities,” Dunn said.

The study used Markov modeling to examine whether detecting peaks in norovirus transmission could forecast norovirus outbreaks in the wider community. Results suggested that the 3-day moving average of sporadic cases was positively associated with the probability of an outbreak. However, data for outbreaks were insufficient to draw a statistically significant conclusion.

“Further studies to describe the interrelationship of sporadic norovirus and outbreaks are needed,” Dunn said. “These studies will help elucidate transmission dynamics and potential populations for candidate vaccines.”

Norovirus infections, which are the leading cause of gastroenteritis, caused about 900 deaths, 109,000 hospitalizations, 465,000 emergency department visits, and 2.27 million ambulatory clinic encounters annually from 2001 to 2015, with annual health care costs estimated at $430 million to $750 million, according to a Centers for Disease Control and Prevention study published in 2020.

Several norovirus vaccine candidates are in development, boosted by the discovery of an antibody that inhibits multiple strains of norovirus. The antibody, A1431, is able to neutralize numerous strains of the virus.

Advancements in detection also have supported the fight against the virus. Last year, investigators at the University of Arizona unveiled a smartphone-based device that uses a fluorescent microscope assay to detect norovirus in water. ▲
A majority of public say they would get vaccinated

BY KEITH A. REYNOLDS

Millions of coronavirus disease 2019 (COVID-19) vaccine doses are starting to be distributed across the United States, a survey from the Kaiser Family Foundation (KFF) has found that the general public is becoming more receptive to receiving the shots.

According to the KFF COVID-19 Vaccine Monitor for December 2020, 71% of respondents say they definitely or probably would get a COVID-19 vaccine if it were deemed safe by scientists and available for free and on demand. This is up from 63% of respondents in a September survey and is an increase across racial and ethnic groups, as well as among Democrats and Republicans.

Americans continue to place their trust in their personal doctors, with 85% of respondents saying they trust them at least a fair amount when it comes to information on COVID-19 vaccines, according to a KFF news release.

Other key findings of the survey include:

Even if the vaccine were free and deemed safe by scientists, 27% of the public is still vaccine hesitant. This view is most prevalent among respondents who were Republicans (42%), aged 30 to 49 years (36%), and rural residents (35%).

Respondents who said they definitely or probably will not get vaccinated included 35% of Black adults, who have been particularly hard hit by the pandemic; 33% of essential workers; and 29% of health care workers.

Adverse effects were the top concern of 59% of vaccine-hesitant respondents, and 55% cited a lack of trust in the government to ensure the vaccine is safe and effective. Another concern was that the vaccine is too new (53%). And 51% of respondents didn’t like the role politics played in the vaccine’s development.

A vaccine likely will be widely available for anyone who wants it in the United States by summer 2021, according to 71% of respondents. ▲

To read more, visit https://bit.ly/2LTQTCV.

Model Shows Benefits and Drawbacks of COVID-19 Pool Testing

BY RACHEL LUTZ

Pooled screening may report more false-negative cases of coronavirus disease 2019 (COVID-19) and is less sensitive than single-sample testing, according to a research letter published in JAMA Network Open.

Investigators from Duke University School of Medicine in Durham, North Carolina, conducted a diagnostic study to determine if COVID-19 pool testing was comparable with single-sample testing for different populations. The authors said that as policy makers promote pooled testing as a strategy to increase the number of individuals tested for COVID-19 during the pandemic, considerations such as decreasing the sensitivity of these tests and increasing the complexity of the testing should be considered. Noting all of this, they developed the COVID19 Pool Tool, an online tool using actual COVID-19 virus copy number data to model how pooled testing compared with traditional testing.

The investigators modeled 3 curves based on the United States Food and Drug Administration’s Emergency Use Authorization PCR-qualitative tests. From there, their online model was able to show a defined sample size, pool size, positivity rates, and test characteristics. The model also allowed for the comparison between pooled and single-sample testing using actual virus copy number data pulled from preprocedural screening samples as well as outpatient diagnostic samples, the authors explained.

Using both sets of data mimics symptomatic and asymptomatic patients with COVID-19.

Their tool also generated random virtual pools with positive samples pulled from virus copy number data that mirrored the expected positive rate, the authors explained. The tool used virus copy numbers combined with user-defined test characteristics to predict positive pools and samples that were detected or missed, as well as the sensitivity of pooled and single-sample testing and the number of tests performed.

There were 74 preprocedural screening sample virus copy numbers and 2910 outpatient diagnostic sample virus copy numbers used to simulate COVID-19 cases in the tool.

Pooled testing increased the number of false-negative cases per 1000 cases and decreased the sensitivity of COVID-19 detection, especially for low virus copy number samples and asymptomatic patients, the investigators learned.

“For example, the mean sensitivity of 5-sample pooled testing for detection of asymptomatic patients with a 10% positivity rate in the population was 77.57% (4.40%) vs 92.83% (8.38%) for single-sample testing,” the authors explained.

Additionally, the investigators’ model showed that pooled testing decreased the number of tests needed to screen 1000 patients, but this effect was reduced by repeat testing to identify cases from positive pools for contact tracing, they said, especially at a high prevalence. They also were able to demonstrate that pooled testing identified more positive patients per 1000 tests performed by testing more patients, but repeat testing reduced this benefit.

The study’s authors said that pooled testing is useful for population screening and resource-restricted settings, due to its ability to stretch COVID-19 testing supplies, increase the number of patients tested, and increase the number of cases detected. However, there are drawbacks, including the complicated workflow, lower sensitivity, and need to repeat tests from positive pools.

Using a sequential, 2-stage pooling may be a way to reduce the burden of retesting from positive large pools, the study authors added.

“This tool offers policy makers an easy-to-use tool to inform regional and national decision-making about the pros and cons of pooled testing,” the authors concluded. ▲
Microbiome-Based Therapeutic for *Clostridioides difficile* Demonstrates Extended Efficacy

BY KENNETH BENDER, PHARMD

An investigational, microbiome-based therapeutic against *Clostridioides difficile* was effective in reducing recurrence of infection for at least 3 months after administration, according to study findings reported at the 2020 American College of Gastroenterology (ACG) annual meeting held virtually in October.

"The data presented at ACG show that the very promising efficacy seen with SER-109 at 8 weeks posttreatment is sustained out to 12 weeks post treatment," the study’s lead author, Bret Lashner, MD, director of the Center for Inflammatory Bowel Disease at Cleveland Clinic in Cleveland, Ohio, told *Contagion®*. "They also show SER-109 had similar treatment benefits in both younger and older patients and regardless of antibiotic treatment," Lashner added.

SER-109 is a microbiome-based therapeutic that delivers spores from the species *Firmicutes*. Although derived from the stool of healthy human donors, the manufacturing process yielding fractionated, purified *Firmicutes* bacteria in spore form avoids concerns about undesirable bacterial or viral content, including SARS-CoV-2, in transplanted fecal microbiota. The purified *Firmicutes* spores also are resistant to gastric acid, facilitating an oral formulation.

The investigators screened 281 patients at 75 sites in the United States and Canada who were experiencing 3 or more unformed stools per day for 48 or more hours and who tested positive for *C. difficile* toxin to confirm and distinguish active infection from colonization. After completing a 10- to 21-day course of vancomycin or fidaxomicin, 182 participants were randomized 1:1 to receive either 4 capsules of SER-109 daily for 3 days or matching placebo. The age, antibiotic use, and number of prior episodes were similar in both groups.

"Antibiotics targeted against *C difficile* bacteria are necessary but insufficient to achieve a durable clinical response because they have no effect on *C difficile* spores that germinate within a disrupted microbiome," Lashner and colleagues explained.

The early results at 8 weeks, previously reported in *Contagion®,* had demonstrated a statistically significant difference of 30.2% in the proportion of active treatment patients who had *C difficile* recurrence compared with those on placebo. The current results show that a similar difference in recurrence of infection between those receiving active treatment (16.7%) and placebo (48.7%) was maintained 12 weeks after treatment.

The results correspond to an absolute risk reduction of 31.1% (relative risk, 0.35; 95% CI, 0.21-0.58), which was consistent with results at 8 weeks. The measure of "sustained clinical response" was achieved in 88.9% of patients in the SER-109 group.

Participants were stratified for analysis of treatment response in those younger than 65 years and those 65 years or older, with comparable results found in both age groups. Results also were similar regardless of the baseline antibiotic treatment.

The investigators reported that SER-109 continued to be well-tolerated in the extended study, with a safety profile similar to placebo. There were no serious adverse effects, and the most common treatment-emergent adverse effects were mild to moderate gastrointestinal disturbance.

"Recurrent *C difficile* is a very challenging condition to treat, and we’re glad to see additional confirmatory evidence of SER-109’s safety and efficacy," Lashner said. "By enriching for *Firmicutes* spores, SER-109 achieved high efficacy while mitigating risk of transmitting infectious agents."

"Seres’ [Seres Therapeutics] ongoing open-label study in *C difficile* will ideally provide the necessary safety database to ensure SER-109 licensure," Lashner said. ▲
Review the historical background on tetracycline discovery, emerging resistance, mechanism of action, and their spectrum of activity.

Learn about pharmacokinetic and pharmacodynamic similarities and differences of tetracyclines.

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

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

Watch this iPub® to learn more about the tetracycline-class antibiotics in an era of antimicrobial resistance.
The Clinical and Laboratory Standards Institute (CLSI) Subcommittee on Antimicrobial Susceptibility Testing (AST) held its midyear meeting virtually on several dates in September. In addition to the new and revised breakpoints voted on and approved at the January 2020 meeting, the committee members discussed and approved several more at the midyear meeting.

**NEW BREAKPOINTS**

**Lefamulin for *S aureus*, *S pneumoniae*, and *H influenzae***

Pleuromutilins are a class of antibacterial drugs derived from the naturally occurring antibiotic pleuromutilin that act as inhibitors of bacterial protein synthesis via interactions with the ribosomal peptidyl transferase of target pathogens.1 In 2019, the US Food and Drug Administration (FDA) approved lefamulin, the first pleuromutilin for systemic use with both oral and intravenous administration. It is indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) resulting from infection with the following respiratory pathogens: *Streptococcus pneumoniae*, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.2 The approved dose is 150 mg every 12 hours via intravenous infusion over 60 minutes for 5 to 7 days, and 600 mg orally every 12 hours for 5 days. Clinical and in vitro studies of lefamulin have demonstrated minimal resistance development and little cross-resistance with other antibiotic classes commonly used for CABP, including macrolides, fluoroquinolones, vancomycin, and tetracyclines.

Among the targeted organisms, MSSA, *H influenzae*, and *S pneumoniae* were granted susceptibility breakpoints by the FDA. The drug manufacturer requested CLSI approval of these breakpoints, as well as the susceptibility breakpoint for methicillin-resistant *S aureus* (MRSA). The AST committee reviewed the pharmacokinetic (PK) and pharmacodynamic target attainment analysis and clinical efficacy studies. Data from lung infection studies in neutropenic mice and PK studies in humans presented target attainments above 90% for all proposed organisms.3 They also showed low affinity of lefamulin for both major plasma binding proteins, resulting in rapid tissue distribution.4 Phase 3 trials established the general efficacy and safety of lefamulin in patients with CABP per FDA guidance. Additionally, lefamulin exhibited comparable success rates to moxifloxacin, the standard of care for pathogens consistent with CABP, and efficacy against community-acquired MRSA pneumonia at a 2- to 3-fold lower dose compared with linezolid and vancomycin.3,4

From the data presented, the AST subcommittee approved the FDA-proposed breakpoints and decided that an intermediate susceptibility category was not justified at this time due to the lack of resistant isolates. The manufacturer and AST agreed that resistant isolates should continue to be monitored in the future. Motions were passed to accept the *S aureus* (MSSA and MRSA), *S pneumoniae*, and *H influenzae* minimum inhibitory concentration (MIC) and disk diffusion breakpoints. A final motion was passed for a comment to be added to the lefamulin breakpoints that they should not be reported for cerebrospinal fluid or urinary tract isolates.
REVISED BREAKPOINTS

Azithromycin against Shigella species

Azithromycin is an azalide and part of a subclass of macrolide antibiotics with both bactericidal and bacteriostatic activities. Its mechanism of action is the inhibition of the translocation step of protein synthesis by reversibly binding to the 50S subunit of the 70S ribosome. Azithromycin is used to treat Shigella species (spp) infections, though clinical outcomes are uncertain. In the 30th edition of CLSI’s M100: Performance Standards for Antimicrobial Susceptibility Testing (M100-S30), there is a singular investigational (ie, not FDA approved for use in the United States) azithromycin breakpoint for Enterobacteriales (for Salmonella enterica serovar Typhi only), whereas Shigella sonnei and Shigella flexneri have separate epidemiological cutoff values (ECVs). An increased incidence of non–wild type (NWT) Shigella spp has been noted in clinical isolates, based on the 2015 ECV of 32 µg/mL or more for S sonnei and 16 µg/mL or more for S flexneri, according to the National Antimicrobial Resistance Monitoring System. The Centers for Disease Control and Prevention (CDC) National Center for Emerging and Zoonotic Infectious Diseases proposed to establish a singular unified breakpoint for Shigella spp, as clinical laboratories are not performing susceptibility testing for azithromycin due to the lack of established breakpoints.

Results of several studies have found poor clinical outcomes when Shigella infections, specifically those caused by NWT, were treated with azithromycin. In one such study in Dhaka, Bangladesh, MICs ranged from 4 to greater than 256 µg/mL for S sonnei, 1 to greater than 256 µg/mL for S flexneri, and 1 to 4 µg/mL for other Shigella spp. The results found high rates of azithromycin resistance in the Shigella tested, notably higher in S sonnei, leading to poor clinical outcomes when the patients were treated with azithromycin. According to data from the California Department of Public Health presented at the CLSI midyear meeting, patients whose NWT Shigella spp infections were treated with azithromycin had worse outcomes of longer duration of diarrheal symptoms and increased length of hospital stay compared with patients treated with another appropriate antibiotic.

These data support the need to establish unified breakpoints for azithromycin against Shigella spp, which the CDC proposed. The proposed MIC (susceptible ≤ 8 µg/mL, intermediate 1–16 µg/mL, resistant R ≥ 32 µg/mL) and disk diffusion (S ≥ 16 mm, I = 11-15 mm, R ≥ 10 mm) breakpoints differ slightly from the previously established Enterobacteriales breakpoint from the M100-S30 document (Table). The breakpoints proposal passed as written by the subcommittee. Along with the proposed breakpoints, it was noted that MIC testing is recommended, as the disk diffusion may, in some cases, be too hazy and difficult to measure.

**LINEZOLID SUSCEPTIBILITY AS A SURROGATE TO PREDICT TETIZOLID SUSCEPTIBILITY**

Tedizolid is an oxazolidinone antibiotic that the FDA indicated for the treatment of acute bacterial skin and soft tissue infections of the same tedizolid-susceptible strains in addition to its other indications. AST’s objective was to evaluate the validity of linezolid use as a surrogate for predicting tedizolid susceptibility against FDA-approved species as proposed by EUCAST. Surveillance isolates from the Surveillance of Tedizolid Activity and Resistance Program were tested with broth microdilution (BMD) methodology per CLSI guidelines and then analyzed with scattergram plots for surrogacy. Notably, there was no analysis for predicting the resistance of tedizolid.

The data for each of the 5 organisms presented confirmed that linezolid susceptibility MIC breakpoints predicted the susceptibility of tedizolid for S aureus (n = 21,969), S pyogenes (n = 2035), S agalactiae (n = 1556), S anginosus group (n = 408), and E faecalis (n = 2986). Moreover, no organisms with MIC susceptibility to linezolid but resistance to tedizolid were identified. A motion was thus passed to add footnotes to M100 tables 2C, 2D, 2H-1, and 2H-2, stating that pathogens considered susceptible to linezolid by MIC can also be considered susceptible to tedizolid.

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**TABLE Notable New CLSI Interpretive Criteria and Breakpoints Approved at the CLSI 2020 Midyear Meeting**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Organism</th>
<th>Minimum inhibitory concentration</th>
<th>Disk Diffusion (mm)</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefamulin</td>
<td>Streptococcus pneumoniae</td>
<td>≤ 0.5</td>
<td>N/A</td>
<td>≥ 1</td>
<td>≥ 17</td>
<td>N/A</td>
<td>≤ 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>≤ 0.25</td>
<td>N/A</td>
<td>≥ 0.5</td>
<td>≥ 22</td>
<td>N/A</td>
<td>≤ 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae</td>
<td>≤ 2</td>
<td>N/A</td>
<td>≥ 4</td>
<td>≥ 17</td>
<td>N/A</td>
<td>≤ 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Shigella spp</td>
<td>≤ 8</td>
<td>16</td>
<td>≥ 32</td>
<td>≥ 16</td>
<td>11-15</td>
<td>≤ 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterobacteriales&lt;sup&gt;a&lt;/sup&gt; (Salmonella enterica serovar Typhi only)</td>
<td>≤ 16</td>
<td>N/A</td>
<td>≥ 32</td>
<td>≥ 13</td>
<td>N/A</td>
<td>≤ 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CLSI, Clinical and Laboratory Standards Institute; MIC, minimum; N/A, absence of MIC breakpoint.

<sup>a</sup>Previous breakpoint from the 30th edition (2020) of the CLSI M100 document.
Improving the Diagnosis of Intracardiac Infections

This technology is effective in cases that are difficult to diagnose.

BY NATALIA E. CASTILLO ALMEIDA, MD; ZERELDA ESQUER GARRIGOS, MD; MARYAM MAHMOOD, MB, CHB; AND M. RIZWAN SOHAIL, MD

(continued from cover page)

remained largely unchanged over the past 2 decades. Increasing use of endovascular hardware further limits the sensitivity and specificity of echocardiography, which has been used as the gold-standard imaging modality as part of modified Duke criteria. For this reason, novel imaging modalities have been incorporated into current IE guidelines to improve its diagnosis and associated complications. Over the past decade, 18F-fluorodeoxyglucose (18F-FDG) PET/CT has been shown to improve the diagnostic accuracy in patients with suspected prosthetic valve IE and intracardiac device infection. Moreover, 18F-FDG-PET/CT has several advantages over echocardiography, including detection of embolic infectious complications. Here, we discuss the role of 18F-FDG-PET/CT in establishing the diagnosis of IE and associated complications.

18F-FDG-PET/CT

18F-FDG-PET/CT has shown promise as a complementary imaging modality to echocardiography, primarily in prosthetic valve IE and in detection of extracardiac complications. 18F-FDG-PET/CT performs worse in detecting native valve IE than in detecting prosthetic valve IE; this is likely due to the small size of the vegetation, minimal FDG tracer deposition in the valve’s vegetation, and fewer inflammatory cells and fibrosis in native valves compared with prosthetic valves. A key feature of 18F-FDG-PET/CT in IE evaluation compared with imaging protocols for oncology purposes is patient preparation. Normal myocardium has a great avidity for glucose; therefore, a myocardial suppression diet promotes free fatty acid metabolism and suppresses physiologic glucose metabolism, which is necessary for a 18F-FDG-PET/CT. Current guidelines recommend a low-carbohydrate, high-fat diet for 12 to 24 hours or a fasting period of 12 to 18 hours before imaging with or without the use of intravenous heparin 15 minutes before FDG administration. Patients are also counseled to avoid excessive exertion for 12 to 24 hours before imaging, because increased glucose uptake in the myocardium may lead to higher catecholamine levels, which would lower the quality of the 18F-FDG-PET/CT images. Imaging is typically performed 60 minutes following FDG administration. As proposed by Leccisotti et al, following the results of a case series of 27 patients with IE in the transvenous lead of their cardiac implantable electronic device (CIED), another series of delayed images may help to further optimize the visualization of small foci of infection. Image reconstruction with and without attenuation correction is also recommended to enhance image quality and FDG uptake quantification.

However, an overestimation of FDG avidity is possible, leading to higher rates of false-positive results primarily around prosthetic valves and CIEDs. False-negative findings secondary to elevated blood glucose concentration, prior administration of antimicrobial therapy, and small vegetation size may occur.

THE ROLE OF 18F-FDG-PET/CT IN PROSTHETIC VALVE IE

Both the pretest probability of IE and type of prosthetic cardiac material should be taken into account when evaluating patients with suspected IE (Table). In patients with a high level of clinical suspicion for IE, who have a prosthetic valve, and who meet criteria for “possible” or “rejected” IE by modified Duke criteria, an 18F-FDG-PET/CT can be considered because the pooled sensitivity and specificity is high (80.5% and 79%, respectively). Contrary to previous hypotheses, early 18F-FDG-PET/CT changes are not associated with postoperative reactive inflammation following prosthetic valve implantation within the first 3 months. During the first year after surgery, “normal” or “negative for infection” is defined as the absence of FDG distribution or a diffuse/homogeneous FDG uptake and a standardized FDG intensity, including a maximum standardized uptake value (SUV_max) ≤5.96/6.46, blood pool SUV_max ≤3.19/3.66, and a valve uptake index ≤0.45/0.41. Similar findings were reported in a study that imaged only aortic prosthetic valves. Based on these observations, 18F-FDG-PET/CT is a reasonable option for assessment of early prosthetic valve IE using quantitative measures.

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**TABLE.** 18F-fluorodeoxyglucose PET/CT for the Evaluation of Intracardiac Infections

<table>
<thead>
<tr>
<th>TYPE OF INTRACARDIAC MATERIAL</th>
<th>INDICATION</th>
<th>BENEFITS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valve</td>
<td>Possible or rejected IE by modified Duke criteria</td>
<td>High sensitivity and specificity; can be used within the first year of prosthesis implantation</td>
<td>Early imaging changes could be associated with postoperative reactive inflammation</td>
</tr>
<tr>
<td>TAVI</td>
<td>Possible TAVI-IE</td>
<td>Can reclassify to definite or rejected TAVI-IE</td>
<td>False-positive results due to artifacts around the TAVI prosthesis</td>
</tr>
<tr>
<td>CIED</td>
<td>Suspected CIED-IE, positive blood cultures, and negative echocardiography; S. aureus bacteremia</td>
<td>High sensitivity and specificity for pocket infection, less for lead CIED infection</td>
<td>Inconsistent imaging protocols and data acquisition techniques</td>
</tr>
<tr>
<td>LVAD</td>
<td>Differentiate and localize the site and extension of infection (central vs peripheral driveline)</td>
<td>High sensitivity and specificity</td>
<td>Specificity considerably varies among studies. No consensus in qualitative and quantitative data</td>
</tr>
</tbody>
</table>

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18F-FDG, 18F-fluorodeoxyglucose; CIED, cardiac implantable electronic device; IE, infective endocarditis; LVAD, left ventricular assist device; TAVI, transcatheter aortic valve implantation. *18F-FDG-PET/CT identifies unexpected embolic localizations and metastatic infections. †Sensitivity and specificity depends on patient preparation and data acquisition techniques.
THE ROLE OF 18F-FDG-PET/CT IN TRANSCATHETER AORTIC VALVE IMPLANTATION INFECTION

As in prosthetic valve IE, the diagnosis of transcatheter aortic valve implantation (TAVI) IE can also be challenging, and its presence can be associated with poorer outcomes. Limited data on the utility of 18F-FDG-PET/CT in TAVI-IE diagnosis exist to date based on a theoretical risk of false-positive results caused by the metal stent around the TAVI prosthesis. 18F-FDG-PET/CT could potentially reclassify a “possible” case to either “definite” or “rejected,” especially when used in combination with cardiac CT angiography (CTA). For instance, in a cohort of 22 possible TAVI-IE cases, 5 cases were reclassified as “definitive” and 5 additional cases as “rejected” TAVI-IE. The addition of 18F-FDG-PET/CT and CTA can diagnose up to 78% of TAVI-IE cases that were not visible with echocardiography.

THE ROLE OF 18F-FDG-PET/CT IN CIED INFECTION

In recent years, rates of CIED insertion and associated infections have significantly increased, resulting in a substantial health care burden. CIED infections can be broadly categorized into generator pocket infection and lead infection or lead IE. 18F-FDG-PET/CT has demonstrated a sensitivity (96%) and specificity (97%) for pocket infection diagnosis. However, in most pocket infection cases, the diagnosis is established based on physical exam findings and the presence of inflammatory changes at the pocket generator site. In contrast, a timely diagnosis of endovascular infection with an intact pocket can be challenging, as a transesophageal echocardiogram cannot reliably distinguish between an infected and noninfected echodensity attached to a device lead. Results of a recent meta-analysis including 492 patients showed that the diagnostic accuracy of 18F-FDG-PET/CT was low for lead infections, with pooled sensitivity of 76% and specificity of 83%. The sensitivity increased to 92% and specificity decreased to 81% with myocardial suppression protocols. Thus, when considering the significant complications and the financial burden associated with device removal, the decision to obtain an 18F-FDG-PET/CT should be individualized.

THE ROLE OF 18F-FDG-PET/CT IN LEFT VENTRICULAR ASSIST DEVICE INFECTION

Similar to CIED implantation, left ventricular assist device (LVAD) use has considerably increased over the past several years. Although LVAD implantation (image above) can be a lifesaving procedure, LVAD infections occur in 20% to 40% of patients within approximately 1 to 2 years of the procedure. LVAD infections may present as local infection, involving the driveline (most common) or pump pocket, or as an endovascular infection (Figure). 18F-FDG-PET/CT can differentiate and localize the site and extent of infection within the device’s central portion or along the peripheral driveline. Infection in the pump pocket site, which is the central portion, is associated with lower survival compared with infection along the driveline. A retrospective cohort study addressed the value of 18F-FDG-PET/CT in 31 patients with a high clinical suspicion of LVAD infection. The imaging had a sensitivity of 100% and specificity of 80%. These results influenced the therapeutic management in 85% (34 of 40) of 18F-FDG-PET/CT examinations. Similar results were observed in another study of 35 patients, in which 18F-FDG-PET/CT detected infection in 80% of cases, mainly at the level of the cannula and/or the pump pocket site.

In a recent case series and systematic review, the pooled sensitivity and specificity of 18F-FDG-PET/CT in diagnosing LVAD infections was 92% and 83%, respectively. However, specificity varied considerably among studies (25% - 100%). Both qualitative and quantitative data can provide greater sensitivity and specificity than visual grading alone. Preliminary data showed lower average measured SUVmax values in the absence of infection vs presence of infection (2.3 ± 1.0 to 3.6 ± 1.0 vs 4.0 ± 2.2 to 6.4 ± 3.8). The number of patients included in most studies is small, and in making a diagnosis, imaging should be an adjunct to the features of clinical presentation and to laboratory diagnostic tools. Moreover, a careful review of each patient’s surgical report could improve the objective assessment of LVAD infection by 18F-FDG-PET/CT.

CONCLUSIONS

18F-FDG-PET/CT has high sensitivity and specificity, but it is still considered a diagnostic tool adjunctive to routine clinical evaluation. When interpreting an 18F-FDG-PET/CT, patient preparation (myocardial FDG uptake suppression), surgical technique, and type of material implanted should be carefully considered. The addition of 18F-FDG-PET/CT to the evaluation of possible IE has the potential to improve diagnostic accuracy considerably.
Emerging Infectious Diseases During COVID-19

Resources shifted away from other viruses when COVID-19 became the priority.

By Krutika Kuppalli, MD, FIDSA; and Syra Madad, DHSc, MSC

Infectious diseases have repeatedly reshaped the course of civilization, resulting in significant human suffering and death along with substantial economic costs. Over the past 40 years, there has been a 4-fold increase in the number of emerging pathogens, such as extensively drug-resistant tuberculosis (XDR-TB), severe acute respiratory syndrome coronavirus (SARS-CoV), the H1N1 pandemic, middle east respiratory syndrome coronavirus (MERS-CoV), Nipah virus, Zika virus, multidrug-resistant organisms (MDROs), and Ebola virus disease. Public health threats and infectious diseases respect neither boundaries nor barriers, and 70% of the world is underprepared to prevent, detect, and respond to them effectively.

In this era of increasingly mobile and connected populations, it is possible for an infection to spread around the world in 24 to 48 hours, due to urbanization, human behavior and rapid transportation networks. SARS-CoV-2, the virus responsible for the coronavirus 2019 (COVID-19) pandemic, is the latest novel pathogen to emerge, leading to over 95 million cases and 2 million fatalities globally as of January 18, 2021. Although the pandemic has had a broad human, economic, and social impact, it is one of many infectious diseases that has had important public health implications over the past year (Table). In this article, we review and discuss some of the most notable infectious disease outbreaks, and trends of the past year and where appropriate, indicate how they were impacted by COVID-19.

EBOLA
As the world rang in 2020, most of the global health community was focused on the 10th Ebola virus disease (EVD) outbreak that had been ravaging eastern Democratic Republic of the Congo (DRC) since August 1, 2018. Although DRC had successfully contained more EVD outbreaks than any other country in the world, trying to end the one in the eastern North Kivu and Ituri provinces was difficult given the challenges it occurring in a war zone. This outbreak was unlike any in the past; insecurity from years of violence had caused deep-seated community mistrust, intensifying the largest and most complex outbreak in the country’s history.

As COVID-19 gained traction across the globe, attention and resources shifted away from Ebola toward understanding and containing the newly emerging pathogen. Despite this pivot, the global community’s investment in developing fundamental principles of outbreak response and their commitment to deploying a vaccine in eastern DRC were critical to declaring an end to the Ebola outbreak on June 25, 2020. Similarly, it was the swift implementation of these principles that allowed DRC to quickly detect, isolate, contain, trace, and declare an end to their 11th EVD outbreak in less than 6 months, which arose in Equateur Province on June 1, 2020, and was declared over on November 18, 2020.

The core principles of an Ebola response are anchored in any good infectious disease outbreak response. They include disease surveillance, strengthening laboratory capacity, infection prevention and control, isolation and quarantine of suspect cases, contact tracing, and investment in building health care systems. Investment in these components began in 2018 at the beginning of the Ebola outbreak; thus, when COVID-19 emerged, the country was prepared to tackle this new threat. Since the emergence of the COVID-19 pandemic, the government has reinforced public health measures such as the mandatory wearing of face masks in public and limiting the number of individuals who can gather in crowds. They have also partnered with nongovernmental organizations to implement community awareness campaigns and engagement around COVID-19 via radio, SMS communications, and mobile caravans. The combined efforts have been positive, and as of January 18, 2021, the DRC has reported approximately 20,625 cases of COVID-19.

VACCINE-PREVENTABLE DISEASES
While the world fights a new foe, we are still in the midst of combating long-standing adversaries such as vaccine-preventable diseases. Despite historic achievements in vaccine development and availability, more than 1.5 million people worldwide die each year from vaccine-preventable diseases. The COVID-19 pandemic has disrupted the way we fight diseases such as measles, diphtheria, and polio by hindering routine immunization services around the world. This puts at least 80 million children under age 1 in at least 68 countries, both poor and...
and has caused havoc in the US over the past few years. As of September 2020, 22 states have reported 1433 confirmed and 30 probable cases. Although COVID-19 has dominated the headlines, MDROs continue to spread, often unchecked, with ongoing delays in reporting and tracking. A recent health advisory in California from August 2020, for example, noted that staying vigilant and preventing the spread of MDROs and \( C\) \( \text{auris} \) is still of the utmost importance amid the ongoing pandemic, as increased numbers of \( C\) \( \text{auris} \) continue to be reported. In fact, the advisory noted that \( C\) \( \text{auris} \) cases in California had more than doubled in health care facilities from May (\( N = 15 \)) to June (\( N = 40 \)) 2020. In July 2020 cases (\( N = 73 \)) also exceeded the combined total number of cases in April, May, and June (\( N = 59 \)) 2020. This noted increase is attributed to conservation strategies that facilities were using for COVID-19, such as extended use and reuse of personal protective equipment (PPE), and other containment practices such as grouping patients based on COVID-19 status. \( C\) \( \text{auris} \) is not the only MDRO to emerge during the pandemic. A hospital in New Jersey also reported 34 cases of carbapenem-resistant \textit{Acinetobacter baumannii} (CRAB), which peaked during the spring surge of COVID-19 hospitalizations due to deviations in infection control strategies.

In India, probable hospital-acquired \( C\) \( \text{auris} \) bloodstream infections in critically ill patients with COVID-19 were noted in 2.5% of intensive care unit patients between April and July 2020. The potential attribution of infection was via indwelling invasive devices, contamination of the hospital environment, and incorrect and extended use of PPE leading to self-contamination and transmission of the opportunistic fungal pathogen. Likewise, the COVID-19 pandemic is affecting antimicrobial stewardship activities and driving antimicrobial resistance around the world. Overall, COVID-19 is leading to increased hospitalization rates of high-acuity patients, longer hospital stays in crowded facilities, antimicrobial overuse, extended use and reuse of PPE, and shortages of staff. Such factors play a role in contributing to the emergence of and increase in health care–acquired infections with MDROs.

**CONCLUSIONS**

Currently, the global health workforce and its resources are stretched thin and are mostly dedicated to combating the COVID-19 pandemic. If Ebola, Zika virus, \( C\) \( \text{auris} \), SARS-CoV-2, and other emerging infections have taught us anything, it is that we must work with partners in other countries, particularly those that have limited resources, to combat emerging infectious diseases. These are where novel pathogens are likely to emerge but unlikely to be recognized and reported quickly as a result of fragile health care infrastructure.

As a result, we also must invest in strengthening global capacities such as public health and health care systems, to prevent, detect, and respond to infectious disease threats in resource-limited settings. These measures will help move us toward strengthening the global health security agenda and meeting global pandemic preparedness goals. Finally, we need sustained resources to support resource-limited countries in strengthening surveillance and reporting systems, laboratory capacities, infection control efforts, and health care workforce training. This will ensure we have a robust capacity and capability to develop new tools and approaches to respond to infectious diseases with pandemic potential.

The world is constantly changing. We have altered how we live and the planet on which we live, including the way we interact with nature, manmade environments, and animals. We have changed the way we travel and our climate. This has created the perfect storm for infectious disease outbreaks and unprecedented opportunities to prevent and respond to them. It is critical that we work together as a global community to address COVID-19 and prepare for future emerging infectious disease threats.

References are available at ContagionLive.com.
Impact of SARS-CoV-2 Infection and the COVID-19 Pandemic on People With HIV

Non-HIV comorbidities appear to confer the most risk for severe COVID-19 with people living with HIV. However, CD4 cell counts under 200 also seem to be associated with worse outcomes.

BY ERIC A. MEYEROWITZ, MD

(continued from cover page) pneumococcal pneumonia for PWH, clinicians were concerned there might be a similar elevated risk for this new viral infection. Additionally, it quickly became clear that many common comorbidities found in PWH, including obesity, diabetes, and cardiovascular disease, were risk factors for severe COVID-19 outcomes. Although there is still much to learn, some preliminary conclusions can now be made based on the accumulated global experience to date. We will primarily address 4 key questions: (1) Are PWH at increased risk for SARS-CoV-2 infection? (2) Are they at higher risk for hospitalization after diagnosis? (3) Is HIV status or degree of HIV-related immune deficiency a risk for severe outcomes? (4) Do antiretrovirals used for HIV have activity against SARS-CoV-2?

The impact of HIV status on the likelihood of SARS-CoV-2 diagnosis is currently unknown. An analysis of 23 studies that included PWH with positive SARS-CoV-2 tests in the context of a general population found that PWH were overrepresented. However, without correcting for unequal access to SARS-CoV-2 testing, it is difficult to interpret these findings. A large population-based study from New York City, with a local HIV prevalence of around 1.5%, found that PWH represented 1.06% of the nearly 205,000 total COVID-19 cases and were therefore not overrepresented during the study period. Serological surveys may eventually be able to shed additional unbiased light on this issue. With well-described, overlapping structural factors determining risk for both infections, there is reason to believe PWH may be at higher risk of SARS-CoV-2 infection. Racial and economic disparities are well described in the HIV global epidemic, with Blacks and Hispanics far more likely to be diagnosed with HIV than Whites, and poverty also a driving risk factor for infection. Race and poverty are similarly key determinants of risk for SARS-CoV-2 infection. A study at a large hospital system in Boston during a major local epidemic found that almost 80% of PWH diagnosed with SARS-CoV-2 were Black or Hispanic/Latinx compared with 40% in the HIV clinic population. Racial disparities seen in COVID-19 outcomes are attributable to differential infection rates.
Many studies have tried to assess the risk for hospitalization for PWH after COVID-19 diagnosis. According to findings from a New York City-based study that included data from 5 hospitals, 72 of 93 PWH with COVID-19 were hospitalized, though no comparison was made to the general population. Results from a multicenter study with over 50,000 people with COVID-19, including 404 with HIV, used propensity score matching and found that PWH were more likely to be hospitalized (19.3% vs 11.4%). Investigators found no increase in severe outcomes based on HIV status, suggesting that there may have been a lower threshold for admission for PWH who were diagnosed with COVID-19 rather than a medical necessity for hospitalization. Study investigators from a referral hospital in Cape Town, South Africa, of the first 116 hospitalized patients with COVID-19 reported that 21% were PWH, compared with a local seroprevalence of 12.6%. A pooled analysis of multiple studies found no overall difference in hospital admission for PWH compared with those without HIV; this suggests there may be regional or institutional differences that would explain some of the differences reported in various studies.

Investigators continue to describe the association of HIV status and severe COVID-19 outcomes. According to results of an early study of a cohort of over 3.5 million people with an HIV prevalence of 16% from the Western Cape in South Africa, there were 625 COVID-19 deaths and 22,308 total diagnoses during the study period. HIV status was associated with COVID-19 mortality with an adjusted hazard ratio over 2. The authors adjusted for location to try to control for structural factors that might have contributed to increased risk of infection or mortality, but residual confounding is possible. Of the PWH in this study, 33% had a CD4 cell count measured during the admission for COVID-19 and 35% of those had CD4 cell counts of 200 cells/mL or less, which was associated with death. Findings from a multicenter study that included 286 PWH with confirmed COVID-19 showed that a CD4 cell count of less than 200 was similarly associated with more severe outcomes. Another multicenter retrospective cohort study identified 49,763 people without HIV and 404 PWH and COVID-19. Investigators performed propensity score matching and found that HIV was not a risk factor for mortality; instead, non-HIV comorbidities were the drivers of increased severity. The authors did not report CD4 cell counts for PWH included in this study. The accumulating evidence suggests that non-HIV comorbidities are the major drivers of COVID-19 severity for PWH, though those with CD4 cell counts of less than 200 are likely at higher risk for worse outcomes.

Investigators continue to describe the association of HIV status and severe COVID-19 outcomes. From the Western Cape in South Africa, there were 625 COVID-19 deaths and 22,308 total diagnoses during the study period.

The HIV protease inhibitor lopinavir/ritonavir was known to have in vitro activity against the major protease of SARS-CoV and Middle East respiratory syndrome coronavirus and there was early interest in using this combination for SARS-CoV-2. Lopinavir/ritonavir has been extensively studied in multiple negative, randomized controlled trials to date. Results of pharmacokinetic studies suggest the levels of lopinavir achieved with standard dosing are nowhere near what would be required to inhibit SARS-CoV-2 in vivo. Clinicians have considered tenofovir as a possible treatment through the inhibition of the SARS-CoV-2 RNA-dependent RNA polymerase. Among a large cohort of nearly 80,000 PWH on antiretroviral therapy across many clinics in Spain, there were 236 cases of COVID-19 and 20 deaths during a study period. The 16% of individuals on the nucleoside reverse transcriptase inhibitor combination of tenofovir-disoproxil fumarate with emtricitabine (TDF/FTC) had the lowest risk of hospitalization; however, the authors did not control for possible differential age distribution or comorbidities between the subgroups. Many have pointed out that it is quite plausible that the participants on TDF/FTC may be younger or have less kidney disease or fewer other comorbidities, which could explain the findings. According to results from an observational study of HIV-negative individuals from Spain that included 250 people not receiving pre-exposure prophylaxis (PrEP), 409 receiving TDF/FTC, and 91 receiving tenofovir-alafenamide with emtricitabine (TAF/FTC) for PrEP, there was a higher SARS-CoV-2 seroprevalence among those taking PrEP. However, the investigators made no adjustments for possible differences in exposures or behaviors. Although studies will continue, there is currently no evidence for clinically meaningful activity of any HIV drugs against SARS-CoV-2.

From the extensive global experience reported to date, risk for severe COVID-19 is largely driven by age and non-HIV comorbidities, similar to what is seen for people without HIV. However, those with CD4 cell counts under 200 may be at elevated risk for worse outcomes. Infection risk is driven by similar social determinants of health that define risk for HIV infection. Study findings have inconsistently shown increased rates of hospitalization, but this is more likely due to a lower threshold for admission for PWH in some settings.

One area of possible significant impact on PWH, but with too few data to date, concerns the effects of pandemic-related care disruption on HIV outcomes. Clinic closures may lead to delays in visits or lapses in medication refills. Additionally, job loss and worsened food and housing insecurity related to the pandemic may disproportionately impact PWH. Thus, although it is important to make some preliminary conclusions, the full toll of COVID-19 on PWH is likely to be significant. Long-term interventions should target not just improving acute outcomes but also structural determinants of risk for both infections.

References are available at ContagionLive.com.
Bacterial Coinfections in US Patients With Coronavirus Disease 2019

A discussion on the implications for antimicrobial use and antimicrobial resistance.

BY DEANNA J. BUEHRLE, PHARMD

In one study, 15% of the respiratory gram-negative isolates were multidrug-resistant.

In one study, 15% of the respiratory gram-negative isolates were multidrug-resistant.

Altogether, 3.5% (59/1705) of patients had a bacterial coinfection, including 3.2% (55/1705) with positive blood or respiratory cultures. However, despite those low rates, 56.6% of patients received empirical antibacterial therapy within 2 days of hospitalization. Empirical treatment included agents covering only community-acquired infection (35.9%), therapy against methicillin-resistant Staphylococcus aureus (MRSA; 14.6%), antipseudomonal therapy (14.9%), and anti-MRSA combined with antipseudomonal therapy (10.8%).

In a similar study of community-onset bacterial coinfection among hospitalized patients with COVID-19, Karaba and colleagues found that 1.2% (12/1016) had proven or probable community-acquired pneumonia, 2% (20/1016) had bloodstream infection (BSI), 3% (30/1016) had urinary tract infection (UTI), and 0.2% (2/1016) had Clostridioides difficile infection. The most common organisms associated with BSI were Staphylococcus aureus (6/20), coagulase-negative Staphylococcus (5/20), and Escherichia coli (5/20); the most common organisms associated with UTI were E coli (10/30), Proteus species (spp; 5/30), and Klebsiella spp (4/30). Nonetheless, 71% (717/1016) of patients received at least 1 dose of an antibiotic directed at bacterial community-acquired pneumonia. As the study period progressed, a lower percentage of patients were started on antibiotics (61% in May vs 77% and 75% in March and April, respectively) and the median duration of antibiotic therapy became shorter.

Results of a study by Lehmann and colleagues showed that 1.2% (7/321) of patients admitted from the community to a hospital in Chicago, Illinois had community-acquired bacterial coinfection. Of those 7 patients, 4 received a diagnosis by positive S pneumoniae urinary antigen. Similar to the other studies’ findings, empirical antibiotic use was high, with 69% of patients receiving antibiotics. The largest study to date to include hospital-acquired secondary infections in the United States during the COVID-19 pandemic was conducted by Nori and colleagues at a single center in New York, New York. Of 4267 patients evaluated, 3.6% (156/4267) had positive blood or respiratory cultures during their...
initial hospitalization for COVID-19 or a hospitalization within 30 days of their positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus responsible for COVID-19 disease). Of patients with coinfections or secondary infections, 65% were admitted to ICUs and 74% received mechanical ventilation.

The study’s results showed that the median length of hospitalization was 13 days. By infection site, 60% of patients had respiratory infection, 54% had BSI, and 14% had both. The median time between positive respiratory bacterial culture or positive blood culture and SARS-CoV-2 test results was 6 days (interquartile range [IQR], 2-8) and 7 days (IQR, 3-14), respectively. Respiratory culture results were consistent with nosocomial pathogens, including *S. aureus* (44%), *P. aeruginosa* (16%), *Klebsiella* spp (10%), *Enterobacter* spp (8%), and *E. coli* (4%). Fifteen percent of the respiratory gram-negative isolates were multidrug-resistant (MDR) and 5% were carbapenem-resistant *Enterobacteriales* (CRE).

The top 3 sources for BSI were catheters (central venous, peritonal dialysis, and hemodialysis), respiratory tract, and genitourinary tract. The organisms causing BSI most frequently were *Enterobacterales* (65% of patients admitted to ICUs).10 Among the studies that reported antibiotic prescribing, 71.8% of patients received antibiotics. It should be noted that these analyses were limited by differences in diagnostic criteria or case definitions, an inability to differentiate colonization and infection, and the absence of treatment and antimicrobial resistance data. Further, secondary infections were not primary end points in most of the studies that were included. Future studies should be conducted to address these shortcomings.

Despite low overall rates of coinfection and secondary bacterial infections among COVID-19 patients, several US studies have reported an increase in overall antibiotic DOT per 1000 patient-days (PDs) during the pandemic.11,12 Although our group, the Veterans Affairs (VA) Pittsburgh Healthcare System, also reported an increase in overall antibiotic DOT/PDs, we observed a decrease in absolute antibiotic DOT, primarily driven by decreased overall hospitalizations early in the pandemic.11 A study of national VA data found increases in DOT/PDs of the broad-spectrum agents used for community-onset respiratory infections and for hospital-onset infections.12

In the ambulatory care space, our group described substantial decreases in US prescriptions of the 10 most commonly prescribed outpatient antibiotics.14 Taken together, these data signify that absolute antibiotic use has likely decreased in both the inpatient and outpatient settings. However, antibiotic DOT/PDs have increased in the inpatient setting during the pandemic. It is possible that an overall decrease in antibiotic use nationally during the pandemic was due to decreased health care access. At the same time, it appears that antibiotic use increased among patients admitted to acute care settings. The impact of such prescribing on national AMR patterns is unknown, but it will be a focal point of future studies. At a single center in Maryland, Bork and colleagues found although there was no difference in acquisition of MDR gram-negative infections when comparing the same periods in 2020 and 2019, there was a 3% increase in MDR gram-negative infections per PDs for every positive SARS-CoV-2 test per week.13 Notably, antimicrobial resistance patterns may significantly differ among localities, regions, and nations. Within hospitals, there may also be significant differences between general medical wards vs ICUs, and COVID-19 units vs non-COVID-19 units.

It is reasonable to hypothesize that as clinical experience and COVID-19 testing protocols were established, more judicious antimicrobial use followed. ASPs can leverage data showing low risk of bacterial coinfections to withhold or discontinue antibiotics among patients admitted for COVID-19 with no evidence of bacterial infection. Likewise, the relatively low rate of bacterial secondary infection development can be used to implement antibiotic timeouts and early antibiotic discontinuation if bacterial infection is not diagnosed. Other core stewardship strategies, including the use of rapid diagnostics, culture-directed therapy, short courses, and early oral switches, can also be employed. Although the utility of procaldacin in COVID-19 illness is not fully known, it appears to be useful in guiding the need for antibiotics early during a patient’s course of COVID-19. Among patients who are critically ill, it remains unclear whether higher levels of procaldacin are due to severe disease or related to bacterial coinfection or secondary infection.15 Many questions are still unanswered regarding bacterial infections, antimicrobial use, and AMR among patients with COVID-19. There is significant heterogeneity in the way that bacterial infections in these patients have been classified to date. Many studies do not clearly differentiate between community-acquired coinfection and hospital-acquired secondary infection. The risk of bacterial infection stratified by underlying conditions, COVID-19 severity, admission to an ICU, mode of oxygen delivery, and hospital length of stay are not yet clear. The epidemiology and susceptibility patterns of bacterial coinfection and secondary infections are not well defined. Further, the risk of development of AMR infection among COVID-19 patients is not yet clear.

It is possible that an increase in secondary bacterial infections will be observed over time during the pandemic. Patients with severe COVID-19 may have prolonged hospitalizations and necessary admissions to nursing facilities after hospital discharge; they may also experience COVID-19–related complications requiring readmission to hospitals. Substantial changes have also occurred in the management of COVID-19 since the pandemic’s start, such as the use of corticosteroids or other immunosuppressants. Influenza and other respiratory viruses beyond SARS-CoV-2 may affect rates of secondary bacterial infections. Clearly, additional well-designed studies are needed to focus on describing the epidemiology of bacterial infections among COVID-19 patients, antibiotic use, and long-term effects on local and national AMR patterns. 

The top 3 sources for BSIs were catheters, respiratory tracts, and genitourinary tracts.
What makes an N95 respirator different from standard surgical masks is that it is a particulate-filtering face piece designed to filter at least 95% of airborne particles measuring as small as 3 μm in diameter. To extend the quantity of available respirators, PPE reuse—something once done only in low-resource settings—has become necessary in resource-rich settings as well, as recommended by the CDC in situations where PPE is running low.1

To complement reuse strategies, PPE decontamination has become a topic of great interest and research. First, it is important to distinguish between cleaning and decontaminating PPE. Cleaning is the initial step of removing organic material including microorganisms from equipment, but it does not necessarily inactivate enough microorganisms to render the equipment safe for usage. Decontamination inactivates or eliminates pathogenic microorganisms, allowing for safe usage. Therefore, in all the following decontamination strategies, masks with visible soiling are discarded prior to decontamination during the quality assessment phase.

Finally, to increase the PPE supply, a successful decontamination method must achieve adequate target organism inactivation without compromising respirator fit and filtration. Here, we will review 3 common sterilization modalities currently in use for N95 respirator decontamination, how they work, and their strengths and limitations.

ULTRAVIOLET GERMICIDAL IRRADIATION

Ultraviolet (UV) light has long been used for environmental disinfection in health care; UVC wavelength (as opposed to UVA or UVB) light has been studied and approved by the National Institute for Occupational Safety and Health for use in health care settings to kill organisms harder than viruses, such as Mycobacterium tuberculosis.2 Ultraviolet germicidal irradiation (UVGI) works by exposing nonporous surfaces, water, or air to UV light–producing lamps, usually to a peak UVC wavelength of 254 nanometers. That light breaks and creates new bonds in the organismal RNA and DNA nucleic acid, preventing replication and inactivating pathogens. No residual byproducts remain on the masks that would result in user injury once decontamination is complete. One of the earliest N95 respirator reprocessing protocols to emerge during the ongoing COVID-19 pandemic was from the University of Nebraska, using UVC-based UVGI.3 Subsequent studies have demonstrated that UV irradiation successfully inactivates severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) whereas UVA and UVB irradiation do not.4

(continued from cover page)

From Single-Use to Multi-use: A Brief Review of N95 Respirator Decontamination Strategies

As this indispensable personal protective equipment (PPE) became short in supply, reuse strategies developed into a topic of great interest.

BY CHRISTINA YEN, MD; AHMED ABDUL AZIM, MD; AND PREETI MEHROTRA, MD, MPH

Christina Yen, MD, completed her clinical infectious diseases fellowship at Beth Israel Deaconess Medical Center in New York and has stayed on to be the infection control/hospital epidemiology fellow. Her interests are in diagnostic stewardship, antimicrobial stewardship, and strategies to prevent central line–associated bloodstream infections.
A key consideration with UVGI reprocessing is the need to ensure that both the interior and exterior surfaces of the N95 are not obscured from the lamp, which would prevent UVC from reaching and subsequently sterilizing those areas. Practically, this means personnel must be trained to properly hang masks and to include quality assurance steps prior to and after irradiation to look for shadowing. Another issue is the adequate decontamination of mask straps; this can be achieved, but only at higher wavelengths, which risks strap and mask damage.5

HEAT AND HUMIDITY
Heat, with or without humidity, has been a decontamination strategy of significant research interest, given its easy accessibility and low cost. This involves exposing N95 respirators to heat sources such as autoclaves, which are often readily available in health care settings and are easy to adapt. Furthermore, most hospitals already use heat-based sterilization for nonporous equipment and have personnel who are familiar with the technology, eliminating the need for a training period. In one study, SARS-CoV-2 inactivation occurred when N95 respirators were exposed to 70 °C dry heat. However, quantitative fit testing found that those heat-treated N95s were able to maintain acceptable fit only for 1 to 2 rounds of decontamination, leading the authors to conclude that heat was a less practical real-world option compared with vaporous hydrogen peroxide (VHP) and UV treatments for masks. Masks treated with the latter 2 methods retained adequate filtration and fit for 3 or more rounds. Studies on moist heat have also been successfully applied to inactivate influenza virus on N95 respirators.7

Although one major obstacle to the widespread usage of heat is the aforementioned change to fit, another is filtration retention, which diminishes with higher temperatures and multiple cycles. A third obstacle is the need for different temperatures and humidity levels depending on the mask model.8 Studies recommend a range of temperatures between 70 °C and 80 °C and humidity percentages of 50% to 85% for decontamination.7 This can be a challenge for health care settings that use several respirator models: Some may have disparate heat and humidity needs, and others may have not yet been assessed for an ideal temperature and humidity. Finally, although other reprocessing strategies have been shown to inactivate bacteria and mold on respirators, heat and humidity sterilization has not proved to inactivate SARS-CoV-2.7,9

VAPOROUS HYDROGEN PEROXIDE
VHP has been widely used in health care environmental decontamination for many years. The vaporization of liquid hydrogen peroxide inactivates pathogens, including SARS-CoV-2, when the covalent bonds between oxygen and hydrogen break; this releases free oxygen radicals. These radicals then penetrate cell walls, inactivating microorganisms, and the atoms then take new form as molecules of water vapor and oxygen gas. Safety and efficacy when VHP has been applied to N95 respirators have been confirmed to a maximum of 50 cycles in 1 study and 20 in others without fit or filtration failure. Furthermore, 2 protocols were published early in the pandemic by both Duke and Yale universities that confirmed SARS-CoV-2 inactivation and feasibility with VHP.10,12

Of the 3 reprocessing methods, VHP is the most time-consuming, requiring a decontamination period lasting 40 to 45 minutes. This does not include the time required for several other critical steps in the process, such as the vaporization of liquid hydrogen peroxide. Depending on the manufacturer’s protocol, there can also be recommendations for a longer or shorter dwell phase to provide time for adequate amounts of gaseous hydrogen peroxide to settle on the exposed surfaces of the N95 respirators and straps. Moreover, an aeration phase of at least 2 hours is required. Aeration of the VHP room and respirators is necessary, allowing any residual hydrogen peroxide gas to break down into water vapor and oxygen; otherwise, lingering gas can cling to the mask and cause skin irritation to the end user. The entire process from start to finish can thereby last upward of 2 hours. VHP also requires the presence of trained personnel, who may not be available at every institution, to monitor hydrogen peroxide gas levels throughout the decontamination process. Ultimately, all 3 methods have either the potential or evidence to demonstrate SARS-CoV-2 inactivation; however, limitations of the 3 sterilization methods lie in the number of processing cycles that can be performed until fit and filtration are compromised (Table).13-15

As the pandemic continues and PPE remains in short supply, more real-world, controlled studies are required to assess a safe duration of N95 respirator reuse until production can meet demand. To complement these efforts, innovations in N95 respirator decontamination must continue to augment the supply of available PPE. Numerous studies from environmental and occupational health, infection prevention, and other disciplines have since emerged to translate traditional environmental decontamination technologies into PPE decontamination strategies, as well as to test the safety and efficacy of these processes. Whether this innovation will be a temporary feature of the infection prevention and PPE landscape, or a permanent addition, has yet to be seen. However, it behooves the infection control community to consider the viability and longevity of these technologies and their roles in PPE stewardship, environmental waste, and ascertaining the true lifespan of N95 respirators.

References are available at ContagionLive.com.

**TABLE.** Comparison Across UVGI, Heat/Humidity, and VHP N95 Decontamination Strategies13-15

<table>
<thead>
<tr>
<th>DECONTAMINATION PERIOD</th>
<th>FDA EUA OBTAINED?</th>
<th>STUDIES CONFIRMING SARS-COV-2 INACTIVATION</th>
<th>COST</th>
<th>N95 DAMAGE WITH REPROCESSING</th>
<th>MAXIMUM RECOMMENDED CYCLES</th>
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</thead>
<tbody>
<tr>
<td>UVGI</td>
<td>15 minutes</td>
<td>Yes</td>
<td>$5</td>
<td>Seen with higher UV doses</td>
<td>10-20</td>
</tr>
<tr>
<td>Heat/humidity</td>
<td>30-60 minutes</td>
<td>Yes</td>
<td>$</td>
<td>Seen with increasing</td>
<td>Variable depending on</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>temperatures</td>
<td>the N95 model</td>
</tr>
<tr>
<td>VHP</td>
<td>~45 minutes (full process can be closer to 2-3 hours)</td>
<td>Yes</td>
<td>Yes</td>
<td>$$$None if kept to 20 cycles; at 30, strap damage visualized</td>
<td>20-50</td>
</tr>
</tbody>
</table>

EUA, emergency use authorization; UV, ultraviolet; UVGI, UV germicidal irradiation; VHP, vaporous hydrogen peroxide.
On September 10, 2020, MJH Life Sciences™ introduced the COVID-19 Coalition, a partnership with renowned health care thought leaders across multiple medical disciplines. The coalition presents biweekly webinars that give providers resources to improve patient outcomes during the coronavirus disease 2019 (COVID-19) pandemic. The first webinars addressed issues related to influenza and COVID-19, myths and controversies, treatments, vaccines and prophylactic therapies, and long-term physical and psychological effects.

**BATTLING DUAL THREATS: INFLUENZA AND COVID-19**
Moderator Angela L. Rasmussen, PhD, of Columbia University Mailman School of Public Health; Andreas Handel, PhD, of the College of Public Health at the University of Georgia; and Juliet Morrison, PhD, of the University of California, Riverside, participated in this webinar on September 15, 2020.

**COVID-19 and Influenza: A Tale of 2 Viral Pathogens**
Rasmussen noted that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses have distinct taxonomy, genomics, and evolutionary origin, as well as modes of entry into and replication inside the cell. In addition, the higher mutation rate of the influenza virus is related to its ability to reassort its genome. She added that SARS-CoV-2 appears to have a stronger effect on the central nervous system and gastrointestinal tract and infects the cardiovascular system directly. Pathogenic strains of the influenza virus, on the other hand, affect the cardiovascular system through the increased entry of macrophages. Rasmussen also noted that the differential pattern of pathway induction in the immune response suggests that these viruses induce distinct host responses. She added that case reports show coinfection of SARS-CoV-2 and influenza does occur, but the effect on disease severity is unclear.

**Population-Level Patterns of COVID-19 and Influenza: What Should We Expect?**
Handel said that behavior changes and the nonpharmaceutical interventions (NPIs) implemented for COVID-19 have likely had an effect on the influenza rate. He pointed to data showing that rates in the 2019-2020 season were lower than expected in multiple countries, which, along with lower test positivity rates in China and a minimal number of influenza-related hospitalizations in Australia, suggests a true decrease in influenza cases (vs reduced reporting of cases). He concluded that key factors that will dictate the interaction between COVID-19 and influenza in the long term include the effects of a COVID-19 vaccine on influenza vaccine uptake, NPIs, and individual behavior patterns; development of a universal flu vaccine; and COVID-19 treatments.

**Influenza and COVID-19 Vaccines**
Morrison noted that although several COVID-19 vaccines are currently in phase 3 trials, their rapid development has contributed in part to high levels of vaccine hesitancy among the general public. She added that this skepticism has prompted vaccine developers to make a historic pledge stating that they will uphold the integrity of the scientific process, and ensure that regulatory filings and approvals are up to par and no corners are being cut. She concluded that educating the public about the perceived threat of COVID-19 and the effectiveness and safety of the vaccines that become available are key to fighting vaccine hesitancy.

Watch the webinar on-demand: [bit.ly/2MxtxmG](bit.ly/2MxtxmG)

**FACT OR FICTION? COVID-19 MYTHS AND CONTROVERSIES**
Moderator Saskia V. Popescu, PhD, MPH, infectious disease epidemiologist and infection preventionist in Phoenix, Arizona; Emily Ricotta, PhD, MSc, of the National Institute of Allergy and Infectious Diseases, National Institutes of Health; and Angela L. Rasmussen, PhD, addressed common COVID-19 myths and controversies in a COVID-19 Coalition webinar on September 29, 2020.

**MYTH 1: “SARS-CoV-2 is totally airborne”**
Rasmussen said that SARS-CoV-2 is primarily transmitted through short-range respiratory droplets or aerosols between individuals in close contact for long periods of time. “The word ‘airborne’ is often misleading because a lot of times people think of long-range transmission,” she said.
Ricotta added, “We need to be clearer in the way that we’re communicating this, and I think that’s where some of the confusion has come in.” However, both panelists agreed that these discrepancies in definition do not affect current recommendations for preventing transmission (such as mask usage).

**MYTH 2: “Herd immunity is achievable through natural infection”**
Ricotta said that herd immunity through natural infection would likely require 40% to 70% of the population to be infected and have sustained immunity. In addition, as not all the long-term effects of COVID-19 are known, many people would be at risk with this strategy. Rasmussen added that global herd immunity through natural infection has not been achieved for any pathogen and does not keep the pathogen out of the environment in the long term.

**MYTH 3: “We can’t trust data quality”**
Ricotta said that the data source, consistency in reporting, interruptions in collection, and consistency in criteria for positivity can affect data. “It’s not necessarily the quality of data. You just have to be really careful when you’re working with and interpreting them,” she said.

Rasmussen added that communicating with the public about the appropriate use of mathematical models has been a tremendous challenge. “They’re only as good as the information that goes into building them at the time, and that’s constantly changing.”

**MYTH 4: “There is no asymptomatic transmission”**
Rasmussen said that distinguishing asymptomatic from presymptomatic transmission and estimating the prevalence of asymptomatic cases, which is a substantial source of transmission, have been difficult. This is because most asymptomatic cases are based on self-reported data, symptoms can develop after a positive test, and people may not recognize that mild, nonspecific symptoms are related to COVID-19.

**MYTH 5: “Any SARS-CoV-2 vaccine won’t be safe”**
Rasmussen said the purpose of clinical trials is to ensure vaccine safety and efficacy. Ricotta added that postmarket evaluation of vaccines is performed and possible vaccine-associated events are reported in a tracking system. Although vaccines have risks, Ricotta said they are often considered acceptable relative to the risks associated with the disease.

**MYTH 6: “Young people can’t get sick”**
According to Ricotta, although young patients often have fewer symptoms than older patients, some require hospitalization and have had blood clots, strokes, and myocarditis. Rasmussen and Popescu pointed out that cases in children may be underreported.

**MYTH 7: “COVID-19 antibodies wane”**
The immune system response to SARS-CoV-2 immunoglobulin G (IgG) is consistent with that of other viruses. Rasmussen said. Memory immune cells likely persist, even if IgG decreases to undetectable levels, and assumptions about long-term immunity cannot be made based on antibody levels.

**MYTH 8: “Hydroxychloroquine is a miracle drug”**
Rasmussen said that none of the high-quality randomized controlled trials and observational studies show a clinical benefit for prophylaxis or treatment, and the drug can cause ocular problems or cardiac arrhythmias.

**MYTH 9: “COVID-19 is no worse than the flu”**
Although both viruses affect the respiratory tract and have similar modes of transmission, comparing COVID-19 to influenza is “like comparing apples to oranges,” Ricotta said. Getting tested for both viruses is important to guide treatment. Rasmussen added that aside from the fundamental differences in the viruses, the 2 diseases should not be compared because of the differences in treatment and vaccination recommendations.

Watch the webinar on-demand: bit.ly/3ouj9JF

**NAVIGATING THE COVID-19 TREATMENT LANDSCAPE**
This October 13, 2020, webinar included moderator Jason Pogue, PharmD, of the University of Michigan College of Pharmacy; Susan L. Davis, PharmD, of Wayne State University; and Jason C. Gallagher, PharmD, of Temple University School of Pharmacy.

**Remdesivir**
Davis said that although updated results showed differences in mortality at day 15, illness severity, hospital stay, and time to recovery are also important measures to consider when deciding whether to give remdesivir. Additionally, the guidelines for use from the National Institutes of Health and the Infectious Diseases Society of America were based on the drug’s limited availability early in the pandemic. The increase in availability and advent of new therapies since then may change when and which patients receive the drug, according to Davis.

**Dexamethasone**
The panelists stated that a wide range of patients, including those with minimal need for supplemental oxygen, would likely benefit from dexamethasone. Gallagher cautioned against making assumptions about when a patient is in the “inflammatory phase” of the disease, given that knowledge about its clinical course is continuing to evolve. Moving forward, he recommended focusing on clinical data when assessing clinical benefit from dexamethasone.
**Convalescent Plasma**

Although an emergency use authorization (EUA) was given, Gallagher said the data from the nonrandomized Mayo Clinic Expanded Access Program are difficult to interpret. Further, he remarked that the benefits appear to be primarily in patients who have not produced their own antibodies to SARS-CoV-2. Davis noted that the primary intention of the program was to improve access for patients and that it was not designed as a clinical trial. Pogue added that convalescent plasma may have lower levels of antibodies than the levels the patient has produced.

**Monoclonal Antibodies**

Although the data published in press releases appear promising, Davis said such data from pharmaceutical companies is insufficient for rational decision-making in the clinic. When companies apply for an EUA, closer communication with the FDA can expedite additional treatment options in a pandemic, but a completed clinical trial is necessary for an agent’s widespread use in the clinical setting, she continued. “EUA is a tool for a health emergency,” said Davis. “It is not a replacement for the normal drug approval process.”

Gallagher added that monoclonal antibodies may predict progression in patients who are readmitted to the hospital but the logistical challenges, such as the need for intravenous infusion, will likely limit their overall impact on reducing transmission and improving outcomes.

**RACE FOR A VACCINE: THE LATEST UPDATES IN COVID-19 PREVENTION**

Moderator: Margaret A. Liu, MD, CEO of PAX Therapeutics and chairman of the board of the International Society for Vaccines; Myron S. Cohen, MD, head of monoclonal antibody clinical testing in the COVID-19 Prevention Trials Network; and Lawrence (Larry) Corey, MD, head of vaccine testing in the COVID-19 Prevention Trials Network, participated in this webinar, held October 27, 2020.

**Monoclonal Antibodies**

According to Cohen, key advantages of monoclonal antibody therapy include the ability to offer immediate protection to exposed or unvaccinated individuals in high-risk settings, provide an option for patients unlikely to respond to or who are allergic to a vaccine, and stop viral replication and disease progression. Several phase 3 trials are ongoing for monoclonal antibody therapies, including one (NCT04452318) that is evaluating the efficacy of REGN10933 + REGN10987 (which prevents the receptor binding domain of the spike protein from reaching the ACE2 receptor) for preventing infection in the household contacts of individuals who test positive for COVID-19. Another is the BLAZE-2 trial (NCT04497987), which is investigating the antibody LY-CoV555 for preventing infection in residents and staff of skilled nursing and assisted living facilities.

**Vaccine Development**

Corey said that several features of SARS-CoV-2, including its relatively high infection cure rate, mutation rate of 2 base pairs per month with little variation in neutralizing areas of the spike protein, and recent evidence of past infection protecting against acquisition, have made COVID-19 vaccine development more straightforward than that for HIV.

The conceptual framework for COVID-19 vaccine development involves developing multiple vaccine platforms (protein, viral vector, and RNA based) and having a coordinated effort from the US government to involve global vaccine manufacturing companies, said Corey. He emphasized the importance of having a common data safety monitoring board for these efficacy trials using different vaccine platforms, with decisions for a given candidate based on the context of the other trials. According to Corey, the main goal of these trials is to evaluate each candidate vaccine for safety and efficacy for reducing COVID-19 disease, with approximately 30,000 individuals enrolled per trial; measure 150 disease end points; enroll Black, Latinx, and tribal communities; and evaluate vaccines in epidemiologic settings of individuals at greatest risk for complications based on comorbidities, age, and race.

“A vaccine that protects from medically complicated COVID-19 disease would provide enormous help in relieving the uncertainty that accompanies work, travel, and gatherings with family, friends, and community,” said Corey.

**The Uninvited Guest: Promoting Mental Health and Wellness During COVID-19**

Cicchetti said that issues related to the COVID-19 pandemic, racism, and economic downturn in 2020 have contributed to multiple layers of stress in many individuals. Ongoing mental health challenges for many individuals include a sense of inequity, structural racism, heightened exposure to stress and trauma, social isolation and disconnection, limited access to community programs and support, changes to routine and structure, barriers to accessing health care and other services, and educational disruptions for children.

Cicchetti emphasized the importance of providers addressing stress directly with clients using tools such as Stoddard and Kaufman’s Coronavirus Impact Scale and the UCLA Brief COVID-19 Screen for Child/Adolescent PTSD. She recommended that parents respond to their children using principles of trauma-informed care, including creating a safe environment, building relationships and connectedness, and supporting and teaching emotional regulation. Create a sense of predictability and establish routines to enhance children’s safety and security, she suggested, and provide them with love and support. Additionally, allowing them to ask questions, supporting their emotional regulation, and letting them figure out how to support themselves with self-care activities will help them reduce stress, cope with challenges, and enhance their sense of wellbeing.

**Long-term Health Consequences of Covid-19**

Del Rio estimated that 10% to 15% of patients do not recover quickly based on findings from the COVID Symptom Study, and the persistence of symptoms is independent of age, comorbidity burden, and severity of acute illness. He added that cardiac injury, myocarditis, arrhythmias, cardiogenic shock, and thromboembolic disease may occur in the acute phase. These can lead to myocardial fibrosis or scarring, arrhythmias with cardiac arrest outside the hospital setting, and cardio-myopathy in the postacute phase. Pneumonia, acute respiratory distress syndrome, and hypoxic respiratory failure can occur during the acute phase and be followed by restrictive lung disease in the postacute setting. Del Rio added that renal function may also be compromised long-term, with persistent kidney dysfunction or requirement for dialysis even in patients who did not require renal replacement therapy during hospitalization. Finally, he cited emotional and behavioral concerns, including feelings of isolation and loneliness, a sense of hopelessness, and ongoing psychological effects, and identified the need for an integrated research agenda to conduct observational studies and randomized trials and a multidisciplinary approach to treatment in post–COVID-19 clinics.
Virtual Meeting, October 21-25, 2020

**THE FORGOTTEN INFECTIOUS DISEASES DURING COVID-19**

We asked our IDWeek experts a simple question: Has COVID-19 taken attention away from any greater infectious disease issues?

[contagionlive.com/idweek4](contagionlive.com/idweek4)

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**KAREN GIULIANO, PHD: ORAL CARE TO REDUCE HOSPITAL INFECTIONS**

New data may provide evidence of oral care as a therapeutic measure to reduce bacterial and viral spread.

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**ANTIBIOTIC PRESCRIBING INCREASED IN VA CLINICS DURING COVID-19**

New data show that the pandemic affected 4 years' worth of stewardship.

[contagionlive.com/idweek6](contagionlive.com/idweek6)
Invasive Pulmonary Aspergillosis Rates in ICU Patients With Influenza Are Surprisingly Low

BY ALEXANDRA WARD, MA

Despite recent studies identifying invasive pulmonary aspergillosis (IPA) as a common complication of severe influenza, even in patients who are immunocompetent, a retrospective look at the past 9 influenza seasons at a US health care center tells a different tale.

In a poster presented virtually at IDWeek 2020, investigators at Northwestern University Feinberg School of Medicine determined IPA incidence among critically ill patients with influenza over multiple seasons, seeking to track outcomes and home in on predisposing risk factors.

Data were collected at a single health care center in Chicago, Illinois, across 9 influenza seasons (March 2009-March 2018). The data included patients above the age of 18 who were admitted to the intensive care unit (ICU) with respiratory distress and had a positive influenza polymerase chain reaction test.

The investigators relied on criteria from the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) to define IPA, as well as the revised aspergillosis ICU criteria.

The study population comprised 224 patients admitted to the ICU with influenza, and the overall rate of IPA was 3.1% (7/224). History of stem cell transplant was a statistically significant risk factor for IPA (P = .015), with hematologic malignancy (P = .09), lung disease (P = .098), and obesity (P = .051) tending toward significance. Only 1 of 7 patients with IPA was not immunosuppressed.

Length of hospital stay was significantly increased for patients with IPA (P = .046), but there was no significant difference in need for mechanical ventilation, renal replacement therapy, or death in these patients.

Other coinfections were common in these patients, with 31.3% bacterial, 7.6% viral, and 8.9% nonaspergillosis fungi infections reported.

“The incidence of IPA was significantly lower (3.1%) in our study over 9 influenza seasons than has been reported in similar studies,” the investigators concluded. “History of stem cell transplant was a risk factor strongly associated with the development of IPA. IPA did not significantly predict morbidity and mortality among critically ill influenza patients.” ▲

SURE-1 Trial: Results of Sulopenem vs Ciprofloxacin

BY JOHN PARKINSON

Uncomplicated urinary tract infections (uUTIs) are most common in young, active women, who typically have a normal, unobstructed genitourinary tract and no history of recent instrumentation. The area of issue tends to be in the lower urinary tract.

Sulopenem is a novel penem anti-infective agent that has both oral and intravenous formulations, and is being developed to treat infections caused by multidrug-resistant bacteria.

Investigators of the SURE-1 trial (NCT03354598) studied the oral formulation of this agent vs oral ciprofloxacin in the treatment of uUTIs in adult women. Specifically, they wanted to look at sulopenem’s efficacy and safety and its clinical success at test of cure (TOC) and end of treatment (EOT).

For the study, 1671 women with pyuria, bacteriuria, and signs and symptoms of uUTI were randomized to sulopenem twice daily for 5 days or ciprofloxacin twice daily for 3 days.

“Two independent primary analyses, each with a separate alpha assigned, were incorporated into the design of the study with the primary end point being overall success (combined clinical and microbiologic success) at the TOC visit,” said the investigators.

They looked at 2 cohorts: the micro-MITTTR population (patients with baseline pathogen resistant to ciprofloxacin), in which they compared sulopenem for superiority over ciprofloxacin; and the micro-MITTS population (patients with baseline pathogen susceptible to ciprofloxacin), in which they compared both agents for noninferiority.

The investigators used prespecified testing, and stated they would further test their primary efficacy end point if either superiority or noninferiority was declared in the MITTR or MITTS cohort.

“In the micro-MITTTR population, sulopenem demonstrated superiority to ciprofloxacin. In the micro-MITTS population, sulopenem was not noninferior to ciprofloxacin for the primary end point, driven primarily by the higher rate of asymptomatic bacteriuria post treatment in patients on sulopenem,” the investigators reported. “In the combined analysis of all randomized patients with an organism identified at baseline (MITTR + MITTS), sulopenem was noninferior to ciprofloxacin.”

The investigators saw some benefit in the potential application of the novel agent.

“Sulopenem was superior to ciprofloxacin for the treatment of adult women with uUTI due to quinolone nonsusceptible pathogens,” they wrote. “Sulopenem was not noninferior in the treatment of quinolone susceptible pathogens, driven by a lower rate of asymptomatic bacteriuria in patients receiving ciprofloxacin, but was noninferior in the combined population of patients.” ▲
DAV132 Protects Intestinal Microbiota From Antibiotic-Induced Dysbiosis

BY ALEXANDRA WARD, MA

The composition of the gut microbiome is easily disrupted by antibiotics, leaving the host susceptible to further infection or other disturbance of gut flora that can lead to both short- and long-term deleterious effects.

To combat antibiotic-induced dysbiosis, investigators overseas have developed a novel product, DAV132, that works as a colon-targeted adsorbent for patients treated with quinolones. Results from the phase 2 SHIELD (NCT03710694) trial were presented virtually at IDWeek 2020.

“The gut microbiota has long been known by clinicians but, until recently, it was not clear how it was intervening in the overall health of individuals. During the last decade, the multiple roles of the microbiota have been unveiled, and links with infectious diseases, immunology, oncology, and antimicrobial resistance have been uncovered,” Jean de Gunzburg, PhD, and Antoine Andremont, PhD, told Contagion® in emailed comments.

“The SHIELD study is the culmination of this quest for a safe and efficient product to spare the microbiota when patients need antibiotics,” continued de Gunzburg and Andremont, both of Da Volterra, the biotechnology company behind DAV132. “The overarching goal of the team was to demonstrate that antibiotics (lifesaving drugs) could be used in patients when needed without the detrimental impact on the gut microbiota and its consequences.”

A total of 243 patients from 23 sites, all of whom were hospitalized and receiving oral or intravenous (IV) fluoroquinolones (FQ) for the treatment or prophylaxis of febrile neutropenia, were randomized to receive 7.5 g of DAV132 orally 3 times per day at the time of their antibiotic receipt. Participants were followed for up to 51 days.

Investigators measured plasma FQ levels via liquid chromatography with tandem mass spectrometry (LC-MS/MS) at day 4 and collected fecal samples during and up to 30 days after receipt of FQ. The team assessed for free fecal FQ levels (LC-MS/MS), gut microbiome α/β diversity (16S rRNA), and resistance to colonization by Clostridioides difficile.

Median participant age was 71 years with 1 or more chronic comorbidity (95%). Quinolones received included levofloxacin (43%), ciprofloxacin (40%), or moxifloxacin (18%). The primary end point was the proportion of patients who received DAV132 and/or had FQ-related adverse events (AEs).

Participant plasma levels did not change significantly with DAV132 vs no DAV132, but fecal FQ levels decreased by more than 97% with DAV132 vs no DAV132 during FQ receipt. DAV132 also significantly protected microbiome diversity, the investigators determined, but the proportion of patients who received DAV132 and/or experienced FQ-related AEs did not differ significantly (14.8 vs 10.8%; difference of proportions, 3.9%; 95% CI, -4.7 to 12.6).

There were no reports of C difficile infection, but patients who received DAV132 with FQ maintained resistance to C difficile colonization (P = .035) compared with patients receiving FQ only. In addition, DAV132 reduced the acquisition of fecal carriage of vancomycin-resistant enterococci (P = .019).

“DAV132 was well tolerated in elderly hospitalized patients with comorbidities. It neither altered antibiotic plasma levels nor elicited changes in concomitant drugs regimens,” the investigators concluded. “Intestinal microbiota diversity was protected and resistance to colonization by [C difficile] was preserved. DAV132 is a promising, novel product to prevent antibiotic-induced intestinal dysbiosis.”

Future clinical studies will evaluate DAV132’s role in reducing the risk of C difficile infection and reducing the burden of antimicrobial resistance. They will also explore its role in reducing the severity of graft-versus-host disease in patients with hematologic malignancies receiving hematopoietic stem cell transplants, and in increasing the overall survival of patients with cancer.

“For clinicians, this means that microbiota-protective therapies such as DAV132 are 1 step closer to the patients’ beds and could provide significant clinical benefits in a variety of pathologies associated with intestinal microbiota disruption,” de Gunzburg and Andremont said.
**Mycobacterium abscessus in a Patient With Recent COVID-19 Pneumonia**

Highlights of the complications associated with the virus

BY MALIHA AHMED, DO

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**FINAL DIAGNOSIS:**

**MYCOBACTERIUM ABSCESSUS PNEUMONIA WITH COVID-19**

**HISTORY OF THE PRESENT ILLNESS**

A 40-year-old man, with a medical history of obesity, presents to an outside hospital with 2 days of shortness of breath, cough, and fevers. He recently tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 2 days before coming to the hospital. Upon his initial evaluation, he is found to be hypoxic, requiring a nonrebreather mask for oxygenation. Because of increased oxygen requirements and the elevated work of breathing, he was subsequently intubated within 24 hours of admission.

**MEDICAL HISTORY**

Obesity

**KEY MEDICATIONS**

None

**EPIDEMIOLOGICAL HISTORY**

The patient is married and has a monogamous relationship with his wife, with whom he has 5 children. Born and raised in Puerto Rico, he has been living in Philadelphia, Pennsylvania, for over 15 years. He works as a commercial truck driver, traveling within Pennsylvania and New Jersey. He has not traveled outside those states in over 6 months.

**PHYSICAL EXAMINATION**

On examination, he was intubated, on extracorporeal membrane oxygenation (ECMO), with findings significant for a diffuse morbilliform rash on the arms, legs, and abdomen. He had coarse breath sounds, which were diminished at the bases. His invasive lines and peripheral lines all appeared clean and dry, without bleeding or purulent drainage.

**STUDIES**

The patient’s comprehensive metabolic panel was significant for an elevated alanine aminotransferase (ALT) level of 84 U/L (normal range, 4-36 U/L). A complete blood count (CBC) was significant for a hemoglobin level of 8.0 g/dL (normal range, 13.2-16.6 g/dL), and a hematocrit level of 24.5% (normal range, 38.3%-48.6%). His admission chest x-ray showed multifocal airspace opacities and was read as a possible superimposed multifocal pneumonia. A CT chest scan showed diffuse patchy ground glass opacities with central cavitation, small bilateral pleural effusions, and increased supraclavicular lymphadenopathy.

**CLINICAL COURSE**

During his hospitalization the patient received a 10-day course of intravenous remdesivir, as well as convalescent plasma. He was placed in the prone position in the intensive care unit, and received dexamethasone for 5 days, as well as epoprostenol, with no improvement in his oxygenation. Sixteen days after his initial admission, the decision was made to place him on venovenous ECMO. He was canulated for ECMO and then transferred to a tertiary care center for further care. Upon arrival at the tertiary care center, he was afebrile, intubated, and sedated. His updated physical exam was significant for a diffuse morbilliform rash on the arms, chest, and abdomen.

A laboratory evaluation after transfer revealed a comprehensive metabolic panel with mild elevation in ALT level to 84 U/L, and a CBC with a hemoglobin level of 8.0 g/dL. Of note, his SARS-CoV-2 nasopharyngeal swab was negative at this time (18 days after his first positive SARS-CoV-2 test). A chest x-ray taken upon transfer showed multifocal airspace...
opacities and was read as a possible superimposed multifocal pneumonia. The primary team started empiric antibiotics, vancomycin and piperacillin-tazobactam, to cover a nosocomial pneumonia. Next, a CT chest scan showed diffuse patchy ground glass opacities with central cavi- 
Figure 1. Initial CT scan. 

tation, small bilateral pleural effusions, and increased supraclavicular lymphade- 
Figure 2. Follow up CT scan. 

The CT chest scan showed diffuse patchy ground glass opacities with central cavi- 
tation, small bilateral pleural effusions, and increased supraclavicular lymphadenopathy (Figure 1).

After 5 days of empiric antibiotics, the patient’s blood cultures remained negative and a sputum culture showed normal respira- 
Figure 1. Initial CT scan. 

tory flora. His antibiotics were discon- 
Figure 2. Follow up CT scan. 

continued, and he developed a fever, with a temperature of 100.9°F on the same day. Repeat blood, urine, and sputum cultures were checked, and an astute microbiology lab technician noted gram variable rods on his sputum gram stain.

DIAGNOSTIC PROCEDURES AND RESULTS

A sputum acid-fast bacillus (AFB) stain was performed 3 times, and each was positive for 2+ to 3+ AFB staining. Subsequently, the microbiology laboratory ran Mycobacterium tuberculosis polymerase chain reaction testing on the patient’s sputum samples, all of which were negative. Five days later there was growth from the AFB media, and samples were sent to National Jewish Health hospital for identification and sensitivity testing.

TREATMENT AND FOLLOW UP

The patient was started on empiric antimicrobials to cover rapidly growing mycobacteria. The regimen chosen was eravacycline, azithromycin, moxi- 
Figure 1. Initial CT scan. 

floxacin, and imipenem. He eventually switched to imipenem, amikacin, and 
Figure 2. Follow up CT scan. 

clarithromycin. People with cystic fibrosis have decreased 
affection of their T cells.3

Thus, it is not surprising that patients 
Figure 1. Initial CT scan. 

with no other medical history should become infected with a nontuberculous mycobacterium organism after a significant insult to their lymphocytes. M abscessus itself is an interesting organism. It is part of the rapidly growing mycobacteria groups and classified as such because it produced mature growth on media places within 7 days.4 It is also known to contain the erm gene, which conveys resistance to macrolides.4 Though the gene is not always active, it must be taken into consideration when choosing empiric therapy. For this reason, multi- 
Figure 2. Follow up CT scan. 

drug therapy is used.

High-level resistance was seen in the patient’s case, and what is more surprising is how the patient recovered after being on inadequate antimicrobial therapy. It implies that the patient’s recovered immune system was more responsible for his improvement than the antimicrobials he was taking. This case highlights the gaps in our understanding of the types of opportunistic infections that may occur as a result of COVID-19 infections. As time goes on, these gaps will start to fill, and hopefully allow medical practitioners to be better equipped to treat this complicated disease.

Despite this, the patient had returned 
Figure 1. Initial CT scan. 

to his normal baseline, and was able to go back to work just 2 months after his hospitalization.

DISCUSSION

This case highlights the possible complications associated with coronavirus disease 2019 (COVID-19) infection, outside the immediate effects of the virus itself. It is now known that both CD8+ and CD4+ cells decrease with severe disease.1 This depression of the immune system leaves patients vulnerable to the complications associated with T-cell lymphopenia. Coincidentally, the degree of lymphopenia is directly correlated with the severity of disease.1 There are several theories as to the cause of T-cell lymphopenia. One theory is that the massive cytokine release of tumor necrosis factor alpha (TNF-α) and interleukin-6 leads to T-cell apoptosis, whereas another proposes that SARS-CoV-2 infects the T cell itself and causes cell death.2 Another still is that the disease causes T-cell exhaustion, which leads to dysfunctional cells.2 The unique predicament of having COVID-19 was what left this particular patient so susceptible to the type of secondary infection he developed.

M abscessus typically affects people 
Figure 1. Initial CT scan. 

who was resistant to both imipenem and clarithromycin. People with cystic fibrosis or elderly people.

M. Lymphopenia during the COVID-19 infection: what it shows and what can be learned. Immunol Lett. 2020; 
Figure 2. Follow up CT scan. 


References

What is the power of the microbiome?

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

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