**ID Week 2018**

**Infectious Diseases and Transplantation: A Look Ahead**

A look at the infectious disease risks posed by transplantation and what the future might hold indicates that new diagnostics, immunotherapies, and transplants are on the horizon.

Kimberley Hanson, MD, MHS, University of Utah School of Medicine, Salt Lake City, provided an overview of recent diagnostic innovations that are, or will be, clinically applicable in transplantation. Progress beyond the growth-based detection of bacteria and viruses to the direct detection based on DNA or RNA is revolutionizing infectious disease scrutiny prior to transplantation. Highly multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) allows for the detection of microorganisms directly from tissue destined for transplantation. The molecular approach can also rapidly determine antimicrobial

(continued on page 24)

**Addition of Fosfomycin Improves MRSA Bactemia Outcomes**

Results of a phase 3 clinical trial indicate that the combination of daptomycin and fosfomycin was more effective than daptomycin alone for the treatment of methicillin-resistant Staphylococcus aureus (MRSA).

The combination treatment has demonstrated synergistic and bactericidal effects in animal models of MRSA, but until now, data on humans were lacking.

“The aim of the study was to test the hypothesis that [a] high-dose of daptomycin combined with fosfomycin can achieve a better response than therapy with a high-dose

(continued on page 25)

**HIV/AIDS**

**Ibalizumab Effective for Multidrug-Resistant HIV-1 Infection**

By Sofia Kuriakose, PharmD, BCPS-AQ ID

I n March 2018, the US Food and Drug Administration (FDA) approved ibalizumab (Trogarzo) for the treatment of multidrug-resistant (MDR) HIV-1 infection in heavily treatment-experienced adults failing their current antiretroviral (ART) regimen.

This humanized IgG4 monoclonal antibody is a postattachment inhibitor and represents a new class of antiretroviral therapy (ART). The last time a novel class of medication for HIV treatment

(continued on page 12)

**HIV Glasgow 2018**

**LATTE-2 Results Are Favorable at 160 Weeks**

ViV Healthcare announced new favorable results for the phase 2B LATTE-2 study of their long-acting 2-drug injectable regimen for HIV. These findings indicate the combination drug maintained high rates of virological response, long-term durability of the response, and good overall tolerability at 160 weeks.

LATTE-2 is a multicenter, parallel-group, open-label study of the long-acting 2-drug injectable regimen of cabotegravir and rilpivirine (Edurant) in treatment-naive adults with HIV. The new data presented at the

(continued on page 26)

**FLAIR Study Meets Primary Endpoint in Virally Suppressed Adults**

The phase 3 FLAIR study met its primary endpoint of showing similar efficacy of an investigational monthly injected 2-drug regimen (2DR) compared with a daily, oral 3-drug regimen in virally suppressed adults with HIV.

“The FLAIR data provide further evidence that a long-acting, injectable 2DR of cabotegravir and rilpivirine may offer an alternative to daily oral therapy for people who have previously achieved viral suppression,” John C. Pottage Jr, MD, chief scientific and medical

(continued on page 26)
Lessons From a Year Full of Infectious Disease Firsts

As I approach the terminus of my first full year as Contagion’s editor-in-chief, the natural urge to reflect is kicking in. There’s no doubt that 2018 was a year of interesting developments in the infectious diseases space.

In drug development, we saw the approval of 4 new antibacterial agents, a novel influenza medication, new HIV therapies and combinations, and even new medications for smallpox, malaria, and river blindness. Three of the 4 antibacterials are systemically active against multi-drug-resistant organisms—although none are specifically approved for those pathogens.

Our armamentarium against resistant infections continues to grow; however, not all the news is positive. In recent weeks, both Achaogen and Melinta have announced layoffs because of poor sales of their new antimicrobial agents. Our “push” incentives1 have successfully developed drugs that are doing poorly in the market, and something must change, lest we let development slow to a crawl during a time when we need it most.

Viral infections also put their telltale insidious nature on display once again this year. Despite the continuing hard work of so many scientists and physicians, the Ebola virus launched back into the headlines. Although an effective vaccine is available for compassionate use, the outbreak in the war-ravaged Democratic Republic of Congo has escalated to become the second largest in history.2 Closer to home, we learned that the 2017-2018 influenza season brought increased mortality compared with recent years.3 The US Centers for Disease Control and Prevention reported an estimated 80,000 deaths, which is higher than any flu season in decades.2 More recently, cases of acute flaccid myelitis that are likely related to viral infections continue to be reported (see page 16).

As infectious diseases take their toll on humanity, it’s our duty as infectious disease practitioners to identify new opportunities for advancement. Although recently reported increased estimates of the numbers of deaths from resistant infections look bleak,4 it is likely to lead to more mainstream and scientific attention placed on this challenge that might lead to better resources and improved understanding. Antimicrobial stewardship programs continue to mature in the United States and are beginning to concentrate their focus on areas that need it most, such as outpatient practice and long-term care facilities.

Our discipline is one that continues to evolve and, as such, keeps us in a state of constant vigilance. That’s exactly what drew me to infectious disease practice, and I am proud to share that responsibility with you every day.

Until next year, continue to look for the latest infectious diseases news on our website and social media channels, (@Contagion_Live on Twitter and ContagionLive on Facebook). I wish you fulfillment and happiness in the year to come.

Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS
Editor-in-Chief
Contagion®
FEATURE

Ibalizumab Effective for Multidrug-Resistant HIV-1 Infection

This orphan drug is for patients with limited antiretroviral treatment options.

BY SAFIA KURIKOSO, PHARMD, BCPS-AQ ID

IN THE LITERATURE

6 Partial Oral Treatment of Infective Endocarditis Can Be Effective in Selected Patients: Review of the POET Trial

BY ANDREW J. HALE, MD, AND DANIELA DIMARCO, MD

7 High-Dose Daptomycin Use for Enterococcal Bacteremias: MIC Matters

BY TIFFANY LEE, PHARMD

MEDICAL WORLD NEWS

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

INSIGHTS

22 The Impact of Social Media on Antimicrobial Stewardship Programs: Background on Management of Drug-Resistant Bacterial Infections

BY GINA BATTAGLIA, PHD

MEETING COVERAGE


CASE STUDY

28 Cryptosporidium: A Potentially Fatal Cause of Diarrhea in a Heart Transplant Recipient

Expanding the differential for diarrhea beyond Clostridium difficile.

BY ANNE BORJA, MD; ANDREW LEE, MD; BENJAMIN BLUEN, MD; SHELLEY HANKINS, MD; DONG HEUN LEE, MD

STEWARDSHIP & PREVENTION

20 A Look Into the Antimicrobial Stewardship Collaborative of South Carolina

Providers in other states can learn from this multiorganization collaborative that aims to improve antimicrobial utilization and prevent the emergence of antimicrobial resistance across South Carolina.

BY HANA RAC, PHARMD
**Orbactiv® (oritavancin) for injection**

Single-dose ORBACTIV® is an alternative to a multi-dose vancomycin course of therapy for acute bacterial skin and skin structure infections for susceptible indicated gram-positive infections.1,2*

**Efficacy profile for single-dose ORBACTIV® (oritavancin) established in 978 patients1,2**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>ORB N=978</th>
<th>VAN N=981</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response at 48–72 hours (primary endpoint)§</td>
<td>81.2% (794)</td>
<td>80.9% (794)</td>
</tr>
<tr>
<td>Clinical success at 14–24 days (secondary endpoint)¶</td>
<td>81.2% (794)</td>
<td>80.2% (787)</td>
</tr>
</tbody>
</table>

* Early clinical response defined as a composite of the cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibiotic drug at 48–72 hours.
* Clinical evaluations were also performed at days 7–10 or the day the patient stopped study drug (SOC).
* Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms at post-therapy evaluation at day 14–24 and no further treatment with antibiotics was needed.

** importante safety information**

**Contraindications**

Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after ORBACTIV® administration because the activated partial thromboplastin time (aPTT) test results are expected to remain falsely elevated for approximately 120 hours (5 days) after ORBACTIV® administration.

ORBACTIV® is contraindicated in patients with known hypersensitivity to ORBACTIV®.

**Warnings and Precautions**

Coagulation test interference: ORBACTIV® has been shown to artificially prolong aPTT for up to 120 hours, and may prolong PT and INR for up to 12 hours, ACT for up to 24 hours, and D-dimer for up to 72 hours.

Hypersensitivity reactions have been reported with the use of antibacterial agents including ORBACTIV®. Discontinue infusion if signs of acute hypersensitivity occur. Monitor closely patients with known hypersensitivity to glycopeptides.

Infusion-related reactions have been reported. Slow the rate or interrupt infusion if infusion reaction develops.

*Clostridium difficile*-associated colitis: Evaluate patients if diarrhea occurs. Concomitant warfarin use: Patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin.

Osteomyelitis: Institute appropriate alternate antibacterial therapy in patients with confirmed or suspected osteomyelitis. Prescribing ORBACTIV® in the absence of a proven or strongly suspected bacteriological infection is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

**Adverse Reactions**

The most common adverse reactions (≥3%) in patients treated with ORBACTIV® were headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea.

**References:**


Learn more about single-dose ORBACTIV® please visit: www.ORBACTIV.com

Please see following page for Brief Summary of ORBACTIV® Prescribing Information.
**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Please see package insert for full Prescribing Information.

**1. INDICATIONS AND USAGE**

**1.1 Acute Bacterial Skin and Skin Structure Infections**
ORBACTIV® (ortovancin) is for injection for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillin- susceptible and methicillin-resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group (includes S. anginosus, S. intermedius, and S. constellatus), and Enterococcus faecalis (vancomycin-susceptible isolates only).

**1.2 Usage**
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORBACTIV® and other antibacterial drugs, ORBACTIV® should be used only to treat 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 empirical selection of therapy.

**4. CONTRAINDICATIONS**

**4.1 Intravenous Unfractionated Heparin Sodium**
Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after ORBACTIV® administration because the activated partial thromboplastin time (aPTT) test results may remain falsely elevated for up to 120 hours (5 days) after ORBACTIV® administration [see Warnings and Precautions (5.3) and Drug Interactions (7.2)].

**4.2 Hypersensitivity**
ORBACTIV® is contraindicated in patients with known hypersensitivity to ORBACTIV®.

**5. WARNINGS AND PRECAUTIONS**

**5.1 Coagulation Test Interference**
ORBACTIV® has been shown to artificially prolong aPTT for up to 120 hours, PT and INR for up to 12 hours, and activated clotting time (ACT) for up to 24 hours following administration of a single 1200 mg dose by binding to and preventing action of the phospholipid reagents commonly used in laboratory coagulation tests. ORBACTIV® has also been shown to elevate D-dimer concentrations up to 72 hours after ORBACTIV® administration.

For patients who require aPTT monitoring within 120 hours of ORBACTIV® dosing, a non- phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered [see Contraindications (4.1) and Drug Interactions (7.2)].

ORBACTIV® has no effect on the coagulation system in vivo.

**5.2 Hypersensitivity**
Serious hypersensitivity reactions have been reported with the use of ORBACTIV®. If an acute hypersensitivity reaction occurs during ORBACTIV® infusion, discontinue ORBACTIV® immediately and institute appropriate supportive care. Before using ORBACTIV®, inquire carefully about previous hypersensitivity reactions to glycopeptides. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during ORBACTIV® infusion in patients with a history of glycopeptide allergy.

In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in ORBACTIV®-treated patients was 1.2 days and the median duration of these reactions was 2.4 days [see Adverse Reactions (6.3)].

**5.3. Infusion Related Reactions**
Infusion related reactions have been reported with ORBACTIV® including pruritus, urticaria or flushing. If reactions do occur, consider slowing or interrupting ORBACTIV® infusion [see Adverse Reactions (6.3)].

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

C. difficile produces toxins A and B which contribute to the development of CDAD. Prolonged use of antibacterial drugs, particularly in patients with narrow host-range antibacterial drugs, can alter the normal host flora of the colon, and may permit overgrowth of C. difficile.

If CDAD is suspected or confirmed, antibiotic use directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

**5.5 Potential Risk of Bleeding with Concomitant Use of Warfarin**
ORBACTIV® has been shown to artificially prolong prothrombin time (PT) and international normalized ratio (INR) for up to 12 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 12 hours after an ORBACTIV® dose [see Warnings and Precautions (5.3)].

Patient's should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin [see Drug Interactions (7.3)].

**5.6 Osteomyelitis**
In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the ORBACTIV®-treated arm than in the vancomycin-treated arm. Monitor patients for signs and symptoms of osteomyelitis. If osteomyelitis is suspected or diagnosed, institute appropriate alternate antibacterial therapy [see Adverse Reactions (6.2)].

**5.7 Development of Drug Resistant Bacteria**
Prescribing ORBACTIV® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Patient Counseling Information (17)].

**6. ADVERSE REACTIONS**
The following adverse reactions are also discussed in the Warnings and Precautions section of labeling:
- **Hypersensitivity Reactions** [see Warnings and Precautions (5.2)]
- **Infusion Related Reactions** [see Warnings and Precautions (5.3)]
- **Clostridium difficile-associated Diarrhea** [see Warnings and Precautions (5.4)]
- **Osteomyelitis** [see Warnings and Precautions (5.6)]

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

ORBACTIV® has been evaluated in two, double-blind, controlled ABSSSI clinical trials, which included 976 adult patients treated with a single 1200 mg intravenous dose of ORBACTIV® and 983 patients treated with intravenous vancomycin for 7 to 10 days. The median age of patients treated with ORBACTIV® was 45.6 years, ranging between 18 and 89 years of age with 8.8% ≥65 years of age. Patients treated with ORBACTIV® were predominantly male (65.4%), 64.4% were Caucasian, 5.8% were African American, and 26.1% were Asian. Safety was evaluated for up to 60 days after dosing.

In the pooled ABSSSI clinical trials, serious adverse reactions were reported in 5/796 (0.6%) patients receiving ORBACTIV® and 5/793 (0.6%) patients treated with vancomycin. The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/796 (1.4%) in ORBACTIV® and 12/793 (1.5%) in the vancomycin arms, respectively.

The most commonly reported adverse reactions (>3%) in patients receiving a single 1200 mg dose of ORBACTIV® in the pooled ABSSSI clinical trials were: headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea.

In the pooled ABSSSI clinical trials, ORBACTIV® was discontinued due to adverse reactions in 36/796 (3.7%) of patients; the most common reported reactions leading to discontinuation were cellulitis (4/796, 0.4%) and osteomyelitis (3/796, 0.3%).

Table 1 provides selected adverse reactions occurring in ≥15% of patients receiving ORBACTIV® in the pooled ABSSSI clinical trials. There were 540 (55.3%) patients in the ORBACTIV® arm and 559 (56.9%) patients in the vancomycin arm, who reported a adverse reaction.
7.1 Effect of ORBACTIV® on CYP Substrates

A screening drug-drug interactions study indicated that ORBACTIV® is a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or inducer (CYP3A4 and CYP2D6) of several CYP isoforms [see Clinical Pharmacology (12.3)]. A drug-drug interaction study that assessed the interaction potential of a single 1200 mg dose of ORBACTIV® on the pharmacokinetics of S-warfarin (CYP2C9 probe substrate) showed no effect of ORBACTIV® on S-warfarin Cmax or AUC.

Avoid administering ORBACTIV® concomitantly with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes, as co-administration may increase or decrease concentrations of the narrow therapeutic range drug. Patients should be closely monitored for signs of toxicity or lack of efficacy if they have been given ORBACTIV® while on a potentially affected compound (e.g. patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin).

7.2 Drug-Laboratory Test Interactions

ORBACTIV® may artificially prolong certain laboratory coagulation tests (see Table 2) by binding to and preventing the action of the phospholipid-rich cofactors which activate coagulation in commonly used laboratory coagulation tests [see Contraindications (4.1) and Warnings and Precautions (5.1, 5.3)]. For patients who require monitoring of anticoagulation effect within the indicated time after ORBACTIV® dosing, a non phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered.

ORBACTIV® does not interfere with coagulation in vivo. In addition, ORBACTIV® does not affect tests that are used for diagnosis of Heparin Induced Thrombocytopenia (HIT).

Table 2: Coagulation Tests Affected and Unaffected by ORBACTIV®

<table>
<thead>
<tr>
<th>Elevated by ORBACTIV®</th>
<th>Unaffected by ORBACTIV®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time (PT) up to 12 hours</td>
<td>Chromogenic Factor Xa Assay</td>
</tr>
<tr>
<td>International normalized ratio (INR) up to 12 hours</td>
<td>Thrombin Time (TT)</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT) up to 120 hours</td>
<td></td>
</tr>
<tr>
<td>Activated clotting time (ACT) up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Silica clot time (SCT) up to 18 hours</td>
<td></td>
</tr>
<tr>
<td>Dilute Russell's viper venom time (DRVVT) up to 72 hours</td>
<td></td>
</tr>
<tr>
<td>D-dimer up to 72 hours</td>
<td></td>
</tr>
</tbody>
</table>

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to oritavancin at the highest concentrations administered, 30 mg/kg/day and 15 mg/kg/day, respectively. Those daily doses would be equivalent to a human dose of 300 mg, or 25% of the single clinical dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicology studies.

There are no adequate and well-controlled trials in pregnant women. ORBACTIV® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.4 Pediatric Use

Safety and effectiveness of ORBACTIV® in pediatric patients (younger than 18 years of age) has not been studied.

8.5 Geriatric Use

The pooled Phase 3 ABSSSI clinical trials of ORBACTIV® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate renal impairment [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]. The pharmacokinetics of ORBACTIV® in severe renal impairment have not been evaluated. ORBACTIV® is not removed from blood by hemodialysis.

8.7 Hepatic Impairment

No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of ORBACTIV® in patients with severe hepatic insufficiency has not been studied [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

10. OVERDOSAGE

In the ORBACTIV® clinical program there was no incidence of accidental overdose of ORBACTIV®. Based on an in vitro hemodialysis study, ORBACTIV® is unlikely to be removed from blood by hemodialysis. In the event of overdose, supportive measures should be taken.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been conducted to determine the carcinogenic potential of oritavancin.

No mutagenic or clastogenic potential of oritavancin was found in a battery of tests, including an Ames assay, in vitro chromosome aberration assay in Chinese hamster ovary cells, in vitro forward mutation assay in mouse lymphoma cells and an in vivo mouse micronucleus assay.

Oritavancin did not affect the fertility or reproductive performance of male rats (exposed to daily doses up to 30 mg/kg for at least 4 weeks) and female rats (exposed to daily doses up to 30 mg/kg for at least 2 weeks prior to mating). Those daily doses would be equivalent to a human dose of 300 mg, or 25% of clinical dose. Higher doses were not evaluated in nonclinical fertility studies.

This Brief Summary is based on the ORBACTIV® Prescribing Information, Rev. 08/2017.

Rx only

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The Medicines Company
8 Sylvan Way
 Parsippany, NJ 07054 USA

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Partial Oral Treatment of Infective Endocarditis Can Be Effective in Selected Patients: Review of the POET Trial

BY ANDREW J. HALE, MD, AND DANIELA DIMARCO, MD

The opioid crisis has altered the epidemiology of infective endocarditis (IE) dramatically in recent years, now affecting more young patients identified as persons who inject drugs (PWID). Traditionally, treatment for IE in the United States adheres to the American Heart Association 2015 guidelines, which recommend up to 6 weeks of intravenous (IV) antibiotics. Although older literature suggested oral therapy was effective for right-sided IE, such an approach is not currently standard. However, the partial oral treatment of IE (POET) trial, conducted in Denmark, is a much-needed addition to the endocarditis literature. The authors performed a non-inferiority comparative trial between patients with IE treated with IV therapy (control arm) to those switched to oral therapy after an initial IV course (experimental arm). Eligible patients were 18 years or older, in stable condition, already on IV antibiotics, had left-sided IE with Streptococci species, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative Staphylococci species, and no absolute indications for valve replacement. IV antibiotic choice was in accordance with European Society of Cardiology guidelines. Oral regimens consisted of 2 antibiotics from different drug classes, guided by bioavailability and minimum inhibitory concentration (MIC) data (Table). The primary composite outcome was all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen within 6 months.

From 2011 to 2017, 400 patients were enrolled and randomized in the study. Mean age was 67 years, 77% of participants were men, 22 (6%) had prosthetic valve endocarditis, 152 (38%) had valve replacement prior to randomization, and 35 (9%) had implanted cardiac devices. Only 5 (1.2%) participants were identified as PWID, and 0 patients had methicillin-resistant Staphylococcus aureus (MRSA). Patients in the experimental arm received a median 17 days of IV antibiotics prior to oral transition. The primary outcome occurred in 24 (12.1%) patients in the IV group and 18 (9.0%) in the oral group, thus the criterion for noninferiority was met, with no significant differences in adverse events between arms.

For patients with IE who meet the POET inclusion criteria, oral step-down therapy appeared to be noninferior to the traditional “all-IV” pathway. It is important to keep in mind patient-specific issues that may interfere with oral drug-absorption. Notably, the POET trial was lacking in key populations: the data represent no patients with MRSA, and only 5 PWID, thus it is uncertain if the POET trial is the answer to the dilemma posed by more PWID with IE requiring long hospitalizations to complete IV antibiotic courses.

By itself, the POET trial should not fundamentally change our current approach to IE treatment. However, as more data emerges, treatment guidelines will evolve and may one day support a less resource-intensive but equally efficacious approach for these patients. For now, POET reassures us that for patients doing well on standard therapy who are poor candidates to continue IV treatment, step-down to oral therapy is a reasonable choice.

References available at ContagionLive.com.

Table: Oral Antibiotic Regimens Recommended in the POET Trial

<table>
<thead>
<tr>
<th>PENICILLIN AND METHICILLIN SUSCEPTIBLE STAPHYLOCOCCUS AUREUS AND COAGULASE-NEGATIVE STAPHYLOCOCCI</th>
<th>METHICILLIN-RESISTANT STAPHYLOCOCCI</th>
<th>ENTEROCOCCUS FAECALIS</th>
<th>STREPTOCOCCI WITH PENICILLIN MIC &lt; 1MG/L</th>
<th>STREPTOCOCCI WITH PENICILLIN MIC &gt; 1MG/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin 1g 4x/day and fusidic acid 0.75g 2x/day</td>
<td>Linezolid 600mg 2x/day and fusidic acid 0.75g 2x/day</td>
<td>Amoxicillin 1g 4x/day and rifampin 600mg 2x/day</td>
<td>Linezolid 600mg 2x/day and rifampin 600mg 2x/day</td>
<td>Moxifloxacin 400mg 1x/day and clindamycin 600mg 3x/day</td>
</tr>
<tr>
<td>Amoxicillin 1g 4x/day and rifampin 600mg 2x/day</td>
<td>Linezolid 600mg 2x/day and rifampin 600mg 2x/day</td>
<td>Amoxicillin 1g 4x/day and moxifloxacin 400mg 1x/day</td>
<td>Linezolid 600mg 2x/day and rifampin 600mg 2x/day</td>
<td>Moxifloxacin 400mg 1x/day and clindamycin 600mg 3x/day</td>
</tr>
<tr>
<td>Linezolid 600mg 2x/day and fusidic acid 0.75g 2x/day</td>
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<td>Linezolid 600mg 2x/day and rifampin 600mg 2x/day</td>
<td>Linezolid 600mg 2x/day and moxifloxacin 400mg 1x/day</td>
<td>Moxifloxacin 400mg 1x/day and rifampin 600mg 2x/day</td>
</tr>
<tr>
<td>Linezolid 600mg 2x/day and rifampin 600mg 2x/day</td>
<td>Linezolid 600mg 2x/day and moxifloxacin 400mg 1x/day</td>
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</table>

MIC indicates minimum inhibitory concentration.
Daptomycin is an agent increasingly being utilized to combat gram-positive organisms, particularly for the treatment of vancomycin-resistant enterococcal bacteremia. The US Food and Drug Administration (FDA)-approved dose for Staphylococcus aureus bacteremia is 6 mg/kg.1 However, epidemiological studies show lower S. aureus minimal inhibitory concentration (MIC) distributions compared with Enterococcus spp.,2 posing a theoretical concern for inadequate dosing for enterococcal bacteremia. Although some evidence exists for more aggressive daptomycin dosing in enterococcal bacteremia, widespread use of higher doses is currently limited by concerns for toxicity and insufficient data to guide dosing. Avery and colleagues sought to investigate optimal daptomycin pharmacodynamics using the free drug area under the concentration time cure (fAUC) to MIC ratio (fAUC/MIC) relative to clinical outcomes and dosing schemes.6

This meta-analysis included 7 observational studies clinically evaluating patients treated with daptomycin for enterococcal bacteremia. Patients were excluded if they received less than 72 hours of daptomycin, received concomitant antibiotics with activity against enterococci, or were placed on continuous renal replacement therapy. The primary outcome was 30-day survival and its association with a daptomycin fAUC/MIC threshold.

The group studies comprised 114 patients receiving daptomycin monotherapy. Results were analyzed for the group as a whole and a subgroup of lower acuity disease. Overall, patients were 58% male and had a mean age of 55 years. The source of bacteremia was largely catheter related (47.4%) or from the gastrointestinal tract (17.5%). A significant proportion of patients were immunocompromised (79.8%). Most enterococcal strains were Enterococcus faecium (90.4%) with a median daptomycin MIC of 2 mg/L. Daptomycin was prescribed, on average, at 7.4 mg/kg.

At 30 days, 67 patients (58.8%) were alive. Following calculation of individual patient pharmacokinetics and application to pharmacodynamic models, the authors identified that a fAUC/MIC threshold of 27.43 was strongly associated with 30-day survival (Table). Although this threshold did not reach statistical significance in the overall group, patients in the low-acuity cohort were significantly more likely to meet a fAUC/MIC > 27.43 (68.9% vs 37.5%, P = .006). Monte Carlo simulations were performed to determine the probability of target attainment (PTA) with various daptomycin dosing regimens.

The FDA-approved dosage of 6 mg/kg/day had a PTA more than 90% only for enterococcal MICs of 1 mg/L or lower. For enterococcal MICs of 2 mg/L or higher, a daptomycin dosage of 12 mg/kg/day was required to achieve a PTA greater than 90%. The authors concluded that patients with enterococcal bacteremias treated with daptomycin monotherapy should be dosed aggressively to reach this pharmacodynamic threshold and improve survival rates. Because of poor PTA with daptomycin 6 mg/kg, the authors suggest re-evaluation of current breakpoints and the addition of a susceptible-dose dependent category for enterococcal isolates with MIC of 2 mg/L for daptomycin 12 mg/kg.

Currently, the Clinical and Laboratory Standards Institute considers all Enterococcus spp with a daptomycin MIC less than 4 mg/L as susceptible.7 However, based on this study’s findings, isolates with MICs of 2 to 4 mg/L, while technically susceptible, clearly require higher daptomycin doses to optimize their bactericidal activity. Until these breakpoints are reassessed, results of this study implore clinicians to pay attention to MIC values when treating enterococcal bacteremias and use higher daptomycin doses as appropriate, with close monitoring for toxicities. •

References available at ContagionLive.com.
Rapid HIV Rebound Found in Semen After Antiretroviral Treatment Interruption
By Nicola M. Parry, BVSC, MRCVS, MSC, DACVP, FRSPH, ELS

Combination antiretroviral treatment (cART) in patients with HIV does not prevent viral load rebound in semen after the treatment is paused, according to the results of a new study published in the journal AIDS.

Recent study results show that short pauses in antiretroviral treatment (ART) in patients with HIV do not result in a long-term increase in the size of the HIV reservoir or cause irreversible damage to the immune system. However, the effect of this treatment pause on HIV replication in the genital tract remains unknown.

With this in mind, investigators aimed to compare the timing of HIV rebound and its level in blood and seminal plasma after patients discontinued ART. They also sought to characterize the rebound HIV populations.

They performed a substudy in men who were infected with HIV-1 and who were enrolled in the VRI02/ANRS149-LIGHT therapeutic vaccine trial. Ten men discontinued ART for 12 weeks, and then provided paired blood and semen samples both before (weeks 32 or 36) and during (weeks 38, 40, 42, 44, and 48) the treatment pause.

The investigators found that HIV-RNA rebounded in the blood plasma and seminal plasma of all 10 men after analytic treatment interruption (ATI). The virus rebounded in blood plasma as early as week 38 in 8 men and in seminal plasma between week 38 and week 40 in 8 men.

“This finding supports evidence of a very high risk of sexual transmission during self-driven cART breaks or during ATI stemming from clinical trials,” the authors emphasized. “Thus, prevention strategies for HIV-negative partners of HIV-infected participants undergoing ATI need reinforcement.”

29 States Are Affected by Multidrug-Resistant Salmonella Outbreak Linked With Chicken
By Michaela Fleming

The US Centers for Disease Control and Prevention (CDC) is working alongside health officials in 29 states to investigate an outbreak of multidrug-resistant Salmonella infections. As of October 15, 2018, 92 cases have been reported across 29 states, with the onset of infection occurring between January 19, 2018, and September 9, 2018.

Those affected range in age from younger than 1 year to 105 years, with a median age of 36. Of the 62 individuals for whom there were available information, there have been 21 hospitalizations with no deaths reported thus far.

Health officials interviewed 54 individuals about food consumption and exposure in the week prior to falling ill, and 48 individuals reported preparing or eating chicken products that were purchased raw, such as ground chicken, chicken pieces, and whole chickens. The outbreak strain, Salmonella infantis, was detected in products from 58 facilities, and whole-genome sequencing indicated that the strain in the human samples was closely related to the strain from the products at the processing facilities.

Whole genome sequencing analysis indicated that 43 ill individuals and 68 product or environmental samples predicted resistance to antibiotics, including “ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, fosfomycin, gentamicin, hygromycin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole,” according to the CDC.

This is an ongoing investigation. Be sure to check the Contagion® Outbreak Monitor, contagionlive.com/link/1793, for updates as they become available.

Antivirals to Treat Herpes Infection May Decrease Risk of Dementia
By Brandon May

According to a review of a lifetime of research literature, herpes simplex virus (HSV) type 1 is associated with an increased risk of Alzheimer disease. Despite this increased risk, new data show that antiviral drug regimens to treat the infection may substantially reduce the risk of senile dementia in patients with severe herpes infections.

“The most important finding is that antiviral antivirals are protective against the development of Alzheimer disease,” Ruth F. Itzhaki, MSc, PhD, of the University of Manchester, Manchester, England, said in an interview with Contagion®.

According to the recent data, the majority of the population is infected with HSV-1 by the time they reach age 70. In middle age, the virus travels to the brain where it remains latent, followed by intermittent reactivation and major inflammation in brain tissue.

Research has shown that the risk of senile dementia was 2.56-fold greater in patients with HSV-1 and HSV-2 compared with healthy controls during a 10-year period. An approximate 10-fold reduction in senile dementia risk was found in another study of patients who were treated with several different antivirals, either as monotherapy or combination therapy. Acyclovir, for instance, inhibits viral DNA replication and is frequently used intravenously against HSV-1.

“Clearly, the types of antiviral which might be used for treating Alzheimer disease should be carefully chosen, especially if combined with an anti-inflammatory agent, as well as the duration of treatment and stage at which their usage would most effective,” Dr. Itzhaki said. “Even if the effects were merely a delay in onset of the disease, this would still be enormously beneficial for patients, careers, and the economy.”
FDA Approves Baloxavir Marboxil to Treat Uncomplicated Influenza

By Contagion® Editorial Staff

In October 2018, the US Food and Drug Administration approved baloxavir marboxil (Xofluza), for the treatment of acute uncomplicated influenza. It is the first new antiviral flu treatment with a novel mechanism of action in nearly 20 years.

Baloxavir marboxil targets the influenza virus by inhibiting the cap-dependent endonuclease protein that is essential for the replication of the virus. The single-dose oral medication is indicated for patients 12 years and older who have been experiencing flu symptoms for less than 48 hours.

In the phase 3 CAPSTONE 1 trial, baloxavir marboxil reduced the duration of flu symptoms by more than 1 day (54 hours vs 80 hours; P<.001). Compared with oseltamivir, the duration of symptoms was estimated to be a median time of 54 hours for both therapies. The most common adverse reactions in patients taking baloxavir marboxil included diarrhea (3%) and bronchitis (2.6%).

The drug has been developed in Japan by Shionogi, but will be sold in the United States and in other countries by Genentech.

Antiretroviral Therapy Initiation Leads to Short-Term Spike in Viral Shedding Among Patients With HIV/HSV-2 Coinfection

By Jared Kaltwasser

Patients with HIV and herpes simplex virus (HSV) coinfection see an increase in herpes viral shedding when they begin antiretroviral therapy (ART), according to new research, although, the effect appears to be short-lived.

To gain a better understanding of how and when worsening of a herpes infection occurs, and whether it is sustained long term, investigators tracked 45 patients who were HIV positive and also infected with HSV-2, some of whom were on ART. The majority, 38 patients, were men. Patients conducted daily genital swabs and tracked their symptoms, and then had follow-up visits with the investigators over up to 3 noncontiguous 60-day periods.

A total of 6425 genital swabs were taken. In patients not taking ART, shedding was detected on 19.4% of days. For patients taking ART, however, during the first 90 days after initiation of ART, genital herpes viral shedding was present 30.2% of days. After 90 days on ART, these patients experienced genital HSV shedding on 23.3% of days. The investigators found that patients on ART saw herpes viral shedding drop at an annual rate of 23%, or about 2% per month.

Security Concerns and Case Counts Rise As Ebola Outbreak Rages On

By Michaela Fleming

The Ebola outbreak in the North Kivu Province of the Democratic Republic of the Congo currently stands as the second largest outbreak of Ebola in history.

As of December 3, 2018, there have been 453 cases of Ebola in the region (405 laboratory-confirmed cases and 48 probable cases) and 268 confirmed deaths. As it stands, the global fatality ratio among confirmed cases in 59%.

The current outbreak has been wreaking havoc on the region since August 2018, and reported cases have been on the rise as violence has also spread throughout the region by armed groups. Violence in the Beni Health Zone has disrupted surveillance and prevention activities, suspending services for many days. The latest violent incidents continue to occur amidst the Ebola outbreak in Beni. Because of the increase in violent events, the US Centers for Disease Control and Prevention relocated health workers that were volunteering in violent areas, effectively pulling the workers from the areas with the most need. Although the risk of global spread remains low, travel and trade restrictions with the DRC have been implemented.
Eravacycline: The IGNITE Growth of the Tetracyclines

The synthetic novel tetracycline offers a new option for complicated intra-abdominal infections.

BY SARA ALOSAIMY, PHARMD, BCPS

The US Food and Drug Administration approved eravacycline (Xerava, Tetraphase Pharmaceuticals) in August 2018 for complicated intra-abdominal infections (cIAIs) in adults 18 years and older.1 It was investigated for urinary tract infections (UTIs), but the outcomes were not advantageous.2 Eravacycline is a synthetic novel tetracycline antibiotic, structurally similar to tigecycline (Tygacil, Wyeth Pharmaceuticals).3 It preserves activity against the 2 acquired tetracycline-specific acquired-resistance mechanisms: efflux pumps and ribosomal protection.

PHARMACOLOGY

In a similar matter to other members of the tetracycline class, eravacycline disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit. This process prevents amino acid residues from being integrated into the peptide chains.3,5 Although bacteriostatic against gram-positive bacteria, bactericidal activity had been observed against strains of *Escherichia coli* and *Klebsiella pneumoniae* in vitro.

SPECTRUM

Eravacycline established broad-spectrum antimicrobial activity against several multidrug-resistant (MDR) organisms identified by the US Center for Diseases Control and Prevention as urgent or serious threats.6,7 Examples of these include: carbapenem-resistant Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamases–producing Enterobacteriaceae, vancomycin-resistant enterococci, and MDR *Acinetobacter* and *Bacteroides fragilis*. Notably, eravacycline is inactive against *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*. Compared with tigecycline, eravacycline is at least twice more potent against gram-negative bacilli and gram-positive cocci.6,7

RESISTANCE

Because of substitution patterns that are not present in other tetracyclines, eravacycline is uniquely positioned to overcome the most common tetracycline-specific resistance mechanisms: ribosomal protection proteins (tetM) and efflux pumps (tetA, tetB, tetK).6,7 Resistance to eravacycline is thought...
to be associated with target-site modifications and upregulated intrinsic MDR efflux.

**PHARMACODYNAMICS AND PHARMACOKINETICS**

Eravacycline is at least 79% protein bound. The volume of distribution at steady state is approximately 321 liters. The elimination half-life is about 20 hours. Eravacycline is metabolized by the liver; specifically, cytochrome P450 3A4 (CYP3A4) and flavin-containing monoxygenase mediated oxidation and excreted in the urine and feces.

**DOSE AND ADMINISTRATION**

The recommended dosage for patients with normal hepatic function is 1 mg/kg every 12 hours administered as an intravenous infusion over 60 minutes. Because the drug is hepatically metabolized, it does not warrant dose adjustment in renally impaired patients. Patients with severe hepatic impairment should have their dose adjusted to 1 mg/kg every 24 hours on the second day and for the remaining duration of therapy. The dose should be calculated based on actual bodyweight for all patients, including those with a body mass index over 30 kg/m^2.

**SUPPLY AND STORAGE**

Eravacycline is supplied as a yellow-orange, preservative-free powder for reconstitution in a single-dose 50-mg/10-mL clear glass vial. Each should be kept in its original carton until usage. Vials should be stored at 2 °C to 8 °C (36 °F-46 °F) prior to reconstitution.

**DRUG INTERACTIONS AND CONTRAINDICATIONS**

Use of strong CYP3A4 inducers may decrease eravacycline exposure and potentially efficacy, therefore the dose may need to be adjusted. In addition, since tetracyclines have the potential to decrease prothrombin activity, the dose of anticoagulants should be reduced.

**ADVERSE REACTIONS, WARNINGS, AND PRECAUTIONS**

In general, eravacycline has a favorable safety profile. The most common adverse reactions are infusion-site reactions, nausea, and vomiting. Clinically significant warnings and precautions include hypersensitivity reactions and *Clostridium difficile*–associated diarrhea. Similar to other members of the tetracycline class, eravacycline can cause tooth discoloration, enamel hypoplasia, bone growth inhibition during development, azotemia, pancreatitis, and hyperphosphatemia.

**PREGNANCY AND LACTATION**

Because eravacycline is a synthetic tetracycline, it has the potential to cause tooth discoloration and bone growth inhibition during the second and third trimesters of pregnancy. Although, eravacycline is excreted in human milk, the degree of absorption is unknown.

**CLINICAL STUDIES**

Eravacycline was approved for cIAIs in adults following the IGNITE1 and IGNITE4 studies. The 2 trials were phase 3, randomized, double-blind, active controlled multicenter trials in patients with cIAIs requiring surgery or percutaneous drainage and compared eravacycline (1 mg/kg every 12 hours) with ertapenem (Invanz, Merck; 1 g every 24 hours) or meropenem (Merrem, Pfizer; 1 g every 8 hours) for 4 to 14 days. Patients who had at least 1 baseline intra-abdominal infection microorganism were included in the intent to treat (ITT) population.

The primary endpoint was clinical cure, defined as complete resolution or significant improvement of signs or symptoms at the test of cure (TOC). The clinical cure rates in the eravacycline and ertapenem groups were 86.8% and 87.6%, respectively in IGNITE1. In IGNITE4, eravacycline had cure rates of 90.8% compared with 91.2% in the meropenem group. Such difference exceeded the predetermined noninferiority margin.

Two phase 3, randomized, double-blind, active controlled multicenter trials also assessed the efficacy and safety of eravacycline in complicated UTIs: the IGNITE2 and IGNITE3 trials. In IGNITE2, eravacycline (1.5 mg/kg intravenously [IV] every 24 hours followed by 200 mg orally every 24 hours) was compared with levofloxacin (750 mg IV every 24 hours followed by 750 mg orally every 24 hours). The IGNITE3 trial compared eravacycline (1 mg/kg IV every 24 hours) to ertapenem (1 g IV every 24 hours). The coprimary efficacy endpoint was a combination of clinical cure and microbiological success in the ITT population at the end of intravenous treatment and TOC. Both trials could not demonstrate efficacy for eravacycline compared with ertapenem or levofloxacin.

**PATIENT COUNSELING**

Clinicians should ask patients about previous hypersensitivity reactions to antibacterial drugs, particularly within the tetracycline class, as serious allergic reactions may occur. Because of its effect on tooth color and bone growth, women of childbearing age should be counseled to avoid eravacycline during the second and third trimesters of pregnancy. Lactating women should be advised not to breastfeed during therapy and for 4 days after the last dose.

**PLACE IN THERAPY**

Although eravacycline may not be used as a first line treatment for cIAIs, infectious diseases experts have anticipated several clinical scenarios for which eravacycline may have a significant place in therapy. First, eravacycline may replace tigecycline due to its favorable tolerability profile including, but not limited to, side effects, drug interactions, and serum levels. Second, eravacycline can serve as a last resort for patients with MDR and multiple drug allergies, particularly carbapenems and fluoroquinolones. Third, patients who are at high risk for *C difficile* infections may benefit from the relatively safe profile for eravacycline, particularly if proven to be as safe as the other tetracyclines.

**FUTURE RESEARCH**

Even with the observed similarities between eravacycline and tigecycline, it remains unclear how the 2 would compare in terms of efficacy, resistance, and adverse effect profile in the real-world setting. It would be interesting to see if Tetraphase continues to develop oral eravacycline, particularly if this formulation would be investigated for other indications.

References available at ContagionLive.com.
Ibalizumab Effective for Multidrug-Resistant HIV-1 Infection

This orphan drug is for patients with limited antiretroviral treatment options.

BY SAFIA KURIAKOSE, PHARMD, BCPS-AQ ID

was approved by the FDA was over 10 years ago when the first integrase strand transfer inhibitor, raltegravir (Isentress), was introduced in October 2007.

Ibalizumab does not inhibit binding of HIV glycoprotein (gp) 120 to CD4 receptors. However, it binds to extracellular domain 2 of the CD4 receptors to prevent postattachment conformational changes in the CD4-HIV envelope gp-120 complex and block viral entry into the host CD4 cell. Ibalizumab does not interfere with the binding site of major histocompatibility complex class II molecules, suggesting that it does not affect CD4-dependent immunity. It is active against both CCR5 and CXCR4 tropic strains. Reduced susceptibility is possible and associated with mutations affecting a gp-120 glycosylation site.

Ibalizumab is administered as an intravenous infusion. It should be diluted in normal saline only and administered immediately. It is stable for 4 hours at room temperature or up to 24 hours when refrigerated. An initial loading dose of 2000 mg is administered over 30 minutes, with a postinfusion observation period of 1 hour. If no infusion-related reactions occur, patients then receive infusions every 2 weeks at a maintenance dose of 800 mg administered over 15 minutes, with a postinfusion observation period of 15 minutes. If a maintenance dose is missed by 3 or more days, a loading dose should be repeated as soon as possible, with maintenance dosing resuming every 2 weeks thereafter. Importantly, ibalizumab should be administered with an optimized background regimen that includes at least 1 ARV to which the patient’s virus is fully susceptible.

Ibalizumab has no reported drug–drug interactions. The most common adverse effects are diarrhea, dizziness, nausea, and rash. Immune reconstitution inflammatory syndrome has been reported. The annual whole sale acquisition cost of ibalizumab is $118,000, which does not include infusion services. A patient support program is available to help navigate insurance and coordinate care with in-network infusion centers. Patients without insurance are eligible for financial assistance. Those with commercial insurance but high copayments may be eligible for copay assistance.

Ibalizumab was given fast track, priority review, breakthrough therapy, and orphan drug designations by the FDA. Approval was granted based on a clinical trial with a...
streamlined design tailored to the relevant patient population; patients with MDR HIV-1 infection lacking treatment options to suppress HIV-1 plasma RNA to undetectable levels. Key aspects included assessment of virologic response after 7 days of ibalizumab therapy and safety assessment at 24 weeks, instead of at week 48 for each parameter, which is standard in trials conducted in treatment-naïve patients with HIV.4 TMB-301 was a phase 3, 24-week, open label, single-arm study in which ibalizumab was administered to adults with MDR HIV-1 infection. Among the inclusion criteria, participants had to have failed multiple prior ARV regimens, have an HIV-1 viral load more than 1000 copies/mL while on ART for 8 weeks or more before screening, and have documented genotypic or phenotypic resistance to at least 1 drug in at least 3 ARV classes. The study design consisted of a 7-day control period during which patients continued their failing regimen. The participants then received a loading dose of ibalizumab and then continued their failing regimen. Virologic response was assessed after 7 days; this was the functional monotherapy period. After this point, an optimized background regimen including at least 1 fully active ARV was initiated, and the patients began maintenance dosing of ibalizumab. The primary endpoint was the proportion of patients with at least 0.5 log10 decline in HIV-1 plasma RNA levels after 1 week of ibalizumab functional monotherapy. A 0.5 log10 decline in viral load is associated with reduced clinical disease progression.6

Among the 40 study participants, the median age was 53 years, 85% were male, 55% were white, and 33% were black. The median number of years since HIV diagnosis was 23. The average baseline HIV-1 viral load was 4.5 log10 copies/mL, and the average CD4 count was 150 cells per microliter. A total of 48% of participants had documented resistance to all integrase inhibitors, 53% had exhausted 3 or more classes, 35% had exhausted 4 or more classes, and 15% had exhausted all classes of FDA-approved ARVs.5 In order to fulfill criteria of having at least 1 fully active ARV as part of their optimized background regimen, 43% of patients were treated with fostemsavir, another novel ARV currently in development, which was accessed in participants through co-enrollment in another clinical trial.

In the intention-to-treat population, 83% had at least 0.5 log10 decline in HIV plasma RNA levels after 7 days of ibalizumab functional monotherapy (P<.001 compared with the control period).7 At week 25, 43% had HIV-1 viral load less than 50 copies/mL and 50% had HIV-1 viral load less than 200 copies/mL. The median reduction in HIV-1 viral load was 1.8 log10 copies/mL. The average increase in CD4 count was 62 cells per microliter. Ten patients experienced virologic failure or rebound, 9 of whom had reduced susceptibility to ibalizumab compared with baseline. The most common adverse events were diarrhea, nausea, fatigue, pyrexia, rash, and dizziness. There were no reported infusion-site reactions. One patient developed immune reconstitution inflammatory syndrome associated with progressive multifocal leukoencephalopathy. Four patients died during the course of the study due to causes considered unrelated to the study drug (eg, Kaposi’s sarcoma, hepatic failure, lymphoma, and end-stage AIDS).8

Additional data on ibalizumab safety and efficacy at week 48 (expanded access protocol; TMB-311) was presented at IDWeek 2017.9 Postmarketing surveillance will be important for gathering additional information on the safety and effectiveness of ibalizumab.9

In clinical settings, a few practical points should be considered when initiating ibalizumab treatment. Patients should understand that adherence to their background regimen of other, usually oral ARVs is still important, and reduced susceptibility to ibalizumab is possible. The potential impact of the treatment schedule on the patient’s work or travel plans, among other inconveniences, should be discussed in advance. Ibalizumab treatment requires a significant commitment and may be lifelong, at least until new ARVs become available that have activity against MDR HIV-1 strains and can be administered more easily. Pharmacies and infusion centers should be aware that this agent will need to be obtained through a specialty pharmacy. They should also be cognizant of the short stability of the drug after dilution. One approach may be to complete a brief assessment, prior to preparing the drug order, of the patient over the phone and have the patient confirm that he/she is en route. This not only facilitates drug preparation, but it may also help to reduce patient wait times.10 Reminder calls may also be useful to ensure that patients remember appointments and avoid missed doses. A coordinated, multidisciplinary approach is advisable to ensure successful treatment.

In summary, ibalizumab is a novel ARV agent that inhibits viral entry into the host CD4 cell and an important addition to the armamentarium against MDR HIV-1 infection. ▲

References available at ContagionLive.com.
Invasive aspergillosis affects up to 13% of immunocompromised patients who are in the hospital. Aspergillus is a mold commonly found in environmental sources such as soil, dust, building material, decomposing plant matter, and water. As an infectious pathogen, it primarily causes invasive pulmonary infection, but other infections are possible and may occur as either primary infection (eg, sinusitis or cutaneous) or by hematogenous spread (eg, cardiovascular or central nervous system). The most common species responsible for invasive infection in human hosts is Aspergillus fumigatus; however, species such as Aspergillus flavus, Aspergillus niger, and Aspergillus terreus have been associated with invasive infection. In invasive pulmonary aspergillosis (IPA), the organism is typically acquired via inhalation and the incubation period varies, depending on the strain and available host immune defenses.

Aspergillus is typically inhaled in a conidial form, which must germinate into the hyphal form in order for progression to invasive disease in a susceptible host. The first line of host defense against Aspergillus is phagocytosis of the conidia by macrophages and dendritic cells. These cells are also responsible for signaling and activation of the humoral immune response. If the fungus resists phagocytosis of the conidia form and germinates into the hyphal form, then host neutrophils and monocytes are recruited to the site of infection and play a key role in the destruction of the organism.

Patients who are at risk of developing IPA are those with immunodeficiency, especially that affecting phagocytic function, including lung, liver, or hematopoietic stem-cell transplant (HSCT) recipients; those on long-term high-dose corticosteroid therapy; persons who have some inherited immunodeficiency syndromes; patients with advanced AIDS; those with hematologic malignancy, and patients with prolonged neutropenia. The risk appears to be greater in allogenic HSCT recipients compared with those receiving autologous transplants and is further increased by the presence of graft-versus-host disease (GVHD) due to administration of high-dose corticosteroids. This

Exploring Primary Prophylaxis for Invasive Pulmonary Aspergillosis

Triazoles and echinocandins are among the preferred agents to use.

RYAN W. STEVENS, PHARMD, BCIDP, BCPS, AND KAITE KAMMERS, PHARMD, BCPS

Aspergillus is a mold commonly found in environmental sources such as soil, dust, building material, decomposing plant matter, and water. As an infectious pathogen, it primarily causes invasive pulmonary infection, but other infections are possible and may occur as either primary infection (eg, sinusitis or cutaneous) or by hematogenous spread (eg, cardiovascular or central nervous system). The most common species responsible for invasive infection in human hosts is Aspergillus fumigatus; however, species such as Aspergillus flavus, Aspergillus niger, and Aspergillus terreus have been associated with invasive infection. In invasive pulmonary aspergillosis (IPA), the organism is typically acquired via inhalation and the incubation period varies, depending on the strain and available host immune defenses.

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considered, the most notable risk factor still appears to be prolonged neutropenia. This risk appears to increase as the severity and duration of neutropenia increases. Estimates indicate that the risk of IPA increases by 1% per day during the first 3 weeks of neutropenia and by 4% per day with ongoing neutropenia.¹

Primary antifungal prophylaxis is beneficial in preventing the development of IPA in certain high-risk patients (ie, those with long-term neutropenia or those with highly immunosuppressive drug regimens or disease states). However, a comprehensive list of all patients who may benefit from primary prophylaxis is not immediately clear. The Infectious Diseases Society of America (IDSA) guideline for the treatment of aspergillosis recommends that patients who have undergone HSCT and now have GVHD or those with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who are at high risk for IPA should receive primary prophylaxis.² Similarly, the American Society of Clinical Oncology (ASCO) and IDSA guideline for antimicrobial prophylaxis for adult patients with cancer-related immunosuppression recommends primary antifungal prophylaxis targeted at molds for patients with AML or MDS or those undergoing treatment for GVHD.²

Preferred agents used in the prophylaxis of Aspergillus spp. include triazoles and echinocandins.²⁶ Among the triazoles, posaconazole and voriconazole have the strongest evidence for use as prophylaxis. Itraconazole is limited by poor tolerability and unreliable absorption. Within the echinocandin class, micafungin has the strongest data for this indication.² Patients who are candidates for aspergillosis prophylaxis may frequently be on drugs that interact with azole antifungals. Triazoles should not be administered with vinka alkaloids and cyclophosphamide due to the potential for toxic levels; therefore, echinocandins are preferred in patients receiving these antineoplastics. Additionally, triazoles can have clinically significant drug interactions with calcineurin inhibitors, mammalian target of rapamycin inhibitors, and tyrosine kinase inhibitors, necessitating therapeutic drug monitoring during concurrent therapy.²

Posaconazole is manufactured as an oral suspension (cherry flavored), delayed-release tablet, and an intravenous (IV) solution, all of which can be used for prophylaxis of aspergillosis. Most of the prophylaxis trials with posaconazole were conducted with the oral suspension product; however, the data from these trials are often extrapolated to the tablet and IV product formulations.²⁷,²⁸ When given for prophylaxis, the oral suspension should be dosed at 200 mg twice daily 1 hour before or after a meal. Food and enteral feedings may decrease absorption. Monitoring serum trough concentrations should be considered, specifically in patients exhibiting signs of toxicity, such as hallucinations, visual disturbances, or acute renal failure.²² Rough concentrations of more than 1 to 2 mcg/mL are typically needed to elicit a therapeutic benefit, and concentrations more than 4 to 5 mcg/mL are commonly associated with adverse events necessitating discontinuation of therapy.²³

Micafungin has an excellent safety and tolerability profile, but is only available intravenously, which limits its clinical use for prophylaxis. Prophylactic micafungin is dosed at 50 to 100 mg daily.²⁴

IDSA, ASCO, and National Comprehensive Cancer Network (NCCN) guidelines recommend aspergillosis prophylaxis in patients undergoing intensive chemotherapy for AML, MDS or where the expected period of neutropenia is anticipated to be at least 2 weeks.²⁵ Prophylaxis is started on the first day of chemotherapy and continued until resolution of neutropenia.⁶ Resolution of neutropenia is typically defined as an absolute neutrophil count of 500–1000 for greater than 3 consecutive days. Patients who’ve undergone allogeneic HSCT also benefit from prophylaxis against molds and should start therapy post engraftment until resolution of neutropenia.¹⁰ The risk for aspergillosis pre-engraftment is notably lower, and administration of prophylaxis does not appear to confer a survival benefit unless patient has had a prior Aspergillus infection.¹¹ Prophylaxis should be given to patients with GVHD receiving chronic immunosuppression (corticosteroid equivalent more than 1 mg/kg/day of prednisone for more than 2 weeks or another anti-GVHD therapy) until immunosuppression is no longer necessary.²⁶ Patients who’ve undergone a lung transplant benefit from prophylaxis during the first 3 to 4 months post transplant. For these patients who also undergo augmentation of their immunosuppression with either thymoglobulin, alemtuzumab, or high-dose corticosteroids, re-initiation of prophylaxis is recommended.² Optimal prophylaxis therapies and durations for other disease states are poorly defined.

Long-term prophylaxis with posaconazole or voriconazole can be a significant financial burden to patients. Although fluconazole is often used in various prophylaxis settings, because of its low costs and tolerability, it is not an anti-mold active agent, and NCCN and IDSA guidelines explicitly recommend anti-mold active agents in the prophylaxis of aspergillosis. Oral agents should be selected as first-line therapy, over IV micafungin, unless contraindications preclude their use. The suspension of posaconazole is more affordable than the tablet formulation, but is typically less palatable. ▲

References are available at ContagionLive.com.
Enterovirus A71 and Acute Flaccid Myelitis—What’s the Link?

Despite increased research and investigations, the cause of the spike in cases in the United States is unknown.

BY LAURIE SALOMAN, MS

A recent outbreak of acute flaccid myelitis (AFM) among Colorado children may be due mainly to enterovirus A71, or the blame may lie elsewhere. Investigators have not pinpointed the exact culprit behind the spike in cases.

Nonpolio enteroviruses are a varied lot. Numbering more than 100, these viruses cause up to 15 million infections yearly in the United States. Most of the time, nonpolio enteroviruses cause no symptoms or just mild illness, such as hand, foot, and mouth disease. Sufferers typically recover fairly quickly and without incident.1

One strain of enterovirus that is known to be responsible for many cases of hand, foot, and mouth disease is enterovirus A71, or EV-A71. Outbreaks of EV-A71 are fairly common worldwide, particularly in Asia. However, a recent spike in EV-A71–associated disease in Colorado has raised alarm in the medical community. The number of cases is greater than has previously been seen, and more patients have presented with serious issues such as central nervous system infections.

The outbreak was first noticed in May 2018, when pediatric patients in Colorado were diagnosed with meningitis and encephalitis at higher than normal rates. The Colorado Department of Public Health and Environment reported that the rate of encephalitis caused by an unknown agent, such as a virus, was 2.75 times higher at that time than the 5-year average reported from 2013 to 2017. At the same time, rates of detection of enterovirus and rhinovirus in pediatric patients at Children’s Hospital Colorado in Aurora tripled. After testing specimens from infected children, scientists pinpointed EV-A71 as the culprit in 34 children with neurological illnesses.2

A team of investigators performed a detailed study of the first 13 children whose illnesses were traced to EV-A71 infection in order to get a fuller picture of the infections these children had. Twelve had meningitis, 9 had encephalitis, and 3 had AFM. In its most devastating form, this normally rare infection can interfere with breathing and may be fatal.3 The disease may also cause inflammation of the spinal cord’s gray matter, as seen with MRI imaging, according to Samuel Dominguez, MD, PhD, an infectious disease specialist at Children’s Hospital Colorado and an author of the study. “Historically, the disease that we call AFM now probably would have been polio,” he told Contagion®.

Although small, the rising number of cases of AFM undeniably has drawn attention. And the 2018 Colorado outbreak is hardly the only incidence of children being diagnosed with AFM in the United States recently. According to the US Centers for Disease Control and Prevention (CDC), 134 cases have been diagnosed in 33 states as of November 30, 2018, most in children, with an uptick in symptom onset between August and October. Those confirmed cases represent less than half of the 299 cases considered under investigation in 2018 due to AFM-like symptoms.4 In 2016, 149 patients were confirmed to have AFM. In contrast, the number of cases in 2017 was far fewer, with just 33 nationwide, and in 2015 there were just 22 cases.5 A look at a chart released by the CDC reveals that AFM cases are cyclical, spiking every 2 years, and are most likely to be diagnosed in the summer or fall (Figure).5

Why is the number of children diagnosed with EV-A71–associated illnesses increasing? The medical community is unsure.
"Acute flaccid paralysis, an umbrella term which includes AFM, has been used by the World Health Organization [WHO] for years to do polio surveillance," Vincent Racaniello, PhD, a professor in the Department of Microbiology and Immunology at Columbia University in New York, told Contagion. "In 2014, there was a sudden increase in AFM in the United States, possibly caused by EV-D68, [another nonpolio enterovirus]. At that point AFM was defined, and I think surveillance has increased for this condition. One explanation [for this recent outbreak] is that we are simply looking harder, but I find that not satisfactory, as we should have seen previous increases. It is difficult to argue that the infection is becoming more likely in children because of societal changes [such as] increasing population or [more children in] daycare, because these have been happening long before the current outbreaks."

Some experts say the rise in cases is due simply to the increased prevalence of viruses. "It has to do with more of the [enterovirus] being around," Dr. Dominguez said. "It probably has to do with some genetic background."

He emphasized that despite increasing numbers, serious complications remain exceptionally rare: "Like [we saw with] polio, only a small number got paralytic polio. Just as most children who contracted the polio virus in years past had few, if any, symptoms, most children infected with EV-A71 will not go on to have AFM. Of those who do, the severity varies. "The degree of paralysis is dependent somewhat on the virus and somewhat on the patient," said Dr. Dominguez.

**AFM CAUSES ARE VARIED**

To be clear, AFM is not caused solely by EV-A71. The aforementioned EV-D68 is another potential culprit. The 2014 Colorado outbreak may have been caused by EV-D68, and both EV-D68 and EV-A71 are behind some of this year’s cases. West Nile virus also can cause AFM, although that tends to occur in adults. The CDC is not certain about exactly what is underlying this year's outbreak.

"It may be one of the viruses that we’ve already detected," Nancy Messonnier, MD, director of the CDC’s National Center for Immunization and Respiratory Diseases, said in a November 13 telebriefing with journalists. "It may be a virus that we haven’t yet detected. Or it could be that the virus is kicking off another process and it’s actually triggering, through an autoimmune process, AFM."

As far as outcomes for children with AFM, they are a mixed bag. A study of 12 children in Colorado with AFM diagnosed in 2014 revealed that of the 8 who finished the study, 6 still had problems with limb movement and functional skills a year later, with visible muscle atrophy in 5 subjects. Six of the 8 also had cranial nerve dysfunction, which can result in problems such as double vision and weakness of the facial muscles.6

"We generally know that some patients recover fully from AFM," Dr. Messonnier said. "But at least half of the patients don’t recover. The long-term consequences of AFM, she said, are not fully understood. The CDC plans to closely study current patients with AFM and follow them in the future in order to better understand the disease and its complications.7

Perhaps an equally urgent question is whether AFM can be prevented in the first place. Vaccines for EV-A71 do exist, but only in China, where the virus is much more prevalent than it is here.

"Severe neurological complications after EV-A71 infection are so rare that a vaccine is not warranted," Dr. Racaniello explained. "Remember that poliovirus used to paralyze tens of thousands of children in the United States, which was the impetus for a polio vaccine. To have the China A71 vaccine licensed here would take several years."

Nor are there any antivirals that work against the virus. Intravenous immunoglobulin can be administered, although it is not a licensed here would take several years. "We generally know that some patients recover fully from AFM," Dr. Messonnier said. "But at least half of the patients don’t recover. The long-term consequences of AFM, she said, are not fully understood. The CDC plans to closely study current patients with AFM and follow them in the future in order to better understand the disease and its complications."

References are available at ContagionLive.com.
Antimicrobial resistance (AMR) is an important public health threat.1,2 Higher rates of AMR have several deleterious effects, and AMR is recognized as a global crisis for which urgent interventions are needed. Unfortunately, the prospective enrollment of patients with multidrug-resistant organism (MDRO) infections into interventional studies has been challenging, for several reasons. Patients with MDRO infections often have a high acuity of illness, which translates into a small window during which they may be consented for participation. Chronic illness is also common in this patient population, which means that applying standard exclusion criteria may lead to disqualifying large proportions of at-risk patients. In addition, syndromatic enrollment, which is the industry standard for registrational antibiotic trials (eg, complicated urinary tract infection and complicated intra-abdominal infection trials) is much more straightforward and time-efficient. In organism-specific trials, there is an unavoidable delay between clinical recognition of the infectious syndrome and confirmation of the bacteriologic diagnosis. This delay is further compounded when antibiotic susceptibility data are required for enrollment as well. To address these issues, we have initiated an international network of study sites focused on the study of MDRO infections.

PATHOGENS OF SPECIFIC INTEREST
The World Health Organization (WHO) recently published their list of priority pathogens for novel antibiotic research and development.3 This list represents the result of a large global panel of experts charged with providing a ranking for MDROs. Three pathogen classes, notably all gram-negative bacteria, were deemed highest (“critical”) priority: carbapenem-resistant Pseudomonas aeruginosa (CRPa), carbapenem-resistant Acinetobacter baumannii (CRAb), and Enterobacteriaceae resistant to carbapenems (CRE) and/or third-generation cephalosporins. The second (“high”) priority includes gram-positive organisms such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium, which are often the cause of health care–associated infections.
infections. Also included in the high priority group are gastrointestinal pathogens (fluoroquinolone-resistant Salmonella species and Campylobacter species and clarithromycin-resistant Helicobacter pylori) as well as Neisseria gonorrhoeae resistant to third-generation cephalosporins and/or fluoroquinolones.  

THE ANTIBACTERIAL RESISTANCE LEADERSHIP GROUP
The Antibacterial Resistance Leadership Group (ARLG, arlg.org) under the leadership of Vance Fowler, MD, of Duke University, and Henry Chambers, MD, of the University of California at San Francisco, is funded by the National Institute of Allergy and Infectious Diseases (NIAID), with the mission of developing, designing, and conducting a clinical research agenda to increase knowledge of antibacterial resistance. In addition to funding the Multi-Drug Resistant Organism Network and the studies SNAP, CRACKLE, and POP (referenced below), the ARLG has developed and supported more than 40 other studies in the priority areas of gram-positive infections, gram-negative infections, stewardship, and diagnostics. Other key studies include the following:

- PROVIDE: assessments of optimal vancomycin dosing in patients with bloodstream infection;
- PROOF: safety of different dosing regimens of oral Fosfomycin;
- MASTER-GC: multiple diagnostic platforms for extragenital Neisseria gonorrhoeae;
- SCOUT-CAP: efficacy of 5 versus 10 days of antibiotic treatment in pediatric community-acquired pneumonia;
- RADICAL: platforms to distinguish bacterial versus viral causes of acute respiratory infection; and
- ACUMIN: safety of a tetracycline antibiotic in critically ill adults.

THE MULTI-DRUG RESISTANT ORGANISM NETWORK
Federally supported through the ARLG, the Multi-Drug Resistant Organism Network is a global research network aimed at providing infrastructure for clinical and translational AMR research. In the United States, over 80 hospitals located in 17 states and the District of Columbia participate in the Multi-Drug Resistant Organism Network. Outside of the United States, study sites are actively enrolling patients in South and Central America, China, and the Asia/Pacific region. Currently, the focus of the Multi-Drug Resistant Organism Network is on observational studies that will delineate the global clinical and molecular epidemiology of WHO critical priority pathogens. These data will be used to help design multicenter, prospective, randomized, controlled, interventional therapeutic and diagnostic AMR studies. More important than a network of study sites, the Multi-Drug Resistant Organism Network represents a collaboration between like-minded clinical AMR researchers.

SNAP, CRACKLE, POP
The origin of the Multi-Drug Resistant Organism Network is the Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE). CRACKLE started in 2011 as a local collaboration between the 3 major health care systems in Cleveland, Ohio. Shortly after, sites were added in Akron, Ohio; Pittsburgh, Pennsylvania; Detroit, Michigan; and Chapel Hill, North Carolina. The motivation behind starting CRACKLE was the increased rate of patients with CRE infections seen in Cleveland hospitals and the associated difficulties in treating these patients. In 60 patients with carbapenem-resistant K pneumoniae (CRKp) evaluated retrospectively in a single-center study at Cleveland Clinic, a 42% 14-day mortality was seen. With funding from the Clinical and Translational Science Collaborative of Cleveland, hospitalized patients with CRE were prospectively enrolled and their CRE isolates centrally collected and analyzed. Almost 1000 unique patients had been enrolled in CRACKLE-1 when it concluded enrollment in the summer of 2016.

From CRACKLE-1, as well as other studies, it is clear that in CRKp, sequence type (ST) 258 is the predominant ST that can be divided into at least 2 molecularly and clinically distinct clades. In addition, a 13% non-mcr-1-mediated colistin resistance rate in CRKp was observed. In the same study, there were limitations with clinically used colistin testing methods. This resulted in a recommendation from the Clinical and Laboratory Standards Institute to avoid the use of e-tests for colistin susceptibility testing in clinical microbiology laboratories, which had been common practice. We also recently published an observational comparison between ceftazidime-avibactam versus colistin in CRE infection, one of the first studies showing a mortality advantage to new gram-negative therapies.

CRACKLE-2 started enrollment after conclusion of CRACKLE-1 and represents a geographical expansion of a similar prospective, observational approach of hospitalized patients with CRE. Using the infrastructure established for CRACKLE, the Study Network of Acinetobacter as a Carbapenem-Resistant Pathogen (SNAP), under the leadership of Yohei Doi, MD, PhD, of the University of Pittsburgh, has started to enroll patients with CRAb. To round out the evaluation of critical priority pathogens, the Prospective Observational Pseudomonas (POP) study will start later this year and focus on CRPAs.

FUTURE DIRECTIONS
The ultimate goal of the Multi-Drug Resistant Organism Network is to provide an infrastructure of sites in which interventional therapeutic and diagnostic studies can be performed. The observational studies that are currently ongoing will serve 2 purposes. First, they firmly establish the collaboration between sites and the ARLG. Second, these studies provide baseline data on which study design will be based. For instance, the mortality rates typically are lower in a clinical trial than in observational studies. We can predict the extent to which this will occur by using exact patient-level data on which patients are most likely to be included in a specific trial.

The Multi-Drug Resistant Organism Network will form the basis of practice-changing studies in AMR for years to come. This collaborative project is only possible because many people in many hospitals are willing to participate in these often quite time-consuming and complex studies and because of the vision and support of the NIAID. ▲

More important than a network of study sites, the Multi-Drug Resistant Organism Network represents a collaboration between like-minded clinical AMR researchers.

References are available at ContagionLive.com.
Antimicrobial resistance is an urgent public health threat. State and local health departments can play a critical role in promoting appropriate antimicrobial use and implement prevention strategies to help slow the development of antimicrobial resistance. The Antimicrobial Stewardship Collaborative of South Carolina (ASC-SC) was established in 2016 through a grant from the US Centers for Disease Control and Prevention. The South Carolina Department of Health and Environmental Control was the lead organization on the grant application, partnering with the University of South Carolina School of Medicine and College of Pharmacy. The goals of the collaborative are to coordinate and improve antimicrobial stewardship across South Carolina and to improve surveillance to drive public health action. ASC-SC currently partners with 44 acute care hospitals and 12 long-term care facilities (LTCFs) to improve antimicrobial stewardship efforts in South Carolina.

**FACILITY CONSULTS**
ASC-SC offers free on-site, telephonic, and electronic antimicrobial stewardship facility consults to health care facilities around the state. These focus on helping to initiate or improve existing stewardship programs. The new requirements from the Centers for Medicare & Medicaid Services (CMS) have prompted interest from LTCFs in improving their stewardship programs. During the consults, LTCFs are provided with numerous resources and a visit summary outlining their progress in achieving each of the Core Elements of Antibiotic Stewardship for Nursing Homes. These core elements represent both CMS and Joint Commission requirements for antimicrobial stewardship programs. ASC-SC also offers custom guidance to help improve achievement of each core element. At other facilities (eg, acute care hospitals), ASC-SC consults particularly focus on high-cost and/or high-risk antibiotics, managing certain infectious disease states, or general resource restrictions.

A Look Into the Antimicrobial Stewardship Collaborative of South Carolina

Providers in other states can learn from this multiorganization collaborative that aims to improve antimicrobial utilization and prevent the emergence of antimicrobial resistance across South Carolina.

**BY HANA RAC, PHARMD**

Dr. Rac is the lead antimicrobial stewardship pharmacist of the Antimicrobial Stewardship Collaborative of South Carolina and a clinical instructor at the University of South Carolina College of Pharmacy.
REGIONAL AND STATEWIDE ANTIBIOTIC GRAMS
ASC-SC also leads the state’s effort to generate a statewide antibiogram. All members of the collaborative receive an annual copy of regional and statewide antibiograms. These data are compiled from antibiograms submitted to ASC-SC by facilities around the state. The statewide antibiogram provides facilities with an opportunity to compare their pathogens and antimicrobial resistance patterns to others in the region. This is particularly beneficial when it comes to predicting resistance patterns in organisms that are more likely to be hospital-acquired, such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, and organisms that may spread from facility to facility as patients are transferred. The statewide antibiogram is also useful to facilities and outpatient providers who do not have facility-specific antibiograms as it provides a general view of the resistance seen in a region, particularly when it comes to community-acquired organisms such as *Escherichia coli*. Regional and statewide antibiograms promote conversation on potential statewide research and clinical intervention initiatives as well.

SYNDROME-SPECIFIC INITIATIVES
ASC-SC recognizes that many institutions do not have the resources to put together their own infectious syndrome-specific guidelines and initiatives. To better aid prescribers in the community, ASC-SC has developed several syndrome-specific guidelines to improve prescribing practices. One example comes from ASC-SC’s collaboration with the Midlands Ambulatory Antimicrobial Initiative to develop guidelines for the management of acute sinusitis in adults. In addition, antimicrobial stewardship initiatives targeting emergency departments (EDs) and LTCFs on the management of urinary tract infections (UTIs) and asymptomatic bacteriuria have been developed and implemented. Multicenter projects to improve antibiotic prescribing behaviors in UTIs are ongoing at EDs and LTCFs throughout South Carolina.

EDUCATION
ASC-SC hosts regional and statewide antimicrobial stewardship meetings each year. The goals of these meetings are to provide current antimicrobial stewardship education to those attending, provide a forum for collaboration between participants from different facilities, and update alliance members on current initiatives and opportunities. At these meetings, members are asked to share successful antimicrobial stewardship initiatives at their local facilities to showcase the best antimicrobial practices in the state. Keynote presentations and breakout sessions provide valuable opportunities for education and networking.

ASC-SC also recently started hosting live webinars, with a question-and-answer session on infectious diseases and antimicrobial stewardship topics. They are conducted on the fourth Tuesday of every other month. Although these webinars are intended to educate and provide collaboration for those in South Carolina, everyone is invited to participate and learn from them. Example topics include “Exploring prophylactic therapies for *Clostridium difficile* infection” and “Improving outcomes for patients with penicillin allergies.”

In addition to these scheduled educational meetings and webinars, ASC-SC provides education on an as-needed basis for those who request it. Examples include education for residents and families at nursing homes, presentations targeting certain key challenges to nursing home administrators, and education for consultant pharmacists on how they can play an active role in antimicrobial stewardship.

TRACKING ANTIMICROBIAL UTILIZATION IN HOSPITALS AND AMBULATORY SETTINGS
A major goal of ASC-SC has been to increase the number of facilities in South Carolina submitting antimicrobial use and resistance data to the National Health Safety Network (NHSN) Antimicrobial Use and Resistance Module. The Antimicrobial Use (AU) Option facilitates risk-adjusted intra- and inter-facility benchmarking of antimicrobial usage. The Antimicrobial Resistance (AR) Option facilitates evaluation of resistance data using a standardized approach to help providers with decision-making and to provide facility-specific measures that allow for regional and national benchmarking. To achieve this goal, ASC-SC has provided education on the benefits of the module at regional and statewide meetings and connected institutions around the state that recently started submitting their antibiotic use to NHSN. In 2016, when ASC-SC was formed, no hospital in South Carolina was submitting data to the AU or AR Options. As of November 9, 2018, there are 19 facilities submitting to the AU Option and 12 to the AR Option. ASC-SC has also been analyzing aggregated ambulatory oral antibiotic prescription rates and associated medical claims rate data from Medicaid and the State Employee Health Plan dating back to 2014. These data can be broken down by antibiotic class, prescriber type, geographical setting (urban vs rural), etc. Results have revealed important trends in antimicrobial use and resistance patterns, which have sparked new initiatives and interventions. In addition, ASC-SC is collecting data on *Clostridium difficile* infection (CDI) cases in South Carolina. Recently at IDWeek 2018, Mariam Younas, MD, ASC-SC hospital epidemiologist, presented the oral abstract, “*Clostridium difficile* Infection and Antibiotic Prescription Rates in the Community: Explaining the Gender Gap.” The data demonstrated that the incidence rate of community-associated CDI and the antibiotic prescription rate were higher in women than in men among groups aged 18 to 39 years and 40 to 64 years. However, after adjustment for antibiotic prescriptions, there was no significant difference in community-associated CDI rates in either age group. Using this outpatient oral antibiotic prescription and fill data, we plan to identify provider groups that may benefit from further antimicrobial stewardship education and initiatives to help decrease our ambulatory antibiotic prescribing rates, targeting certain high-risk oral antibiotics, such as the fluoroquinolones, third-generation cephalosporins, and clindamycin.

SUMMARY
ASC-SC is an example of a successful collaboration by a state health department, academic institutions, community hospitals, and LTCFs, with a shared goal of improving antimicrobial utilization and preventing the emergence of antimicrobial resistance across a state. This is being tackled in a variety of ways, including providing education and resources via facility consults, local antibiograms, educational meetings and webinars, syndrome-specific guidelines and initiatives, and data on local antibiotic use and CDI rates.

References are available at ContagionLive.com.
Social media is emerging as a new platform to educate and engage health care professionals and the community on the appropriate use of antimicrobial agents, with goals of optimizing patient outcomes and addressing the increase in antimicrobial resistance, according to panelists who participated in a Contagion® Peer Exchange panel.

“I look at social media, why is it important to me as a clinician,” said Debra Goff, PharmD (@idpharmd on Twitter), “There are so many reasons. It gives me the opportunity to engage, educate, connect, [and] network with experts and consumers and patients around the world. That’s an opportunity that no other vehicle provides.”

Prior to discussing the use of social media for promoting antibiotic stewardship, Dr. Goff and John Nosta, BA, (@JohnNosta on Twitter) summarized current issues related to educating health care providers and the general public on appropriate management of bacterial infections, including the inappropriate prescription of antibiotics to appease patients and treat asymptomatic colonized bacteria, as well as ways to change antibiotic prescribing practices among physicians.

### INAPPROPRIATE PRESCRIPTION OF ANTIBIOTICS

Dr. Goff and Mr. Nosta acknowledged that the complexities of antimicrobial stewardship can be difficult to communicate to health care providers and patients alike.

“If it was as simple as reading a guideline or an article, the world would be successful,” Dr. Goff said. “We have made great progress, but we do not have everybody fully engaged, because it is so complex. It is not just the health care provider that needs to be onboard. We need to have patients onboard.”

She and Mr. Nosta acknowledged that some physicians may prescribe antibiotics inappropriately in the outpatient setting to keep high rates of patient satisfaction and good online ratings. “The satisfaction score a patient provides to a physician is often a function of getting the script,” Mr. Nosta said.

Over 30% of antibiotics prescribed in the outpatient setting are unnecessary, according to the results of a 2016 JAMA study that analyzed data from the 2010-2011 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (see Table). Dr. Goff noted that physicians often unnecessarily prescribe antibiotics for asymptomatic, uncomplicated urinary tract infections that are actually colonized bacteria.

“[Presence of] asymptomatic bacteria is the most common overuse and misuse [symptom] of an antibiotic in the hospital setting,” Dr. Goff said. “[Physicians] feel compelled to treat a lab result, but it is not that simple. You have to look at the patient and put the whole clinical scenario together.”

She added that patients with mild symptoms of an infection may also request an antibiotic prescription because they believe it will make them feel better, even if the infection is not confirmed to be bacterial. “For respiratory tract infections, if [patients] come in sniffling and sneezing and [they]
want an antibiotic because they think that is what is going to treat them, more than likely the physician’s going to give them the antibiotic,” Dr. Goff explained. “It’s sort of feel-good medicine. I’m going to make you happy, and you’re going to like me, and therefore, I’m going to do this. But it is actually inappropriate if they do not have a bacterial infection.”

**CHANGING PRESCRIBING PRACTICES AMONG PHYSICIANS REQUIRES EFFECTIVE COMMUNICATION**

Dr. Goff and Mr. Nosta discussed how antibiotic stewardship requires behavioral changes among physicians, which goes beyond instructing appropriate use of antibiotics and can be difficult when physicians have been practicing for decades.

“If I’m talking to a surgeon and I’m trying to tell them, ‘No, you cannot have this new antibiotic because you have to call me, and I have to approve it,’ right away you set up a brick wall,” Dr. Goff said. “Nobody likes to be told, ‘I have to have your approval to do something that I think I’m an expert in.’ We have to change the way we operate. It is not as simple as, ‘Here’s a set of guidelines,’ and everybody is supposed to follow them. You are not going to follow a guideline if you don’t understand why I am asking you to do this.”

Mr. Nosta and Dr. Goff discussed whether the mistreatment of an infection with a high mortality rate, such as nosocomial pneumonia, is more problematic than mistreatment of an infection with a lower mortality rate, but broader consumer implications, such as a urinary tract infection. Dr. Goff concluded that all misused antibiotics, whether inappropriately prescribed or incorrect for the infectious organism, contribute to the growing problem of resistance. In the hospital setting, selecting the wrong antibiotic is a key contributor to the development of drug-resistant infections, whereas antibiotics prescribed in the outpatient setting are often stopped prematurely when the patient feels better. However, Dr. Goff also noted that the prescribed durations for antibiotic regimens are often not well supported by data.

“Patients, when you give them an antibiotic prescription, generally stop it when they feel better and save it for next time,” she said. “But we have actually learned they might be right. When you look at the evidence of how that duration came to be, there’s [no] good data.”

Dr. Goff also added the importance of ensuring that representatives from pharmaceutical companies are consistent with the recommendations given by pharmacists who educate physicians at a given hospital or practice.

“They might have an antibiotic that has US Food and Drug Administration-approved indications,” Dr. Goff explained. “But at my hospital, I only want it used for this 1 indication. ‘Every physician has [his/her] own personality style, and you’ve got to know that type of style to be most effective,’” she said.

She and Mr. Nosta then went on to discuss how they use Twitter to communicate about infectious diseases and antibiotic stewardship. In her experience, surgeons tend to want “sound bites” of which antibiotics to prescribe and why, whereas hospitalists often want to know more detailed information about why an antibiotic might be best.

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She concluded that knowing the best ways to effectively communicate with each physician is critical for delivering information about antibiotic stewardship. In her experience, surgeons tend to want “sound bites” of which antibiotics to prescribe and why, whereas hospitalists often want to know more detailed information about why an antibiotic might be best.

“Every physician has [his/her] own personality style, and you’ve got to know that type of style to be most effective,” she said.

She and Mr. Nosta then went on to discuss how they use Twitter to communicate about infectious diseases and antibiotic stewardship to a wide base of individuals, from surgeons and hospitalists who treat patients with drug-resistant infections to celebrities who may be personally affected by these infections. More on this topic will be discussed in the February 2019 issue of Contagion®.

**References available on ContagionLive.com.**

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*All conditions included acute respiratory conditions, urinary tract infections, miscellaneous bacterial infections, and other conditions.

**Acute respiratory conditions included ear infections, sinus infections, sore throats, pneumonia, acute bronchitis, bronchiolitis, upper respiratory infections (ie, common colds), influenza, asthma, allergy, and viral pneumonia.
resistance, based on the presence of resistance-associated genes.

The use of multiplex PCR is being explored in 2 clinical trials (NCT01922024 and NCT03361670) that are assessing the approach in the detection of bacteria that cause lower respiratory tract infections. The results will hopefully resolve a conundrum of PCR, namely that all organisms are detected—not just the causative pathogens. Sorting out microorganisms that naturally reside in the locale of the tissue or have contaminated that site from actual disease-causing microbes is a current challenge.

NGS that targets specific genes (tNGS) or examines the entire genome (metagenomic NGS [mNGS]) has shown promise in differentiating pathogens from colonizers in the total microbial population of the lung, as well as for detecting resistance-associated mutations in cytomegalovirus (CMV). An intriguing and ongoing issue is whether the earlier detection of minor variants of CMV, which is possible, could be used to predict failure of transplantation due to CMV contamination.

The T2 Biosystems molecular detection panels enable the detection of resistance genes of Candida and gram-negative bacteria directly from blood. The systems have not yet been approved by the US Food and Drug Administration (FDA). The Verigene gram-negative blood culture test has received FDA clearance; it is capable of detecting carbapenem-resistant Enterobacteriaceae. The FilmArray blood culture panel can specifically detect Klebsiella pneumoniae carbapenemase.

Another novel diagnostic system rapidly determines antibiotic susceptibility by capturing organisms with the support of an electrical charge and then uses fluorescence in situ hybridization technology to identify bacteria. Antibiotic susceptibility can then be ascertained within a day using multivariate logistic regression. Test results have demonstrated accuracies of 95% to 98% for β-lactam and carbapenem-resistant isolates and for Pseudomonas spp. Still, other technologies have been developed and are in the approval pipeline.

"Multiplex and targeted PCR are important first-line tests. MNGS has a role when more rapid targeted testing proves negative. TNGS is useful for antiviral resistance with its capacity to report minor variants," Dr. Hanson said. "Looking forward, the role of host biomarkers and/or the immune response will be important to explore."

**IMMUNOTHERAPIES**

Jay Fishman, MD, Harvard Medical School, Boston, Massachusetts, considered immunotherapies in more detail. Immunosuppressive regimens have reduced the rates of acute graft rejection. Yet, this optimism is tempered by the continuing reality that infection that develops following transplantation is still common and causes graft failure.

"When confronted with a transplant recipient with an active infection, is the solution as simple as reducing immunosuppression? Not likely. There is a balance that needs to be maintained between infection control and graft retention," Dr. Fishman said. Furthermore, the risk for infection may not be related just to the microbial situation at the present time. Prior exposures to pathogens that triggered immune responses, as well as latent infections that have escaped immune surveillance, probably influence the body’s response to a current transplantation.

"The take-home message is that the approach to immunosuppressed patients with infectious syndromes must be considered in the context of the specific organism or organisms and the immunosuppressive regimen being used, as well as the risk for graft rejection," Dr. Fishman said.

Other factors that are influential include integrity of the mucocutaneous barrier, which can be compromised by catheters; disruption of the microbiome: altered colonization patterns, such as occurs in Clostridium difficile infections; neutropenia; lymphopenia; underlying immune deficiency due to a number of conditions, including alcoholism, diabetes, chronic obstructive pulmonary disease, age, and viral coinfection.

Immune function relative to infection and grafts cannot yet be determined in a patient. This is, in part, because many aspects of allograft injury remain unclear. However, progress has been made in unraveling the complexities of the immune function. The signals required for the activation of T cells, a linchpin of the immune response, have been deduced, as have the mechanisms of T cell–mediated immunosuppression. This knowledge has spurred the development of monoclonal antibodies and the discovery of compounds specific for the various crucial immune-related targets. Other molecules that are influential in the immune response include B cells, mammalian target of rapamycin, and interleukin-6.

These and many other discoveries have brought about immunotherapy, where the immune response is harnessed to combat the microorganism of concern. One success has been the use of everolimus to reduce CMV infection in kidney transplant recipients.

Other avenues are being pursued in an effort to maintain the aforementioned balance between immune activity and immune suppression that is the key to transplant success. But, as emphasized by Dr. Fishman, always remember that infection is a risk factor for allograft dysfunction. "When confronted with a transplant recipient with active infection, immune reductions can be made carefully consistent with the effects of each agent."

**NOVEL TRANSPLANTS**

As discussed by Timothy Pruett, MD, University of Minnesota, Minneapolis, transplants not contemplated a decade or so ago are now being done. These include the face, hand, uterus, penis, larynx, and abdominal wall. Xenotransplants are not happening yet, but they are coming. Transplants are complex, messy, and take time, all factors that predispose patients to surgical site infections. "Things that leak or don’t heal get infected," Dr. Pruett said. As well, immunosuppression and other drug-related immune dysfunction can pave the way for infections by CMV, Epstein-Barr virus, herpessvirus, Mycobacterium, and fungus, for example.

The burgeoning emphasis on vascularized composite allotransplantation (VCA) featuring nonliving donors has opened the door for contamination of the transplanted tissue by multidrug-resistant organisms. "[Although] VCA is relatively infrequent, anticipate unique problems with time," Dr. Pruett cautioned. The use of donor tissue from intensive care unit (ICU) patients presents another problem, because ICUs are typically the home of antibiotic-resistant bacteria.

When it came to xenografts, porcine endogenous retroviruses were once a great worry. Advances in their detection have eased concern that they would be introduced into transplant recipients. A concern that remains paramount is the biology of the herd from which the tissue is obtained. Furthermore, the impact of multidrug-resistant organisms and the donor microbiome is unclear. "It’s a brave new world. Be suspicious," Dr. Pruett commented.

Finally, vascularized chimeric tissue is another novel approach. Here, allograft tissue that is transplanted into the host vascularizes and melds with the host tissue. "This approach should have an infectious risk profile similar to the use of biologic tissue in surgical procedures and possibly even less so than xenografts used in reparative procedures," Dr. Pruett said.

These topics were discussed during a Meet-the-Professors session at the IDWeek 2018 Meeting, held in San Francisco, California, October 3-7, 2018.

**DISCLOSURES**

**KIMBERLEY HANSON, MD, MHS:** BioFire Diagnostics, investigator initiated and extramural grants; Jay Fishman, MD: None; Timothy Pruett, MD: None.
Addition of Fosfomycin Could Improve Outcomes of MRSA Bacteremia

BY KRISTI ROSA

(continued from cover)

of daptomycin alone, measured in terms of clinical success and microbiological eradication, among patients with MRSAB bacteremia,” said Miquel Pujol, MD, PhD, Infectious Diseases Department Hospital de Hospital de Bellvitge, L’Hospitalet Ilobregat, Spain. Dr. Pujol presented the results of the phase 3 trial at IDWeek 2018, held October 3-7, 2018, in San Francisco, California.

Adult patients with MRSAB who had at least 1 blood culture that was positive for MRSAB in the 72 hours up to randomization and were 18 years or older were enrolled in the randomized (1:1) open-label clinical trial that was conducted at 18 medical centers throughout Spain. Participants were randomized into 1 of 2 arms: intravenous (IV) daptomycin 10 mg/kg daily plus IV fosfomycin 2 g/6 h or IV daptomycin 10 mg/kg/24 h. The duration of treatment was 10 to 14 days for uncomplicated bacteremia and 28 to 42 days for complicated bacteremia. The 2 primary efficacy endpoints for the trial were treatment success at the test-of-cure (TOC) visit (6 weeks after end of therapy) and treatment success at 7 days, defined as “alive at day 7 and clearance of bacteremia without relapse from 8 to 90 days post randomization.”

A total of 674 patients with MRSAB were evaluated for the trial, which was conducted from December 2013 to November 2017; 155 patients were randomized, according to Dr. Pujol. Seventy-four patients were given the combination treatment, while 81 were given the monotherapy.

Dr. Pujol and his team found that at the TOC visit, a successful outcome was achieved in 54.1% (40/74) of patients who were given the combination therapy compared with 42.0% (34/81) of patients who received the monotherapy (absolute difference, 12.1%; 95% CI, 0%-27.0%). Seven days after the treatment began, a successful outcome was achieved in 93.2% (69/74) of patients who received the combination therapy compared with 76.5% (62/81) of those who were given the monotherapy (absolute difference, 16.7%; 95% CI, 5.4%-27.7%). At the TOC visit, the combination therapy was found to be associated with lower rates of microbiologic failure compared with the monotherapy (0 vs 9 patients; P = .0009).

When assessing for survival, the team noted that the cumulative mortality incidence at day 7 for the combination treatment group was 4% (95% CI, 0.8 to 11.4), while it was 7.4% (95% CI, 2.8 to 15.4) in the monotherapy group.

Ibalizumab should be administered with an optimized background regimen that includes at least 1 ARV to which the patient’s virus is fully susceptible.

The cumulative mortality incidence at TOC was 24.3% (95% CI, 15.1 to 35.7) in the combination therapy group compared with 27.2% (95% CI, 17.9 to 38.2) in the monotherapy group.

A total of 48.6% of those in the combination treatment group experienced adverse events (AEs) compared with 46.9% of those in the monotherapy group. Serious AEs were reported in 40.5% and 42.0%, respectively, and 6.8% reported AEs leading to treatment discontinuation compared with 0%, Dr. Pujol reported. Five patients withdrew from the trial due to serious AE that included heart failure with hypernatremia/metabolic alkalosis/hypokalemia (2), respiratory insufficiency (2), and digestive tract bleeding (1).

Dr. Pujol and his team concluded that the combination therapy was more effective than the monotherapy for the treatment of MRSAB. “The combination therapy was highly effective to negativize blood cultures and avoid relapses and complicated bacteremia,” he said. “Mortality in both groups was similar in the TOC visit; however, a lower mortality was observed with the combination therapy at day 7.”

Overall, the combination therapy was deemed safe. Adding fosfomycin to daptomycin, at least during the first 7 days of therapy, could improve the outcomes of patients with MRSAB, the investigators concluded. ▲
LATTE-2 Results Are Favorable at 160 Weeks

BY CONTAGION® EDITORIAL STAFF

(continued from cover)

HIV Glasgow Drug Therapy Meeting, which was held October 28-31, 2018, in Glasgow, Scotland, included 3-year results from the investigation. “The LATTE-2 3-year data show cabotegravir and rilpivirine as a long-acting injectable regimen may provide an alternative to daily pills, reducing the number of annual doses from 365 to 12. It is encouraging to see these long-term results,” John C. Pottage Jr, MD, chief scientific and medical officer of ViiV Healthcare, said in a statement.

Cabotegravir is being evaluated as a long-acting formulation for intramuscular injection and as a once-daily oral tablet for use as a lead-in to establish the tolerability of cabotegravir prior to long-acting injection. Rilpivirine is a once-daily non-nucleoside reverse transcriptase inhibitor used for the treatment of HIV in combination with other antiretroviral agents in treatment-naïve adult patients with a viral load of <100,000 HIV RNA copies/mL. Long-acting rilpivirine is not approved by the US Food and Drug Administration or regulatory authorities anywhere in the world.

In the LATTE-2 trial, patients were first put on a regimen of oral cabotegravir and abacavir/lamivudine for 20 weeks. After the induction period, suppressed patients were randomized 2:2:1 to receive either the long-acting injectable cabotegravir and rilpivirine every 4 or every 8 weeks or to continue the 3-drug oral regimen. Patients on the long-acting regimen were extended to 160 weeks, and patients on the oral regimen were given the option of transitioning to the regimen every 4 or every 8 weeks at week 96.

At 160 weeks, 104 of 115 participants (90%) and 95 of 115 participants (83%) receiving the injectable regimen, every 8 and 4 weeks, respectively, remained virally suppressed. Of the patients in the oral comparator arm who chose to switch to the injectable regimen at week 96, 33 of 34 participants (97%) and 10 of 10 participants (100%) remained virally suppressed at every 8 and 4-week dosing, respectively.

Through week 48, 2 participants developed protocol-defined virologic failure (PDVF) on the every-8-week dosing arm. No additional PDVF cases were observed in the study between weeks 48 and 160.

Injection-site reactions were reported in a majority of participants through week 160; however, 87% of these reactions were resolved within 7 days. Three of the 274 participants experienced injection-site reactions that led to discontinuation through week 160.

Excluding injection-site reactions, the most common adverse events (AEs) were nasopharyngitis (38%), diarrhea (22%), and headache (22%). Three of 115 patients in the 8-week group, and 12 of 115 participants in the 5-week group had AEs leading to withdrawal.

Rilpivirine is not recommended for patients younger than 12 years. Additionally, the most common adverse effects include depression, headache, insomnia and skin rashes. Hepatic AEs have been reported, and patients with underlying disease, including hepatitis B or C, may be at an increased risk. Redistribution and accumulation of body fat have been observed, as well as autoimmune disorders, including Graves disease, polymyositis, and Guillain-Barré syndrome.

FLAIR Study Meets Primary Endpoint in Virally Suppressed Adults

BY MICHAELA FLEMING

(continued from cover)

FLAIR is the second phase 3 trial to examine the safety and efficacy of monthly dosing of injectable formulations of cabotegravir and rilpivirine and showed that the long-acting regimen, when injected once monthly, had similar efficacy to ABC/DTG/3TC at week 48 based on the proportion of participants with plasma HIV-1 RNA >50 copies/mL.

Overall, safety, virologic response, and drug resistance results for the injectable regimen were consistent with results from both the phase 2 LATTE and LATTE-2 studies. Further details about the results of the FLAIR study will be announced at an upcoming scientific meeting.

In August 2018, ViiV reported positive data from the ATLAS study, which compared a long-acting injectable regimen against the continuation of current daily oral antiretroviral therapy in virologically suppressed, treatment-experienced patients. ViiV plans to use pooled data from the FLAIR and ATLAS studies for future regulatory submissions. ABC/DTG/3TC has a boxed warning of hypersensitivity reactions and exacerbations of the hepatitis B virus. Patients with a prior hypersensitivity reaction to abacavir or who carry the HLA-B*5701 allele are at an increased risk of experiencing a hypersensitivity reaction.

Side effects associated with rilpivirine include depression, headache, insomnia, and skin rashes. Hepatic adverse events have been reported, and patients with underlying disease, including hepatitis B or C, may be at an increased risk. Redistribution and/or accumulation of body fat have been observed along with autoimmune disorders, including Graves disease, polymyositis, and Guillain-Barré syndrome.

The results were presented at the HIV Drug Therapy Glasgow 2018, which was held October 28-31, 2018, in Glasgow, Scotland.
The Contingent Valuation of Antibiotics Against *C. difficile* Infection

**BY MICHAELA FLEMING**

(continued from cover)

Contagion®: What was the goal of your presentation?

Tillotson: I was trying to bring to the audience’s attention that the value, or the perceived value, of our antibiotics, is low—unlike with other drugs, such as cancer drugs, rheumatology drugs, and so on, where people are prepared to pay significantly more [than they would for an antibiotic]—even though we know that just a week of an antibiotic can extend your life by decades. [Drugs for] cancer and other treatments do not have that same sort of effect.

What is the reason for this perception?

I think society has become complacent. Antibiotics have been available for 70 years, and up until recently, they have always worked. We have to pay about $30 for a course of antibiotics, and [then we are cured]. Now that antibiotic resistance has emerged and has become part of the agenda of the World Health Organization [WHO], the US Centers for Disease Control and Prevention [CDC], and even the PCAST [US President’s Council of Advisors on Science and Technology], [people are realizing] antibiotic resistance is more than just a threat; it’s a reality. New drugs are being developed; however, it costs more to develop an antibiotic now than it did 20 years ago. Patients and physicians are not comfortable paying $1000, let alone $5000 and $10,000 for a new antibiotic, which is likely to save their life. Complacency and an ‘antibiotics are disposable’ attitude has developed. [Patients and providers think], ‘There’s always another [antibiotic] I can go to.’ [The reality is that] we are running out of options and at some stage you know someone has got to pay the piper.

What are some potential avenues of treatment or prevention for *C. difficile* infections moving forward?

What underlies *C. difficile*, as an infection, is a profound disturbance to the protective normal flora, and so a course of an antibiotics can do a lot of damage to that protective flora. The most logical thing to think is: Let’s replace that flora; not perfectly but perfectly enough to provide a layer of protection. Restoring the microbial flora is a powerful way forward. It has its problems and pitfalls, several of which originate from the regulators, but that’s beyond this discussion.

I am fascinated about the concept of vaccines, which have been proven to work in a variety of infections; however, there is a problem with uptake. If you do not get enough uptake, then herd immunity will not kick in, and so it questions the validity of the vaccine. In terms of other avenues, we have looked at immunoglobulins and immune status in the past; however, I think that [research] has been a little nonspecific. The specificity of a vaccine is better.

Can you speak to the concept of contingent valuation?

The medical profession has not gotten into contingent valuation, yet, and it really applies to some form of health event, in this case, an infection. We are not just looking at the impact of an infection on 1 patient, but the impact of that event on the patient’s family, workplace, and a lot of things that come together in like a giant jigsaw.

Contingent valuation is used for events such as environmental disasters. [Economists will use it] to come up with a value for the event. [For example,] think about Deepwater Horizon, the oil rig that exploded in Bay of Mexico. The evaluation determined it was valued at almost $19 billion after they worked out all the environmental issues and so forth. I think it is time to assess infectious diseases in exactly the same way. Contingent valuation could help to establish a more realistic pricing for antibiotics. [forcing the industry] to not just go with a price that they think people might pay, but to actually look at the drugs for the impact they have on society [and price them accordingly]. It’s time for us to think about infectious diseases with contingent valuation and to better understand the holistic costs of an infection.

What about cost considerations for *C. difficile* treatment?

There was a study published about 2 years ago where the investigators looked at all of the different components that go into managing and controlling a patient with *C. difficile* infection, and [the value] came to something in the order of $30,000. If that patient happens to fail their treatment and have recurrence, [which is] about a 30% chance, then you have to incur those costs again. Over a period of time, the cost goes from about $30,000 to $60,000 and then $90,000 and so on. [As such], it is difficult to take a singular *C. difficile* infection as [being valued at] just $30,000. It’s the avoidance of the recurrence that matters. With *C. difficile*, when you compare it with other multi-drug-resistant infections, it is probably one of the top most expensive infections to acquire.

**EDITOR’S NOTE:**

This transcript has been modified slightly for readability.

Controversies Arise in *C. difficile* Prevention

**BY KRISTA ROSSI**

(continued from cover)

According to Dr. Petrosillo, there are a few points in infection control procedures that are controversial. One of them is how long the patient should be isolated in contact isolation after the end of diarrhea.

“The guideline says 48 hours,” Dr. Petrosillo explained. “That’s okay, because after 48 hours, there is no more diarrhea and no more risk for spread of spores in the environment because there is no diarrhea.”

However, the spores can survive up to 4 weeks after the end of diarrhea, and so this practice is risky in some settings where the patients are very sick and have a lot of comorbidities. If they acquire this infection, they can have an increased risk of mortality.

“I think that we should consider this measure of 48 hours as very flexible, depending on the setting and patient being treated,” Dr. Petrosillo said. “In some cases, we should [consider] contact isolation for the [entire] stay in the hospital. In some particular cases, it may be needed in order to avoid the spread to other patients.

The second point that is controversial, according to Dr. Petrosillo, is the screening of asymptomatic carriers. “[The] guideline says that asymptomatic carriers should be screened, because otherwise, we do not know what to do with them. What should we treat, what should we not treat? Should we put them in contact isolation? This is constant; this is difficult to manage.”

Results from several studies indicate that for immunocompromised patients, like those who have undergone a bone marrow transplant or elderly people in long-term care facilities, screening of asymptomatic carriers was effective in reducing the rate of *C. difficile* infection in particular conditions. [such as] in outbreak settings and patients with high risk for *C. difficile* infection, he said.

“We should be more flexible and try to understand which patients should be screened: when they are asymptomatic, of course; when they are admitted to the hospital; and which patients and in which settings,” Dr. Petrosillo concluded.
Cryptosporidium: A Potentially Fatal Cause of Diarrhea in a Heart Transplant Recipient

Expanding the differential for diarrhea beyond *Clostridium difficile*.

BY ANNE BORJA, MD; ANDREW LEE, MD; BENJAMIN BLUEN, MD; SHELLEY HANKINS, MD; AND DONG HEUN LEE, MD

**HISTORY OF PRESENT ILLNESS**

A 79-year-old man presented to a New Jersey hospital with a history of 5 days of profuse, watery diarrhea and lethargy. His symptoms started after he ate at a group holiday meal at his senior apartment complex home. He denied any fevers or chills, nausea, vomiting, shortness of breath, chest pain, and palpitations. He was in his usual state of health before the diarrhea and lethargy started. His baseline mental status was alert and oriented to person, place, and time, and he could function relatively independently. At the time of presentation to the emergency department, the patient provided limited history because of his lethargy.

**PAST MEDICAL HISTORY**

The patient had an orthotopic heart transplant in July 2000 secondary to ischemic cardiomyopathy. He was on tacrolimus and mycophenolate immunosuppression and treated with methylprednisolone for rejection 9 months previously. He had a history of myocardial infarction at age 60, atrial flutter status post Medtronic pacemaker placement in 2009, chronic kidney disease stage 3A, hypertension, hyperlipidemia, benign prostatic hyperplasia, and diverticulosis.

**MEDICATIONS**

Aldonronate, calcium carbonate, carvedilol, mycophenolate, dofetilide, finasteride, lisinopril, simvastatin, tacrolimus, rivaroxaban, ezetimibe.

**STUDIES**

Labs showed a normal leukocyte count. His blood urea nitrogen was 145 mg/dL, creatinine level was 4.9 mg/dL (with a baseline creatinine level of 1.3-1.7 mg/dL), and an arterial blood gas showed a...
pH of 7.07, a pCO2 of 15 mm Hg, and a pO2 of 188 mm Hg. A chest x-ray did not show any consolidations or effusions. An echocardiogram showed an ejection fraction of 60% to 65%, mild left ventricular hypertrophy, an enlarged left and right atrium, and a normal right ventricle. There was mild mitral regurgitation, tricuspid regurgitation, and aortic regurgitation. Blood and urine cultures showed no initial growth. Work-up for causes of diarrhea was negative, including *Clostridium difficile* toxin/glutamate dehydrogenase assay, *Salmonella*, *Shigella*, *Campylobacter*, *Giardia*, *Yersinia*, ova, parasites, *Norovirus*, and cytomegalovirus. Respiratory viral panel and microsporidia were also negative (see Table).

**CLINICAL COURSE**

The patient was given 2.5 L of normal saline. He was started on intravenous (IV) vancomycin, cefepime, and levofloxacin and admitted to the intensive care unit (ICU). He was started on norepinephrine and vasopressin infusions, and was transferred to a cardiac ICU in Philadelphia, Pennsylvania, under the care of his transplant cardiologist. The transplant infectious disease team was consulted. Repeat blood and urine cultures were obtained. IV vancomycin and levofloxacin were discontinued, the patient was started on oral vancomycin and IV metronidazole, and cefepime was continued. His mycophenolate was also held. Pressor infusions were resumed.

**DIAGNOSTIC PROCEDURES AND RESULTS**

Stool testing was positive for *Cryptosporidium* antigen enzyme immunoassay using ImmunoCard (Meridian Biosciences; Cincinnati, Ohio). His final blood and urine cultures from both hospitals showed no growth after 5 days.

**TREATMENT AND FOLLOW-UP**

The patient was started on nitazoxanide, and his antibiotics were discontinued. The patient’s pressors were weaned off, and his vitals stabilized. He was transferred out of the cardiac ICU to the general medical floor. He demonstrated complete recovery within several days and was discharged with instructions to complete 2 weeks of nitazoxanide. A thorough local health department investigation did not reveal an identifiable source of his illness.

**DISCUSSION**

*Cryptosporidium* is a chlorine-resistant parasite found in water or soil contaminated with animal or human feces.1 *C hominis* and *C parvum* are the most common causes of human cryptosporidiosis. Infection occurs by ingestion of *Cryptosporidium* oocysts, which are resistant to prolonged environmental exposure as well as many disinfecting agents. However, once the oocysts are ingested, the thick-walled *Cryptosporidium* oocyst ingested by host

<table>
<thead>
<tr>
<th>LIFE CYCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking water</td>
</tr>
<tr>
<td>Recreational water</td>
</tr>
<tr>
<td>1. Thick-walled oocyst (sporulated) exits host</td>
</tr>
<tr>
<td>2. Contamination of water and food with oocysts.</td>
</tr>
<tr>
<td>3. Thick-walled oocyst ingested by host</td>
</tr>
</tbody>
</table>

* Cryptosporidium* antigens, as ova and parasite examination is not always positive.

* Cryptosporidium* infection and elimination of the parasite from the body. 3 A retrospective review of all solid organ transplant patients was conducted at 2 transplant centers from January 2001 to October 2010. Ten patients were found to be infected with *Cryptosporidium*. Infection in these patients was found to be self-limited, and their gastrointestinal symptoms resolved without antiparasitic treatment.4 Diagnosis is made by stool enzyme immunoassay for *Cryptosporidium* antigens, as ova and parasite examination is of lower yield and requires acid-fast staining.5 Although most patients do not require treatment, patients with refractory symptoms and those who develop signs of septic shock may require treatment, which involves reduction in immunosuppression in combination with antiparasitic therapy. The first line of treatment is nitazoxanide. In severely immunocompromised patients who do not respond, a combination of paromomycin and azithromycin may be used as well.6 ▲

**Table: Patient Lab Study Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum WBC</td>
<td>7000/mL 80% neutrophils</td>
<td><em>Cryptosporidium</em> stool Ag</td>
<td>Positive</td>
</tr>
<tr>
<td>Blood and urine cultures</td>
<td>No growth</td>
<td><em>Campylobacter</em> stool culture</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum CMV quantitative PCR</td>
<td>&lt;137 copies/μL</td>
<td><em>Norovirus</em> PCR</td>
<td>Negative</td>
</tr>
<tr>
<td>Respiratory viral panel</td>
<td>Negative</td>
<td><em>Stool ova &amp; Parasite</em></td>
<td>Negative</td>
</tr>
<tr>
<td>Stool WBC smear</td>
<td>Few WBCs seen</td>
<td><em>Salmonella</em> and <em>Shigella</em> stool culture</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Giardia</em> lamblia stool Ag</td>
<td>Negative</td>
<td><em>Yersinia</em> stool culture</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Microsporidia</em> stool</td>
<td>Negative</td>
<td><em>Clostridium difficile</em> toxin/ GDH assay</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Ag indicates antigen; CMV, cytomegalovirus; GDH, glutamate dehydrogenase assay; PCR, polymerase chain reaction; WBC, white blood cell.

References available at ContagionLive.com.
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