AASLD 2018

PWID With HCV Can Achieve SVR Despite Low Treatment Adherence

People who inject drugs (PWID) who have hepatitis C virus (HCV) can achieve sustained viral response (SVR), despite imperfect adherence to treatment, according to the results of a new trial. Although they are at high risk of HCV infection and transmission, PWID tend to be excluded from treatment and coverage of treatment by health insurance because of concerns over adherence to therapy. Because this population is most urgently in need of treatment, a team of investigators, led by Elana Rosenthal, MD, assistant professor of medicine in the Division of Clinical Care and Research at the Institute of Human Virology, University of Maryland School of Medicine, in Baltimore,

(continued on page 24)

C Difficile Infection Is Tied to Higher Mortality Rates in Cirrhosis Patients

Clostridium difficile infection leads to higher rates of overall mortality among patients with cirrhosis compared with those without, according to the results of a new study. "Patients with cirrhosis are vulnerable to C diff infection, frequent bacterial infections, and dysbiosis due to their functional immunosuppression," the investigators of the study wrote. "Despite data demonstrating that C diff infection is becoming more common and is associated with a higher mortality in patients with cirrhosis, there are no data assessing its recurrence and readmissions in this patient population."

Data for the study were collected from Washington, Florida, and New York state inpatient databases between

(continued on page 25)

ASHP 2018

Exploring Pharmacist Intervention and Continued HIV Care

Could pharmacist-led medication reconciliation improve patient continuity of care in individuals with HIV? Investigators at a California medical center are seeking to find out. In a 2-part study, a research team with Desert Regional Medical Center (DRMC) in Corona, California, analyzed the need for pharmacist intervention for patients with HIV. The goal of the study was to find a way to improve continuity of care for these individuals at a higher rate than what the center currently sees.

(continued on page 27)

ASHP 2018

Pharmacists Play a Role in Responding to Drug Shortages

As of September 2018, there were 139 new national drug shortages in 2018, and a total of 238 overall, according to University of Utah (UA) Drug Information Service data. "It’s a lot," Erin R. Fox, PharmD, BCPS, FASHP, senior director for drug information and support services at UA Health, told an audience at a satellite symposium at the 2018 American Society of Health-Systems Pharmacists (ASHP) Midyear Clinical Meeting. The session, which was supported by an educational grant

(continued on page 27)

Drug Shortages

Role in Responding to

Pharmacists Play a

(continued on page 26)

Low Microbiota Diversity Prior to BMT Is Linked With More Complications

Intestinal microbiota diversity is critical for keeping harmful bacteria from dominating the gut, which can result in severe microbiota injury and treatment complications in patients with cancer.

In a new study, a team of investigators determined that individuals who had lower microbiota diversity in their intestine prior to undergoing a bone marrow transplant (BMT) had a higher risk for posttransplant complications, such as graft-versus-host disease or death. "Patients who went into the BMT process with a gut flora that was already disrupted had a higher risk of death after the transplant," Marcel van den Brink, MD, PhD, chief

(continued on page 26)
**EDITORIAL BOARD**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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</tr>
</tbody>
</table>

**EDITORIAL BOARD**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOROTHY MCCOY, PHARM, BCPS</td>
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</tr>
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</tr>
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</tr>
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</tr>
<tr>
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<td>College of Health Sciences, University of Delaware, Newark, Delaware</td>
</tr>
<tr>
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<td>Institute for Healthcare Policy &amp; Innovation, University of Michigan Ann Arbor, Michigan</td>
</tr>
<tr>
<td>ELIZABETH PHILLIPS, MD, FRCPC, FRACP</td>
<td>Vanderbilt University Medical Center, Nashville, Tennessee</td>
</tr>
<tr>
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<td>DMC Sinai-Grace Hospital, Detroit, Michigan</td>
</tr>
<tr>
<td>CASSANDRA D. SALGADO, MD, MS</td>
<td>Department of Internal Medicine, Medical University of South Carolina, Charleston, South Carolina</td>
</tr>
</tbody>
</table>

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Questions related to editorial content and submissions should be sent to Managing Editor Alexandra Ward, MA: AWARD@CONTAGIONLIVE.COM.
Efficacy profile for single-dose ORBACTIV® (oritavancin) established in 978 patients¹²

<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>

Pooled Clinical Data from SOLO I and SOLO II³

§ 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 antibacterial drug at 48–72 hours.

¶ 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.

³ mITT population; SOLO I and SOLO II were two identical, randomized, double-blind, non-inferiority Phase 3 trials comparing ORBACTIV® 1200 mg to vancomycin 1 g or 15 mg/kg twice daily for 7 to 10 days for the treatment of ABSSSI in 1,959 patients.

ORBACTIV® (oritavancin) for injection 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.¹²

INDICATION
ORBACTIV® (oritavancin) for injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused or suspected to be caused by susceptible isolates of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillin-susceptible [MSSA] and methicillin-resistant [MRSA] 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).

IMPORTANT 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 bacterial 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:

Please see following page for Brief Summary of ORBACTIV® Prescribing Information.
1. INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections
ORBACTIV® (oritavancin) for injection is indicated 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 Intraocular Unfractionated Heparin Sodium
Use of 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 (5.1) and Drug Interactions (7.2)].

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

4.3 Pregnancy
Data are insufficient to evaluate whether ORBACTIV® causes fetal harm when administered to pregnant women. Because animal reproduction studies are not always predictive of human response, ORBACTIV® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 (6.1)].

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 (6.1)].

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. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial use not 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 ORBACTIV® dose [see Warnings and Precautions (5.1)].

Patients 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 (6.1)].

5.7 Development of Drug Resistant Bacteria
Prescribing ORBACTIV® in the absence of 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 57/976 (5.9%) patients treated with ORBACTIV® and 58/983 (5.9%) treated with vancomycin. The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/976 (1.1%) in ORBACTIV® and 12/983 (1.2%) in the vancomycin arms, respectively.

The most commonly reported adverse reactions (≥3%) in patients receiving a single 1200 mg dosing 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 36/976 (3.7%) of patients; the most common reported reactions leading to discontinuation were cellulitis (4/976, 0.4%) and osteomyelitis (3/976, 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 ≥1 adverse reaction.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ORBACTIV® (%)</th>
<th>Vancomycin (%)</th>
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<tbody>
<tr>
<td>Headache</td>
<td>12.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.2</td>
<td>6.6</td>
</tr>
<tr>
<td>Limb and subcutaneous abscesses</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0.4</td>
<td>0.3</td>
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The following selected adverse reactions were reported in ORBACTIV®-treated patients at a rate of less than 1.5%:

- Blood and lymphatic system disorders: anemia, eosinophilia
- General Disorders and administration site conditions: infusion site erythema, extravasation, induration, pruritis, rash, edema peripheral
- Immune system disorders: hypersensitivity
- Infections and infestations: osteomyelitis
- Investigations: total bilirubin increased, hyperuricemia
- Metabolism and nutrition disorders: hyperglycemia
- Musculoskeletal and connective tissue disorders: tenosynovitis, myalgia
- Respiratory, thoracic and mediastinal disorders: bronchospasm, wheezing
- Skin and Subcutaneous Tissue Disorders: urticaria, angioedema, erythema multiforme, pruritis, leucocytoclastic vasculitis, rash.

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 benefits justify 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 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

Marketed by:
The Medicines Company
8 Sylvan Way
Parisippany, NJ 07054 USA
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>STEWARDSHIP &amp; PREVENTION</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staying Ahead of the Curve: Implementation of AUC-guided Vancomycin Dosing</td>
</tr>
<tr>
<td></td>
<td>Evidence suggests AUC-guided vancomycin dosing is a safer method than traditional trough-guided dosing. Implementation of this new method is achievable even for nonacademic centers.</td>
</tr>
<tr>
<td></td>
<td>BY JAMIE KISGEN, PHARMD, BCPS-AQ ID, AND MEGAN SEDDON, PHARMD</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>IN THE LITERATURE</td>
</tr>
<tr>
<td></td>
<td>Duration of Antibiotic Therapy for Uncomplicated Gram-Negative Bacteremia: Seven Is the New Fourteen</td>
</tr>
<tr>
<td></td>
<td>BY CHRISTIAN Y. CHO, PHARMD</td>
</tr>
<tr>
<td></td>
<td>Potential Two-Dose Dalbavancin Treatment for Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>BY TIFFANY LEE, PHARMD</td>
</tr>
<tr>
<td>8</td>
<td>MEDICAL WORLD NEWS</td>
</tr>
<tr>
<td></td>
<td>Learn more about important and trending infectious disease news from around the world.</td>
</tr>
<tr>
<td>10</td>
<td>NEWS &amp; BREAKTHROUGHS</td>
</tr>
<tr>
<td></td>
<td>Omadacycline: A New Player for Team Tetracycline</td>
</tr>
<tr>
<td></td>
<td>An oral alternative for patients requiring broad-spectrum therapy in this era of resistance.</td>
</tr>
<tr>
<td></td>
<td>BY MARIA HEANEY, PHARMD</td>
</tr>
<tr>
<td>14</td>
<td>ACUTE INFECTIONS</td>
</tr>
<tr>
<td></td>
<td>In Small Corner of Alzheimer’s Research, “Germ Theory” Begins to Gain Traction</td>
</tr>
<tr>
<td></td>
<td>A new effort makes the case that scientists have been looking in the wrong direction.</td>
</tr>
<tr>
<td></td>
<td>BY JARED KALTWASSER</td>
</tr>
<tr>
<td>16</td>
<td>EMERGING &amp; RE-EMERGING DISEASES</td>
</tr>
<tr>
<td></td>
<td>Amid High-Profile Outbreaks, Benefit of Widespread Asymptomatic Screening Remains Low</td>
</tr>
<tr>
<td></td>
<td>Should patients be screened for emerging infectious diseases based on travel history? Recent studies cast doubt.</td>
</tr>
<tr>
<td></td>
<td>BY JARED KALTWASSER</td>
</tr>
<tr>
<td>20</td>
<td>MULTIDRUG-RESISTANT INFECTIONS</td>
</tr>
<tr>
<td></td>
<td>Emergence of Ceftazidime-avibactam Resistance: What Have We Learned in the Past 4 Years?</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime-avibactam is a novel treatment for CRE infections, but reports of resistance are increasing.</td>
</tr>
<tr>
<td></td>
<td>BY RYAN K. SHIELDS, PHARMD, MS</td>
</tr>
<tr>
<td>22</td>
<td>INSIGHTS</td>
</tr>
<tr>
<td></td>
<td>The Potential of Twitter in Antimicrobial Stewardship</td>
</tr>
<tr>
<td></td>
<td>BY GINA BATTAGLIA, PHD</td>
</tr>
<tr>
<td>24</td>
<td>MEETING COVERAGE</td>
</tr>
<tr>
<td>28</td>
<td>CASE STUDY</td>
</tr>
<tr>
<td></td>
<td>Final Diagnosis: Disseminated Kaposi Sarcoma With Tonsillar and Pulmonary Involvement</td>
</tr>
<tr>
<td></td>
<td>A shocking find on a CT scan leads to an unexpected diagnosis.</td>
</tr>
<tr>
<td></td>
<td>BY ERIN TUTTLE, MD; REBECCA HOPPE, MD; ALEXANDER CUBBERLEY, MD; GINNY MARMOLEJO, MD; AND ANITA KO, MD</td>
</tr>
</tbody>
</table>

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New Year, New Contagion®: Section Editor Lineup Brings Expertise, Insight for 2019

It is my pleasure to begin my second year as editor-in-chief of Contagion®. I have to admit that I was not entirely sure what I was getting myself into last year, but Contagion® has exceeded my expectations and I hope it has met yours as well. This year brings some changes to our publication that I am confident will further improve our offerings and increase the value that Contagion® can bring you.

Contagion® has benefitted from an expert editorial board since its inception, but this year we are welcoming several more section editors to help cultivate, develop, and edit content for nearly all of the sections of Contagion®. Our first 2 section editors are continuing with us in 2019. In the Literature is led by Monica Mahoney, PharmD, BCPS-AQ ID, BCIDP, of Beth Israel Deaconess Medical Center, clinical pharmacy coordinator of infectious diseases. Case Studies is led by Sara Schultz, MD, FACP, of Drexel University, an assistant professor and associate program director of the infectious diseases fellowship program. We look forward to their continued contributions.

The 4 new section editors each come to Contagion® with a wealth of experience in their field. Wendy Bamberg, MD, heads Emerging and Re-Emerging Infections. Dr. Bamberg is a Centers for Disease Control and Prevention-trained medical epidemiologist who directs the Health Care-Associated Infections and Antimicrobial Resistance programs for the Colorado Department of Public Health and Environment. Conan MacDougall, PharmD, MAS, BCPS, BCIDP, a professor at the University of California, San Francisco, leads Stewardship and Prevention. Dr. MacDougall is well known for his work in antimicrobial stewardship and is an author on recent Infectious Diseases Society of America/Society for Healthcare Epidemiology of Hospitals guidelines. Jason Schafer, PharmD, MPH, BCPS-AQ ID, BCIDP, AAHIVP, joins us from Thomas Jefferson University, where he is an associate professor and clinical pharmacy specialist in HIV ambulatory care. Dr. Schafer is leading the HIV/AIDS section. Finally, Ryan Shields, PharmD, MS, an associate professor at the University of Pittsburgh, is leading Multidrug-Resistant Infections. Dr. Shields is well known for his work with multiple facets of resistant infections, notably for recent studies on carbapenem-resistant Enterobacteriaceae.

This is the first issue with all 6 section editors contributing their expertise, and I am looking forward to hearing more of the suggestions and seeing where they take our publication.

Happy New Year, and enjoy this issue of Contagion®.
Duration of Antibiotic Therapy for Uncomplicated Gram-Negative Bacteremia: Seven Is the New Fourteen

BY CHRISTIAN Y. CHO, PHARMD ♦

T
he treatment duration for uncomplicated gram-negative bloodstream infections (BSIs) has traditionally ranged from 7 to 14 days. However, recent retrospective studies and meta-analyses have observed no differences in clinical outcomes in patients treated with shorter courses compared with prolonged courses, especially with urinary sources of infection. In addition, the role of oral stepdown for definitive therapy for gram-negative BSIs has been explored with similar clinical outcomes regardless of duration. These recent studies have led to an increased interest in stewardship efforts to optimize antibiotic utilization and promote appropriate oral stepdown therapy for gram-negative BSIs.

Yahav and colleagues conducted the first prospective, randomized, controlled, noninferiority trial to compare short-course (7 days) versus long-course (14 days) antibiotic therapy for uncomplicated gram-negative BSIs. Patients were included if they were hemodynamically stable and normothermic for 48 hours by day 7 of effective antibiotic therapy and were excluded if an uncontrolled source of infection was present. Overall, 604 patients were randomized to receive either short-course (n = 306) or long-course (n = 298) therapy. The primary outcome was a composite of all-cause mortality; clinical failure defined as relapse, suppurative, or distant complications; and re-admission or extended hospitalization by 90 days. The first day of effective empiric or definitive antibiotics was considered day 1 of therapy. Most patients (92%) received the protocol-specific treatment durations (± 2 days), and about 73% of patients were switched to oral stepdown therapy (fluoroquinolones: 74%; β-lactams: 18%; sulfamethoxazole/trimethoprim: 8%). Patients were generally older than 65 years (67%) and immunocompetent (75%). The most common pathogens identified were Enterobacteriaceae, and the primary sources of infection were urinary (68%) and intraabdominal (12%).

Short-course therapy was noninferior to long-course therapy for the primary outcome (45.8% vs 48.3%, respectively; 95% CI −10.5 to 5.3) or in any of its individual components. No significant differences were observed in any of the secondary outcomes, including resistance development, adverse effects, or Clostridium difficile infections, with the exception of functional capacity needs at 30 days favoring short-course therapy. The authors concluded that 7 days of antibiotic therapy was noninferior to 14 days in patients who had gram-negative BSIs with adequate source control and were clinically stable by day 7 of therapy. This robustly powered study addresses stewardship efforts in the management of uncomplicated BSIs. The findings from this study support the trend of shorter antibiotic courses for infections with adequate source control. In addition, the high rate of use of oral stepdown therapy without clinical compromise demonstrates the ability to avoid placement of central lines and ultimately prevent unnecessary catheter-related adverse effects. Finally, obtaining repeat blood cultures to confirm microbiological clearance is not necessary for clinical success and provides an opportunity for diagnostic stewardship. This landmark study provides high-quality evidence that promotes the duration of 7 days as the correct duration for uncomplicated BSIs. Conversely, caution should be practiced when applying these results in the immunocompromised or BSIs caused by non-Enterobacteriaceae (Table).

![References available at ContagionLive.com.](Image)

### Table. Trends With Shorter Antibiotic Durations

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>STANDARD</th>
<th>SHORT</th>
<th>OUTCOME</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABSSSI/Cellulitis</strong></td>
<td>7-14 days</td>
<td>5 days</td>
<td>Noninferiority of 5 days vs 10 days</td>
<td>Hebbur 2004</td>
</tr>
<tr>
<td></td>
<td>10 days</td>
<td>6 days</td>
<td>Noninferiority of 6 days of tedizolid vs 10 days of linezolid (2 trials)</td>
<td>Prokocimer 2013, Moran 2014</td>
</tr>
<tr>
<td><strong>CAP</strong></td>
<td>7-10 days</td>
<td>5 days</td>
<td>No difference between levofloxacin 750 mg x 5 days vs levofloxacin 500 mg x 10 days</td>
<td>Dunbar 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noninferiority of 5 days (symptomatic driven) vs 10 days (provider guided)</td>
<td>Uranga 2016</td>
</tr>
<tr>
<td><strong>HAP/VAP</strong></td>
<td>10-15 days</td>
<td>7-8 days</td>
<td>Noninferiority of shorter courses</td>
<td>Chastre 2003, Singh 2000</td>
</tr>
<tr>
<td><strong>Acute exacerbation of COPD and chronic bronchitis</strong></td>
<td>7-10 days</td>
<td>5 days</td>
<td>No difference between 5 days vs 7-10 days</td>
<td>El Moussaoui 2008</td>
</tr>
<tr>
<td><strong>Uncomplicated UTIs</strong></td>
<td>–</td>
<td>3 days</td>
<td>Ciprofloxacin x 3 days adequate, but cefpodoxime x 3 days inadequate</td>
<td>Hooton 2012</td>
</tr>
<tr>
<td><strong>Complicated UTIs/pyelonephritis</strong></td>
<td>10 days</td>
<td>5 days</td>
<td>Noninferiority of levofloxacin x 5 days vs ciprofloxacin x 10 days</td>
<td>Peterson 2008</td>
</tr>
<tr>
<td></td>
<td>14 days</td>
<td>7 days</td>
<td>Noninferiority of 7 days vs 14 days of ciprofloxacin</td>
<td>Sandberg 2012</td>
</tr>
<tr>
<td><strong>Otitis media</strong></td>
<td>10 days</td>
<td>5 days</td>
<td>Clinical failure with 5 days vs 10 days</td>
<td>Hoberman 2016</td>
</tr>
<tr>
<td><strong>IAI</strong></td>
<td>7-14 days</td>
<td>4 days</td>
<td>Noninferiority of 4 days vs 8 days, with adequate source control</td>
<td>Sawyer 2015</td>
</tr>
<tr>
<td><strong>Uncomplicated GNR bacteria</strong></td>
<td>10-14 days</td>
<td>7 days</td>
<td>No difference between 7 days vs 14 days</td>
<td>Yahav 2018</td>
</tr>
<tr>
<td><strong>Febrile neutropenia (hematologic malignancies)</strong></td>
<td>Afebrile and ANC &gt;500 cells/µL</td>
<td>Afebrile x 48-72 hours regardless of ANC recovery</td>
<td>No difference in patients with apyrexia x 72 hours regardless of ANC recovery</td>
<td>Aguilar-Guisado 2017</td>
</tr>
<tr>
<td></td>
<td>Afebrile x 48 hours regardless of ANC recovery</td>
<td>5 days regardless of fever or ANC recovery</td>
<td>No difference in patients with apyrexia x 48 hours or automatic stop at day 5, regardless of ANC recovery</td>
<td>Le Clech 2018</td>
</tr>
</tbody>
</table>

ABSSSI indicates acute bacterial skin and skin structure infection; ANC, absolute neutrophil count; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; GNR, gram-negative rod; HAP, hospital-acquired pneumonia; IAI, intraabdominal infection; UTI, urinary tract infection; VAP, ventilator-acquired pneumonia.
Dalbavancin is a lipoglycopeptide antibiotic with potent activity against gram-positive organisms. It has a uniquely extended half-life of approximately 346 hours due to its long lipophilic side chain, allowing for once-weekly dosing. Although it is currently approved by the US Food and Drug Administration for the treatment of skin and soft tissue infections, its distinctive pharmacokinetic profile has piqued curiosity regarding its place in therapy for infections requiring long durations of antibiotics, such as osteomyelitis. The results of preliminary pharmacokinetic studies demonstrate sustained levels in the bone well above minimum inhibitory concentration values of most gram-positive pathogens for durations of up to 8 weeks. While there have been a handful of case reports of dalbavancin use in osteomyelitis, Rappo and colleagues are the first to conduct a more robust clinical evaluation.

This open-label trial randomized patients with acute or chronic osteomyelitis in a 7:1 fashion to receive either intravenous (IV) dalbavancin 1500 mg once weekly for 2 weeks or standard of care (SOC) antibiotics for 4 to 6 weeks. Patients must have had clinical and radiological evidence of osteomyelitis, plus an elevated C-reactive protein. Patients with a history of, or presenting with, multiple sites of osteomyelitis or those who have a prosthesis at the site of infection were excluded. Other notable exclusion criteria included concomitant infections such as endocarditis, necrotizing fasciitis, gram-negative bacteremia, infections secondary to burn wounds, sacral decubitus ulcers, and septic arthritis in an unrelated portion of the body. The primary outcome was the rate of clinical response, defined as resolution of infection without further need for antibiotics, in the clinically evaluable population at 6 weeks.

Seventy patients were randomized to dalbavancin and 10 patients to SOC treatment. Study participants were predominantly white males around 50 years of age. All patients underwent debridement with open biopsy, with the most common sites of infection being theibia, foot, and femur. Both methicillin-sensitive and resistant *Staphylococcus aureus*, as well as coagulase-negative *Staphylococcus* spp, were the most common causative organisms. All patients in the SOC arm initially received IV vancomycin (Vancocin), and 4 patients transitioned to IV linezolid (Zyvox) or IV levofloxacin (Levaquin) to complete the duration of therapy. Clinical cure at 6 weeks was achieved in 65/67 (97%) and 7/8 (88%) patients receiving dalbavancin and SOC, respectively. One clinical failure was noted in the SOC arm due to receiving more than 6 weeks of antibiotic therapy. Rates of clinical cure remained high in both arms, at 6 months and 1 year (Table). As expected, patients in the dalbavancin arm experienced significantly shorter inpatient lengths of stay (15.8 vs 33.3 days) and infusion times (1 vs 101.3 hours) compared with the SOC cohort. Treatment-emergent adverse events were noted in 10/70 (14.3%) dalbavancin patients and in none of the SOC patients. The reported adverse events were not thought to be related to the study drug.

In an era in which focus on outpatient parenteral therapy is steadily increasing, dalbavancin is proving to be a promising agent for difficult and long-standing infections, such as osteomyelitis. Due to its compact dosing regimen, dalbavancin may be ideal for patients intolerant of first-line IV or oral antibiotics or with significant compliance barriers. Although therapy may initially seem cost prohibitive, in theory, dalbavancin decreases labor associated with daily infusions, lab work for monitoring, and the risks and consequences of central line–associated infections. Until more bioavailable and tolerable oral options arrive on the market, 2 doses of dalbavancin appear to be a safe and convenient treatment option for osteomyelitis without apparent risk for poor long-term outcomes or treatment-emergent resistance.

References available at ContagionLive.com.

### HIGHLIGHTED STUDY

**Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety**

[published online December 10, 2018]


### Table. Interval Rates of Clinical Cure in the Modified Intention-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>DALBAVANCIN</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 3</td>
<td>63/67 (94%)</td>
<td>5/8 (63%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>65/67 (97%)</td>
<td>7/8 (88%)</td>
</tr>
<tr>
<td>Month 6</td>
<td>63/66 (95%)</td>
<td>7/8 (88%)</td>
</tr>
<tr>
<td>Year 1</td>
<td>63/66 (95%)</td>
<td>7/8 (88%)</td>
</tr>
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</table>

SOC indicates standard of care.
Atlanta HIV Rates Highlight the Need for Coordinated Effort in US Cities

By Laurie Saloman, MS

A lthough we’ve made strides in preventing and managing HIV in the United States with the advent of treatments like antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP), a hotbed of HIV still exists in the cosmopolitan city of Atlanta. Atlanta currently ranks third of all metropolitan areas in the United States for HIV cases, based on the rate of diagnosis. According to the US Centers for Disease Control and Prevention, in 2017, the Atlanta-Sandy Springs-Roswell area had a rate of 27.3 diagnoses of every 100,000 people, for 1607 new diagnoses.

As in other areas of the country, African Americans are disproportionately affected by HIV in Atlanta. In 2016, African Americans accounted for 44% of HIV diagnoses nationwide even though they make up only 12% of the population. These diagnoses are weighted heavily toward younger men who have sex with men.

Why is Atlanta such a focal point for HIV, particularly in the African American community and among young men? “There are many reasons; many of them systemic,” David Malebranche, MD, MPH, associate professor of medicine at Morehouse University in Atlanta, told *Contagion*. “We are in the South, which is a very racist and sexually prejudiced area of the country. This permeates into every level of policy, research, and treatment and care pertaining to HIV, from HIV criminalization laws, funding for HIV prevention and treatment, lack of Medicaid expansion, voter suppression, etc.”

Carlos del Rio, MD, chair of the Department of Global Health at the Rollins School of Public Health at Emory University and professor of medicine in the Division of Infectious Diseases at Emory University School of Medicine, agreed. “We’ve got the tools to do something,” he told *Contagion*. “Our hands are not tied. But...what is desperately needed is a coordinated citywide response.”

Asian Longhorned Tick Update: Eastern United States, Coastal Pacific Northwest Could Be Prime Survival Areas

By Michaela Fleming

H emaphysalis longicornis, also known as the Asian longhorned tick, is the first invasive tick to emerge in the United States in approximately 80 years. The tick has been classified as a new emerging disease threat by the US Centers for Disease Control and Prevention, and now a new study has found that the Asian longhorned tick could survive in the majority of the eastern United States and the coastal Pacific Northwest.

In the study, published in the *Journal of Medical Entomology*, Ilia Rochlin, PhD, an entomologist associated with the Rutgers University Center for Vector Biology, analyzed variables such as average annual rainfall and temperature from 260 locations in Asia and Australia where the tick has been previously reported and then developed a model that would combine this data with climate data from North America to determine suitable habitats for the tick. “The Asian longhorned tick will most likely become established in many areas of [the] temperate United States and southern Canada,” Dr. Rochlin told *Contagion*. “[W]e know that this tick species readily feeds on humans, pets, and wildlife. All these aspects increase the likelihood that the Asian longhorned tick may become a vector species transmitting some of the numerous tick-borne pathogens already circulating over much of eastern North America.”

Suitable areas for habitation in North America include coastal areas from eastern Canada to Virginia and North Carolina and from southern British Columbia to northern parts of California on the West Coast. The report also notes that suitable habitats were detected through inland North America from northern Louisiana to Wisconsin and into southern Ontario and Quebec, as well as Kentucky, Tennessee, and Missouri.

Top 5 Infectious Disease Concerns to Watch in 2019

By *Contagion* editorial staff

T he world of infectious disease is constantly evolving; an infection that is considered a national or global threat one year could be eliminated the next. After consulting with experts in the infectious disease space, the *Contagion* editorial staff has compiled a list of the top 5 infectious disease, both emerging and re-emerging, concerns to monitor in 2019.

**#5** *Candida auris*, a type of yeast, is particularly pesky because it is often multi-drug resistant, is outbreak prone in health care–related settings, and is difficult to identify.

**#4** Vaccine hesitancy: The growing hesitancy to vaccinate children is something to watch in 2019, as it could lead to the re-emergence of infectious diseases previously eliminated in the United States, such as measles.

**#3** Antibiotic resistance: The US Centers for Disease Control and Prevention released a comprehensive list of US antibiotic resistance threats in 2013 and is working on publishing an updated list for 2019. Considered among the most pressing threats: *Clostridium difficile*, Carbapenem-resistant Enterobacteriaceae, and extended-spectrum β-lactamase-producing Enterobacteriaceae.

**#2** The opioid epidemic could be the culprit of the next major infectious disease outbreak, experts warn. With the rise in drug use–associated infective endocarditis stemming from the use of intravenous drugs, hospitalizations and valve-replacement surgeries have also spiked.

**#1** Ebola and other hemorrhagic fevers: The infectious disease community was particularly focused on the Ebola outbreak in the Democratic Republic of the Congo in 2018. The current uncontrolled outbreak, the funding gaps that are arising, and the long-term efficacy of the deployed Merck vaccine are sure to keep the Ebola virus at the forefront of the public health discourse well into 2019.
Decontaminants Don’t Cut Bloodstream Infection Risk in Ventilated ICU Patients

By Alexandra Ward, MA

The use of digestive and oral decontaminants in patients in the intensive care unit (ICU) who are mechanically ventilated and have moderate to high antibiotic resistance is not associated with a reduction in ICU-acquired bloodstream infections caused by multidrug-resistant gram-negative bacteria.

According to the results of a randomized clinical trial conducted by investigators in the Netherlands and published in JAMA, when compared with standard care, the use of chlorhexidine (CHX) 1% mouthwash, selective oropharyngeal decontamination (SOD), and selective digestive tract decontamination (SDD) made no discernible difference in whether patients developed bloodstream infections from multidrug-resistant gram-negative bacteria.

The standard care routine involved chlorhexidine body washing and a hand hygiene improvement program. Investigators analyzed data from 13 European ICUs where 8665 patients with moderate to high antibiotic resistance had been on mechanical ventilation for at least 24 hours. Following a baseline period of 6 to 14 months, each decontaminant was administered 4 times daily for a 6-month period.

A total of 144 patients contracted ICU-acquired bloodstream infections with multidrug-resistant gram-negative bacteria. The infections occurred in 2.1%, 1.8%, 1.5%, and 1.2% of included patients during the baseline, CHX, SOD, and SDD periods, respectively. The median age of study participants was 64.1 years, and 64.2% of them were men.

“Selective decontamination [is] routinely used in ICUs in the Netherlands, but...has not been widely adopted in other countries, mainly because of limited efficacy data in settings with higher levels of antibiotic resistance and concern about emergence of antibiotic resistance, although the latter is not supported by meta-analyses,” Bastiaan H. Wittekamp, MD, PhD, University Medical Center Utrecht in the Netherlands, and colleagues wrote in JAMA.

“The study by Wittekamp and colleagues...shows no benefits in situations with higher antibiotic resistance patterns that unfortunately still prevail in most ICUs around the world,” Christina MJE Vandenbroucke-Grauls, MD, PhD, of Amsterdam University Medical Center, and Jos W.M. van der Meer, MD, PhD, of Radboud University Medical Center in the Netherlands, commented in an accompanying editorial. References available at ContagionLive.com.

CRISPR and DIY Biohacking: An Infectious Disease Threat to Watch in 2019

By Saskia V. Popescu, MPH, MA, CIC

Genome-editing technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR), allow scientists to edit DNA in specific sections of the genetic code. These methods have grown in popularity as scientists continue to refine the process and work through many of the technical kinks. Researchers are increasingly worried, however, because the use of CRISPR without any sort of oversight triggers a whole host of ethical questions that have yet to be answered.

CRISPR has great potential to improve the human condition through research, medicine, agriculture, etc. With great power, though, comes great responsibility. There is great concern that the technology is moving too fast for its own good and too fast for governance, regulation, and oversight to keep up. Biosecurity experts have been raising a red flag about the disruptive nature of genome editing, pointing out that the manipulation of biological systems and processes can have untold consequences. A recent study published by investigators from George Mason and Stanford universities notes that the technology must be taken seriously and the broader and ever-evolving landscape of biosecurity must be considered. For instance, it is possible that genome editing could one day be used to create biological weapons—think of a totally resistant tuberculosis or an influenza with increased virulence.

The growing popularity of genome editing also means that these technologies are no longer restricted to laboratories where there is some degree of oversight and regulatory processes; they now extend to the everyman’s garage. Do-it-yourself (DIY) biohacking allows people to play around with gene-editing technologies at home, with zero supervision or guidance. It’s not difficult to think about what the repercussions could be if the wrong person experiments with the genomic modification of viral or bacterial DNA.

Consider the 2017 horsepox synthesis that shook the scientific community. A researcher with “little specialized knowledge” synthesized an orthopoxvirus after mail-ordering DNA. Prior to publication, there were concerns within the biosecurity and biosafety communities regarding the implication of publishing a “how-to” for creating an orthopoxvirus and close relative of smallpox. As health security expert and co-author of the George Mason/Stanford biosecurity report Gregory Koblenz, PhD, noted, “This research is all risk and no reward.”

From horsepox to using CRISPR in babies to your DIY biohacker in their garage down the street, there are a host of reasons why genome editing is something to keep on your infectious disease radar in 2019. We mustn’t forget that, beyond the looming threat of CRISPR lie more nefarious possibilities. References available at ContagionLive.com.

First Clinical Trial Launched for Yellow Fever Treatment Candidate

By Michaela Fleming

The first patient has been dosed in the first in-human clinical trial evaluating a candidate drug (TY014) for the treatment of yellow fever. To date, no biologics or small molecules developed for the treatment of yellow fever have advanced to clinical trials.

TY014 is a monoclonal antibody that is being developed by Singapore-based Tychan to target the envelope protein on the surface of the yellow fever virus to prevent viral replication by limiting viral fusion to host cells. To evaluate the effectiveness of the monoclonal antibody in reducing disease severity, the investigators will enroll 67 healthy volunteers.

“We plan to complete safety assessments of TY014 in Singapore in healthy volunteers such that once safety for a certain dose is established, this dose can be tested in patients with yellow fever for tolerability and efficacy,” Ooi Eng Eong, PhD, MBBS, FRCPath, professor and deputy director of the Emerging Infectious Disease Program at Duke-National University of Singapore and an investigator on the clinical trial, told ContagionLive.com.
Omadacycline: A New Player for Team Tetracycline

An oral alternative for patients requiring broad-spectrum therapy in this era of resistance.

BY MARIA HEANEY, PHARMD

TETRACYCLINE HISTORY AND RESISTANCE

Tetracycline development began in the 1940s with the discovery of the natural product, chlortetracycline. One of the first agents termed "broad spectrum," chlortetracycline became widely used in humans because of its activity against rickettsiae and other organisms with no therapeutic options prior to its discovery. Following identification of the 4-ring core structure, which coined the class name “tetracycline antibiotics” in the 1950s, the first of the semisynthetic agents, tetracycline, was introduced. Derived from chlortetracycline, tetracycline has a higher potency and stability and more favorable adverse effect profile. The second-generation semisynthetic compounds, doxycycline and minocycline, were developed via modification of the tetracycline core in the 1960s and 1970s, respectively.

Shortly after the development of minocycline, resistance mechanisms to tetracyclines were identified: efflux pumps that eliminate drug molecules from within the cell and ribosomal protection mechanisms that reduce tetracycline-ribosomal binding. As with many other classes of antibiotics, resistance to tetracyclines increased over time; however, it was not until the early 2000s that minocycline was structurally modified to derive tigecycline. Although tigecycline offers a broad spectrum of activity that includes organisms resistant to tetracycline, its high rate of gastrointestinal toxicity, a US Food and Drug Administration (FDA) warning of increased mortality compared with other agents, and large volume of distribution preclude its use in many patients. These factors left the door open for novel tetracycline antibiotics with activity against organisms possessing tetracycline-resistance mechanisms and a more favorable adverse effect profile to come to market.

In 2018, 2 new tetracyclines, omadacycline and eravacycline, were approved by the FDA. Similar to tigecycline, these agents were designed to have activity specifically against tetracycline-resistant organisms. This article discusses omadacycline, a semisynthetic tetracycline derived from minocycline that has an aminomethyl group added to the C9 position of the tetracyclic core allowing it to overcome efflux systems and ribosomal protection mechanisms that confer resistance to older tetracyclines. It was approved by the FDA on October 2, 2018, for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSIs).

SPECTRUM OF ACTIVITY

Omadacycline is a broad-spectrum agent active against gram-positive organisms, including vancomycin-resistant Enterococcus (VRE) and methicillin-resistant Staphylococcus aureus; gram-negative organisms, including some extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and Acinetobacter baumannii; atypicals; and anaerobes. It is not active against the "MP3" of Morganella morganii, Proteus mirabilis, Providencia spp, and Pseudomonas aeruginosa. In an in vitro surveillance study, omadacycline had a minimum inhibitory concentration for 90% of the isolates (MIC90) of 0.5 μg/mL for S aureus, 0.5 μg/mL for VRE, and ≤0.06 μg/mL for multidrug-resistant Streptococcus pneumoniae compared with 8 μg/mL, 4 μg/mL, and 4 μg/mL, respectively, for doxycycline. The MIC90 of omadacycline was 4 μg/mL for ESBL-producing Escherichia coli and >4 μg/mL for ESBL-producing Klebsiella spp compared with >8 μg/mL for each for doxycycline, and 0.25 μg/mL and 1 μg/mL, respectively, for tigecycline. Omadacycline also demonstrated activity against some strains of Acinetobacter baumannii, although the MIC90 of 8 μg/mL indicates that it will be ineffective for some strains. The approved breakpoints for omadacycline are 4 μg/mL for Enterobacteriaceae, 0.5 μg/mL for S aureus, 0.25 μg/mL for Enterococcus faecalis, and 0.12 for Streptococcus anginosus; group.
In an in vitro environment mimicking the gut microbiome, omadacycline and moxifloxacin were instilled to determine induction of a simulated Clostridium difficile infection (CDI). Moxifloxacin, a fluoroquinolone, was previously observed to induce CDI in an in vitro gut model. Fluoroquinolones carry a high risk of CDI, a reason for avoiding their use in some patients. It was observed in this study by Moura and colleagues that the environment in which moxifloxacin was instilled had spore germination and vegetative cell proliferation, while the environment in which omadacycline was instilled had no vegetative cell proliferation. This suggests that omadacycline may provide activity against C difficile rather than increasing the risk for proliferation and development of CDI such as that seen with the fluoroquinolones.

**CLINICAL STUDIES**

Omadacycline had been studied in 3 phase 3 trials to date: the OASIS 1 and 2 trials for ABSSSIs, and the OPTIC trial for CABP. The OASIS 1 study compared intravenous to oral omadacycline with linezolid for 7 to 14 days for the treatment of ABSSSIs due to gram-positive pathogens in 627 adults. The number of patients with an abscess was capped at 30%, as the primary treatment for these patients is incision and drainage for source control. The primary endpoint was early clinical response, defined as ≥20% reduction in lesion size without receipt of another antimicrobial for ABSSSIs, at 48 to 72 hours of therapy. Omadacycline demonstrated noninferiority with a success rate of 84.8% compared with 85.5% with linezolid, a difference of −0.7% (95% CI, −6.3% to 4.9%). Omadacycline also demonstrated a clinical success rate, defined as sufficient resolution of infection according to the investigator’s analysis at the posttreatment evaluation, of 86.1% compared with 83.6% with linezolid.

The OASIS 2 study mirrored the OASIS 1 design, but compared oral-only omadacycline with linezolid in 720 adults, with up to 25% of randomized patients permitted to receive 1 dose of a short-acting antibiotic prior to the study drug. Omadacycline again demonstrated noninferiority in early clinical response compared with linezolid (87.3% vs. 82.5%) with a difference of 5.0% (95% CI, −0.2% to 10.5%). The clinical success rate at the posttreatment evaluation was 84.2% with omadacycline versus 80.8% with linezolid.

Omadacycline received FDA approval for ABSSSIs at an indicated dose of 200 mg intravenously (IV) once or 100 mg IV every 12 hours on day 1, followed by a maintenance regimen of 100 mg IV once or 200 mg IV once or 300 mg orally once daily.12

**PHARMACOKINETICS**

Following a single 100-mg IV dose, omadacycline achieved a maximum concentration (Cmax) of 1507 ng/mL and an area under the curve (AUC) of 9358 h*ng/mL. The mean steady-state Cmax with intravenous administration is 2120 ng/mL, and AUC is 12,140 h*ng/mL. Omadacycline is 34.5% bioavailable, explaining its oral dosing at 300 mg, which achieved a Cmax of 548 ng/mL and AUC of 9399 h*ng/mL following a single dose. The mean steady-state Cmax with oral administration of 300-mg tablets is 952 ng/mL and AUC is 11,156 h*ng/mL, comparable to the 100-mg intravenous dose. There is a significant food effect with oral administration. When administered 2 hours after a high-fat, nondairy meal, Cmax and AUC were reduced by 40% and 59%, respectively. As with other tetracyclines, concurrent administration with multivalent cations such as calcium should be avoided with the oral formulation.12

The mean volume of distribution with intravenous administration is 190 L, and protein binding is estimated to be 20%. Omadacycline had a steady-state 24-hour mean epithelial fluid lining concentration of 0.41 mg/L and mean alveolar macrophage concentration of 11.06 mg/L, indicating sufficient lung concentrations.12 Omadacycline is not metabolized and does not induce or inhibit CYP450 enzymes. It has a half-life of approximately 15 hours and is eliminated mainly in the feces (81%) unchanged, with 14% renal elimination following oral administration. Dosage adjustment is not required for renal or hepatic impairment.12

**ADVERSE REACTIONS, WARNINGS, AND PRECAUTIONS**

Warnings and precautions associated with omadacycline use are consistent with those reported for older tetracyclines, including tooth discoloration and inhibition of bone growth in children, as well as hypersensitivity. Additionally, omadacycline carries a labeled warning for a mortality imbalance in patients with CABP: 2% with omadacycline versus 1% with moxifloxacin. All deaths occurred in patients over 65 years, most of whom had multiple comorbidities.22 Adverse events most commonly observed in clinical studies were transaminase elevation, headache, and infusion-site reactions.52 Although nausea, vomiting, and diarrhea occurred among patients receiving omadacycline, its structural modification may reduce the incidence of these events compared with that of tigecycline.43 Within 1 hour of dosing omadacycline 100 mg IV, a mean increase in heart rate of 17 bpm was observed, although no symptoms or QTc changes were found.53

**PLACE IN THERAPY**

Although omadacycline shows some activity against resistant bacteria, the in vitro and clinical data for multidrug-resistant organisms are limited at this time. Omadacycline presents an alternative agent for patients with multiple antimicrobial allergies that limit therapeutic options.

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**Omadacycline presents an alternative agent for patients with multiple antimicrobial allergies that limit therapeutic options.**

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References available at ContagionLive.com.
In 1987, pharmacokinetic/pharmacodynamic data from mouse thigh models were presented that showed that the 24-hour area under the concentration time curve to minimum inhibitory concentration ratio, or AUC:MIC, was the best predictor of vancomycin efficacy against *Staphylococcus aureus*. Now, more than 30 years later, we are in the middle of a paradigm shift from trough-guided vancomycin dosing to true AUC-guided dosing.

**LAY OFF THE TROUGH AND EMBRACE THE CURVE**

Consensus guidelines on vancomycin therapeutic drug monitoring, published in 2009, suggest a serum trough concentration range of 15 to 20 mg/L as a surrogate goal for an AUC:MIC ≥400 in patients with moderate to severe *S. aureus* infections. More recent evidence, however, suggests troughs are not an ideal surrogate for AUC, with many patients able to achieve a goal AUC:MIC ≥400 in patients with moderate to severe *S. aureus* infections.

More recent evidence, however, suggests troughs are not an ideal surrogate for AUC, with many patients able to achieve a goal AUC:MIC with troughs less than 15 mg/L. Furthermore, vancomycin troughs of 15 to 20 mg/L have been associated with increased risk of nephrotoxicity, with no corresponding benefit in terms of efficacy. A growing body of retrospective observational evidence, in addition to a few prospective single-center studies, has supported the efficacy of AUC-guided vancomycin dosing for a number of moderate to severe infection types. Prospective, multicenter, observational data have been preliminarily presented, and the full results are eagerly anticipated.

**LEVEL UP AND CRUNCH THE NUMBERS**

There are a handful of methods of AUC estimation that span a continuum in terms of reliability. The Moise-Broder equation, which is the total daily dose of vancomycin divided by a creatinine clearance (CrCl)-based estimate of vancomycin clearance, is a straightforward method requiring no serum concentrations. There is evidence, however, suggesting CrCl-based equations underestimate actual AUC.

Another equation-based process, and the one chosen by our institution, is the Sawchuk-Zaske method, which uses 2-level pharmacokinetics and assumes a 1-compartment model. Two steady state, postdistribution vancomycin levels drawn during the same interval can be used to calculate the...
area of the linear and logarithmic trapezoids of the vancomycin concentration time curve, resulting in a patient-specific AUC estimate. Dosing calculators, whether home-grown, electronic medical record (EMR)-based, or commercially available, can make the Sawchuk-Zaske method achievable for many institutions.

The third major method is map Bayesian modeling, which uses population pharmacokinetic data, as well as 1 or more patient-specific serum vancomycin levels, to create probability distributions. Although this method results in the most accurate AUC predictions, Bayesian modeling software have not historically been widely available for clinical use in a user-friendly format. This has been changing in recent years, and Bayesian modeling may one day be the standard for most hospitals.

THEORY TO BEDSIDE: AVOIDING IMPLEMENTATION EXASPERATION

The first step is determining the best method for calculating AUC at your institution. Multiple Bayesian modeling programs are available or in development. Some can even be incorporated into EMRs, although at a significant cost. AUC calculation based on 2-level pharmacokinetics is likely the least expensive and quickest to implement compared with purchasing and integrating a Bayesian program. Any home-grown calculators, however, will need to be carefully created and validated. If your institution is able to purchase an online software program or create an electronic calculator in the EMR, these would likely be more user-friendly and provide more transparency for physicians and pharmacists. If a significant investment is required (ie, time and money), a simpler approach using a spreadsheet-based or web-based calculator may be preferred.

Once an AUC calculation method is chosen, a new institutional guideline will need to be created for all pharmacists involved in vancomycin dosing. It should provide a clear step-by-step process and outline indications for which AUC-guided dosing is indicated (Table) to minimize errors and confusion. In addition, EMR documentation will need to be updated to incorporate additional vancomycin levels and pharmacokinetic data points involved in AUC calculations.

Once a plan is in place, the next step is obtaining medical and pharmacy staff support. Prior to the 2009 guideline, pharmacists and physicians routinely measured peak and trough concentrations. Then they were told peaks were unnecessary and only troughs mattered. Now with AUC-guided dosing, peaks and troughs are needed again, but for different reasons. Many current pharmacists and physicians haven’t practiced in a world of vancomycin peaks and troughs; now with AUC-guided dosing, peaks and troughs are needed again, but for different reasons. Many current pharmacists and physicians haven’t practiced in a world of vancomycin peaks and troughs. They were told peaks were unnecessary and only troughs mattered. Now with AUC-guided dosing, peaks and troughs are needed again, but for different reasons. Many current pharmacists and physicians haven’t practiced in a world of vancomycin peaks and troughs.

THE FORESEEABLE FUTURE

An updated consensus vancomycin dosing and monitoring guideline is currently under development and is anticipated to support the shift to AUC-guided dosing. Many opportunities remain for prospective studies to add to our current knowledge, and increasing availability of Bayesian modeling software may further revolutionize and simplify AUC-guided vancomycin dosing in the not-too-distant future.

References are available at ContagionLive.com.
A growing number of scientists and investigators are exploring the theory that Alzheimer disease is caused by a germ.

In Small Corner of Alzheimer’s Research, “Germ Theory” Begins to Gain Traction

A new effort makes the case that scientists have been looking in the wrong direction.

BY JARED KALTWASSER

As a trained scientist and longtime medical publisher, Leslie Norins, MD, PhD, knew a thing or two about Alzheimer disease. But when he started to take a closer look at the disease back in 2016, he assumed he had a lot to catch up on.

Dr. Norins lives in Naples, Florida, a city popular with retirees and thus a place with above-average rates of Alzheimer disease. Before his publishing career, Dr. Norins studied venereal disease as a lab director at the US Centers for Disease Control and Prevention (CDC).

“I thought that, simply on general principles, I should update myself on this disease—which I had last studied briefly way back at Duke Medical School,” he told *Contagion*.

What he found was plenty of research, but the same bottom line. Back when he was at the CDC, the cause of Alzheimer disease was a mystery and there was no cure. When he looked into the issue again 2 years ago, he said, “What a surprise—56 years later still same situation!”

And so, he started digging. “One could start at the molecule/cellular level and review journal articles upward to [the] patients/macro/population/epidemiology level. Or vice versa,” he said, “I chose this latter.”

Dr. Norins started to look into whether antibiotics and antivirals had ever been tested in an Alzheimer disease context. He found no evidence of such examination.

Then came another question: Had serum antibody tests ever been performed on samples from patients who would go on to develop Alzheimer disease? In Dr. Norins’ mind, it made sense to test those samples for things like syphilis, chlamydia, retroviruses, and more. Yet, very little of such research was available.

“From my early days at the CDC, I was well aware syphilis could go underground for decades...only to show up 20 to 30 years later as brain damage,” he noted, adding that other viruses can also be latent for decades as well.

“Bottom line,” he said, “nobody has checked for even common agents, let alone rare ones, especially those that can have long latent periods.”

Dr. Norins became alarmed by what seemed to him to be a tremendous void in Alzheimer disease research. At
the same time, he knew he was new to the game and that many in the Alzheimer disease research community had long settled on the idea that amyloid plaques and protein tangles were the culprits. “I began to be haunted by the fairy tale, ‘The Emperor’s New Clothes,’” he said. “Could it be that the ALZ emperor ‘amyloid and tau’ is really not wearing any clothes?”

And so, last year, Dr. Norins published a white paper arguing that researchers needed to look in a new direction, at the idea that a germ might cause Alzheimer disease. He put his money where his mouth was, setting up a $1-million challenge award to be given to any scientist who can offer “persuasive proof” that Alzheimer disease is caused by a germ.

**AN ALTERNATE THEORY**

So far, it’s just a theory. But if part of the goal was to change the conversation around Alzheimer disease, Dr. Norins appears to be making headway. His logic is outlined in the white paper. First, he notes, the brain isn’t sterile; it can contain bacteria. It’s also well known that bacteria, along with other pathogenic organisms, can invade and damage the central nervous system.

Amyloid beta and inflammation, both of which are suspected to play a role in Alzheimer disease, can be sparked by microorganisms. He also noted that antibiotics have been found, in some cases, to have a beneficial impact on the disease.

Dr. Norins even suggests that Alzheimer disease could be transmissible. He points to 2010 study results that suggested spouses of patients with dementia had a higher chance of getting dementia themselves. Another study from that same year found that neurosurgeons face a particularly high risk of dying from Alzheimer disease, which Norins believes could be an indication that an Alzheimer germ is being transmitted in the operating room.

**THE RESEARCH COMMUNITY’S CAUTIOUS REACTION**

If Dr. Norins is running the opposite direction of the Alzheimer disease research “establishment,” he said he hasn’t been met with hostility; however, neither have his ideas been embraced.

“In fact, I would characterize it as coolness and ‘studied avoidance,’” he said. “As in, ‘Let’s hope that skunk leaves the party before he stinks it up for everybody receiving millions of dollars in amyloid-tau grants and the many jobs this provides the scientific community and millions more in the form of bureaucracy or institutional pushback.’

Yet, in some ways, the “germ theory” is gaining traction. Findings from a pair of studies published in summer 2018 suggest that herpesvirus could play a role in the progression of Alzheimer disease.

“These data support the notion that [amyloid-β peptide, or Aβ] might play a protective role in central nervous system innate immunity and suggest an Alzheimer disease etiological mechanism in which herpesviridae infection may directly promote Aβ amyloidosis,” wrote first author William Eimer, PhD, of Massachusetts General Hospital and Harvard Medical School, in one of the studies.

Keith Fargo, PhD, director of scientific programs and outreach at the advocacy group Alzheimer’s Association, said those studies lend scientific credibility to the idea that viruses or other infectious agents might have a role to play in the disease. “We will likely see more scientists taking this hypothesis seriously and perhaps even starting to research it themselves,” he told Contagion. “What’s especially valuable about these 2 papers is that they lay out plausible mechanisms for how microorganisms might be causative in [Alzheimer disease]—something previous investigations largely failed to do.”

In fact, the Alzheimer’s Association has awarded more than $1.5 million in the past 5 years to investigators looking into the role of germs, microbes, and infectious agents in Alzheimer disease and other dementias, Dr. Fargo said.

“There is some preliminary research that suggests that microbes or germs may be in some way associated with the cause or progression of Alzheimer disease and other dementias, but exactly how is still unclear,” he added.

However, Dr. Fargo downplayed the notion that Alzheimer disease itself is transmissible. “It is very important to note that Alzheimer disease is not contagious, so people should not avoid friends or family members with the disease,” he said.

If it were transmissible, there might be geographic patterns or “hot spots” of Alzheimer disease. Dr. Norins said that’s something he’s considered, but there’s no persuasive evidence of zones with high concentrations of Alzheimer disease, and country-level data vary widely depending on public health infrastructure and other factors.

Dr. Fargo, meanwhile, said there are also emerging questions about whether the gut microbiome, and thus diet, have an impact on Alzheimer disease. Data on that question were presented in July at the association’s international conference, he noted.

“[I]t is especially shocking that there have not been large, official trials of every single relatively harmless, already-US Food and Drug Administration–approved antibiotic, antiviral, etc,” he said. “There is almost nothing to lose.”

—Keith Fargo, PhD
When a West African Ebola outbreak overtook international headlines in 2014, the constant media attention was about more than the symptoms and consequences of the deadly virus. It was also about fear that the virus would spread far and wide.

Eleven people were treated for Ebola in the United States, most of whom contracted the disease in West Africa, and all but 2 recovered. Although the outbreak’s impact on Americans was infinitesimal compared with its impact in Sierra Leone and Liberia, the US cases caused outsized panic due to 1 factor: Ebola’s famously long incubation period of up to 3 weeks. Americans knew the numbers were small, but what if those official numbers were hiding something much, much bigger?

CERTAINTY INSTEAD OF PANIC

On one hand, the 2014 Ebola episode is a cautionary tale about the dangers of public panics. On the other hand, it is an example of something epidemiologists cannot avoid: new emerging diseases are appearing—and evolving—in humans, and they are not all easy to detect or contain.

Recently, some researchers have begun asking the question of whether patients ought to be preemptively screened for diseases and other health problems after traveling overseas. John H. Connor, PhD, associate professor of microbiology at Boston University’s School of Medicine and its National Emerging Infectious Disease Laboratories (NEIDL), said there are important reasons to get to the bottom of potential Ebola infections as soon as possible, particularly in the cases of health care workers who have traveled to Ebola outbreak zones and the family members or others with whom they have come into contact upon return.

“For both of these groups, having a test that can look for early signs of infection would be clinically useful because it would allow for more effective quarantine during the early stages of the disease and provide a level of fear reduction to those at risk,” he said.

Dr. Connor is currently working on a test that can do just that. Last month, he and colleagues published findings in Science Translational Medicine showing that their rapid diagnostic test can detect antigens for Ebola, Lassa fever virus, and malaria in less than a half hour.

“We undertook a study recently with colleagues at [the United States Army Medical Research Institute of Infectious Diseases] where we looked at the circulating immune response in nonhuman primates infected with Ebola virus,” he said.

The question was whether something could be identified in the primates’ immune responses that could positively identify a virus at work and differentiate it from other febrile diseases.

“Our work showed there are host responses, not viral RNA, that show up in the blood,” Dr. Connor said. “Importantly, these markers showed up prior to fever in many cases. We
think that a test tracking these host responses would make early infection detection a possibility.”

WHOM TO TEST, AND WHEN?

Jesse Waggoner, MD, an assistant professor of medicine at the Emory University School of Medicine and Rollins School of Public Health, said a proactive approach (including pretravel health care) is the key to safe travel. “Patients should have a low threshold to present to their medical practitioner or contact their travel medicine provider for any new illness that develops during travel or in the few months following their return,” said Dr. Waggoner, who also treats patients at Emory’s TravelWell clinic for pre- and postinternational travel health care.

Patients who travel to countries with malaria, for instance, should seek medical attention even if fever is their only symptom and even if they took malaria prophylaxis prior to departure, he said.

Dr. Waggoner said gastrointestinal illnesses or respiratory infections are also common reasons for posttravel doctors’ visits. And while he said patients should tell their physician where they traveled, patients shouldn’t base their decision to see the doctor on where they traveled.

“The list of infections that we consider as providers will change based on where a patient has been, but individuals should not delay or forgo medical care because of travel to what is perceived to be a low-risk destination,” he said.

What about when there are no symptoms? Dr. Waggoner said that’s a question being studied, but at present, asymptomatic screening decisions need to be answered on a case-by-case basis.

“For common, short-term travel itineraries (days to a few weeks), screening is very low yield and is generally not recommended,” he said. “If individuals have prolonged exposure to freshwater or unsanitary conditions, screening for certain parasitic infections may be warranted.”

Waggoner added that patients who have sex with new partners while traveling might consider proactive testing for sexually transmitted infections.

A number of studies have been performed in recent years looking into the efficacy of asymptomatic screening. They have shown little in the way of concrete benefit. For instance, a 2011 study that examined whether blood eosinophilia could indicate that a traveler had contracted schistosomiasis, strongyloidiasis, filariasis, and toxocariasis, showed the test, “appeared to be of no value in routine screening of asymptomatic travelers.”

Another study, published in 2014, looked at the feasibility of using interferon gamma release assays (IGRAs) to screen patients for tuberculosis (TB) after long-term travel to countries where TB is endemic. They found that the screening could be used, but only 8 weeks after their return. And even then, widespread screening wasn’t necessarily worthwhile.

“One might even argue that IGRA testing should be limited to only those travellers who are going to work in a medical setting,” wrote Floor Elfrink, MD, of the Dutch Public Health Service, and colleagues.

In 2014, Dutch researchers also looked at whether routine screening of patients who undertook long-term travel (median time: 12 weeks) to the subtropics was a worthwhile way to detect parasitic infections. Although the study of 556 patients identified several infected patients, they found that routine screening for most of the parasitic illnesses was not warranted. When it came to schistosomiasis, detection rates were somewhat higher; they were also closely correlated with swimming in particular freshwater lakes in countries where the parasitic illness was endemic. Author Darius Soomawalla, MD, PhD, concluded that such screening be limited to patients with a history of exposure to freshwater in highly endemic countries.

The US Centers for Disease Control and Prevention (CDC) generally has no official position on whether to screen asymptomatic travelers for most diseases. Writing in the CDC’s most recent Yellow Book for international travel, Michael Libman, MD, of McGill University’s School of Medicine, Montréal, said there is little research on the cost-effectiveness of such screening, and he noted that it can be difficult to pin down risk based on patient self-reports.

“[E]xposure history is often unreliable and poorly predictive of infection, the value of a detailed itinerary is limited by incomplete information on where pathogens are endemic, and the type of travel often does not provide a practical assessment of risk,” he wrote.

Dr. Waggoner added that most general practitioners aren’t equipped with the tools or knowledge to screen for emerging diseases. Even though the workup for common symptoms can be done in a general outpatient setting, he said, “it is unrealistic and unfair to expect our general practitioners to remain current on outbreaks in foreign countries and know the appropriate testing for all potential travel-related infections.”

Waggoner said it’s better for patients to see a specialist, if possible, for posttravel illnesses.

PROGRESS FOR SPECIFIC, HIGH-PROFILE VIRUSES

Back at NEIDL, Dr. Connor said the technology he and his colleagues are developing could be used to effectively—and quickly—screen for a number of dangerous diseases, particularly those that initially “hide” in the liver and spleen, like Ebola, Lassa, and Marburg.

“These viruses often don’t enter the bloodstream in significant amounts until a lot of virus replication has gone on, so having earlier indicators of infection are important to find,” he said.

Still, Dr. Connor said these tests would be of primary benefit to people who had visited centers with outbreaks or to health care workers who had treated patients suffering from these infections.

“I think that administration to all returning travelers would likely be too complicated. It would most likely lead to large populations of travelers being tracked for a very low-probability event,” he said. “Focusing on travelers that are at high risk would likely be the best approach.”

References are available at ContagionLive.com.

Patients should have a low threshold to present to their medical practitioner or contact their travel medicine provider for any new illness that develops during travel or in the few months following their return.

—Jesse Waggoner, MD
Antiretroviral therapy (ART) has advanced considerably, from the approval of zidovudine (AZT) in 1987 through the emergence of triple-drug therapy and single-tablet regimens.1,2 Newer agents have fewer adverse effects and provide a life expectancy similar to individuals without HIV infection.3 With clear mortality benefits linked to ART, attention has now turned to the benefits of ART in preventing HIV transmission. HIV treatment as prevention (TasP) has now become an important part of the HIV prevention toolbox.4

The Undetectable Equals Untransmittable, or U=U, movement is a global campaign definitively stating that people living with HIV (PLWH) who have undetectable HIV RNA are unable to transmit HIV.5 By educating people, the hope is that they will get tested and, if necessary, start and stay on treatment. This message has been endorsed by many organizations, including the US Centers for Disease Control and Prevention6 and the HIV Medicine Association.7

For many PLWH, the message of U=U can be life changing. This message that they are not able to transmit the virus if they have undetectable HIV RNA removes some of the stigma of living with HIV. Some patients may have chosen to completely avoid relationships for fear of transmission, but they now can have a feeling of empowerment to make decisions in their own sexual relationships. The U=U message may allow them to feel comfortable pursuing relationships. For health care providers, the U=U movement gives them evidence to present to patients in support of starting therapy. In addition to the mortality benefits patients will receive from ART and achieving virologic suppression, there are transmission benefits to their partners and the general public. Patients are playing their own part in ending the HIV epidemic.

**FOUR STUDIES SUPPORT U=U**

There have been 4 main studies providing data behind the U=U movement. Each builds on the next, with U=U becoming more and more definitive. Although they all have slightly different populations and inclusion criteria, in each study, transmissions were essentially zero.

The HIV Prevention Trials Network (HPTN) 052 study reported an interim data analysis and a study including more than 5 years of follow-up data to assess the effect of ART as prevention of HIV transmission.8,9 The study assigned 1763 index participants (serodiscordant couples, 97% heterosexual) to either early ART (started at enrollment; n = 886) or delayed ART (started when 2 consecutive CD4 measurements fell below 250 cells/mm<sup>3</sup> or if the patient had an AIDS-defining illness; n = 877). Couples were required to have had a stable relationship for at least 3 months and reported at least 3 episodes of vaginal or anal intercourse over this time. HIV-negative partners were encouraged to attend study visits to receive counseling on risk reduction and condom use, treatment of sexually transmitted infections, and management of other medical conditions. After 10,031 person-years of follow-up in the index participants and 8509 person-years in the partners, there were 72 HIV infections for which viral-linkage status could be determined.
with 46 virologically linked to partners (3 in the early and 43 in the delayed ART groups) and 26 virologically unlinked to partners. There were no linked infections when the index participant had stably suppressed HIV RNA. The authors concluded that early initiation of ART led to a sustained decrease in linked HIV infections in sexual partners. HPTN 052 laid the groundwork for U=U; however, the majority of couples were heterosexual and condom use and risk reduction were emphasized. More evidence of men having sex with men (MSM) was needed.

Opposites Attract was an observational cohort study of serodiscordant male homosexual couples recruited from 2012 to 2016. To be included, positive partners must have had HIV RNA less than 200 copies/mL. There were 343 couples with at least 1 follow-up visit, for a total of 588.4 couple-years. In this study, HIV-negative partners were permitted to use pre-exposure prophylaxis. Three new HIV infections occurred; however, none were phylogenetically linked. The authors concluded that HIV treatment as prevention in MSM is effective and that increased HIV testing and linkage to treatment is an important strategy for HIV prevention. Opposites Attract included MSM couples; however, the numbers were small and more evidence was necessary.

The PARTNER (Partners of People on ART—A New Evaluation of the Risks) study enrolled serodiscordant couples between September 2010 and May 2014 who reported condomless sex. PLWH must have had an HIV RNA less than 200 copies/mL. Any transmissions to negative partners were analyzed to determine if the transmission could be linked to the positive partner. Among the 1166 serodiscordant couples enrolled (548 heterosexual and 340 MSM), 888 provided 1238 eligible couple-years of follow-up, with a median of 2 years (interquartile range [IQR], 0.5-6.3) of condomless sex (median 42 condomless sex acts per year) was reported. Condomless sex outside of the main partnership was reported by 285 HIV-negative men. There were 17 HIV transmissions; however, none were phylogenetically linked within couples. The authors concluded that the PARTNER study provides a similar level of confidence of evidence for MSM couples as for heterosexual couples.

It is important to note that in all of these studies, to prevent transmissions, the PLWH who were on ART had an HIV RNA at least less than 200 copies/mL. In a clinical trial, there are many resources to ensure that patients have access to ART, which may not occur in clinical practice. Patients may not have the resources to achieve an undetectable HIV RNA due to medication access issues. They may choose not to start treatment or they may not be ready to start treatment.

**HIV RNA MEASURES 1 TIME POINT**

HIV RNA measurement is a snapshot in time. Patients may start taking medication in the weeks leading up to a doctor’s appointment because they know that they will have bloodwork drawn. They want to be “undetectable” to avoid “being in trouble” with their provider. They want that “pat on the back” from their provider for having their HIV RNA under control and may not understand the far-reaching implications of having detectable HIV RNA between appointments. Patients may have up to 1 year between visits. Providers may believe that patients are undetectable for the entire duration between appointments when, in reality, they were undetectable for that snapshot analysis and their appointment. Patients should be counseled to remain adherent to ART in order to stay undetectable. They should also be encouraged to keep all medical appointments so that they and their partners can be aware of their HIV RNA status.

The message of U=U is an important and groundbreaking one. However, we must be careful of the message that is reaching our patients. The patient must be undetectable at the time of possible transmission, not just 6 months earlier at the appointment when bloodwork was drawn. Medication access and adherence continue to be an important underpinning issue of U=U. The research and data are there behind the message; the delivery remains an important factor.

References available at ContagionLive.com.
The US Food and Drug Administration (FDA) approved ceftazidime-avibactam for clinical use in February 2015, effectively changing the landscape for treatment of carbapenem-resistant Enterobacteriaceae (CRE) infections. Compared with traditional salvage agents (including aminoglycosides, colistin, and tigecycline), treatment with ceftazidime-avibactam is safer and more effective.1-3 Despite these encouraging findings, the emergence of ceftazidime-avibactam resistance has been reported and may pose a serious threat to patients. Over the past 4 years, new insights into the molecular mechanisms and predisposing factors associated with ceftazidime-avibactam resistance have been described.

Avibactam is a novel diazabicyclooctane β-lactamase inhibitor that reversibly inhibits Ambler classes A, C, and some class D β-lactamases. Avibactam does not inhibit class B metallo-β-lactamases (MBLs). In surveillance studies, the combination of ceftazidime-avibactam demonstrated potent in vitro activity against a wide spectrum of gram-negative pathogens, including multidrug-resistant Enterobacteriaceae and CRE.4-6 Categorized by the FDA-approved susceptibility breakpoint (≤8/4 µg/mL), ceftazidime-avibactam was active against 97.5% of contemporary CRE isolates.6 In a subsequent study, 99.3% of Klebsiella pneumoniae carbapenemase (KPC)-producing CRE were susceptible.5 Against a KPC-producing K pneumoniae isolate, Nelson and colleagues demonstrated that a higher copy number of blaKPC-3 plus decreased outer membrane permeability may manifest in resistance to ceftazidime-avibactam.7 Decreased outer membrane permeability contributed to a resistant phenotype in one other KPC K pneumoniae identified through surveillance studies.3 Although drug efflux does not appear to be a major contributor to resistance,10 a rare 4 amino acid insertion into penicillin binding protein 3 (PBP3) has been implicated in decreased susceptibility against a single KPC Escherichia coli isolate.12 Taken together, the data suggest combinations of increased blaKPC-3 copy number, impaired outer membrane permeability, and/or variant PBP3 may contribute to decreased ceftazidime-avibactam susceptibility in a minority of KPC-producing isolates not previously exposed to the agent.

TREATMENT-RELATED RESISTANCE
Of greater concern to clinicians are recent reports describing the emergence of ceftazidime-avibactam resistance following treatment. In a study of 77 patients treated for CRE infections, resistance emerged in 10%, including 14% of patients infected by K pneumoniae and 32% with microbiologic failures.13 Resistant isolates harbored blaKPC-3 Ω-loop mutations that encoded variant KPC-3 enzymes. The most common variant featured a tyrosine for aspartic acid substitution at Ambler amino acid position 179 (D179Y),13,14 which was successfully predicted by prior in high rates of resistance; however, 86% of resistant isolates harbored a New Delhi metallo-β-lactamase that is refractory to avibactam inhibition.9 Against a KPC-producing K pneumoniae isolate, Nelson and colleagues demonstrated that a higher copy number of blaKPC-3 plus decreased outer membrane permeability may manifest in resistance to ceftazidime-avibactam.8 Decreased outer membrane permeability contributed to a resistant phenotype in one other KPC K pneumoniae identified through surveillance studies.3 Although drug efflux does not appear to be a major contributor to resistance,10,11 a rare 4 amino acid insertion into penicillin binding protein 3 (PBP3) has been implicated in decreased susceptibility against a single KPC Escherichia coli isolate.12 Taken together, the data suggest combinations of increased blaKPC-3 copy number, impaired outer membrane permeability, and/or variant PBP3 may contribute to decreased ceftazidime-avibactam susceptibility in a minority of KPC-producing isolates not previously exposed to the agent.

Emergence of Ceftazidime-Avibactam Resistance: What Have We Learned in the Past 4 Years?
Ceftazidime-avibactam is a novel treatment for CRE infections, but reports of resistance are increasing.

BY RYAN K. SHIELDS, PHARMD, MS
**Multidrug-Resistant Infections**

plazomicin), carbapenems, tetracyclines (including eravacycline), potential partner agents include the aminoglycosides (including colistin, and fosfomycin. In vitro colistin does not potentiate the killing of ceftazidime-avibactam against KPC K pneumoniae, and may select for ceftazidime-avibactam resistant subpopulations. Carbapenem combinations may mitigate the emergence of bla_KPC mutations or treat ceftazidime-avibactam resistant subpopulations should they arise. Against KPC K pneumoniae, synergy between meropenem and ceftazidime-avibactam has been reported and shown to prevent the emergence of resistance in preliminary studies. A key factor that may influence the activity of the combination is reverted carbapenem susceptibility, which varies by bla_KPC mutation and the presence or absence of porin gene mutations. Additional studies are needed to define optimized ceftazidime-avibactam combinations in vitro, and subsequently in vivo. Until such data are available, clinicians should exercise caution when implementing combination approaches in patients.

**Clinicians should be particularly vigilant in monitoring for resistance among CRE-infected patients.**

### Patient Characteristics and Risk Factors

To date, 16 cases of treatment-related or emerging ceftazidime-avibactam resistance have been reported in the literature, and at least 4 other cases have been described in preliminary reports at conference proceedings. Of 13 available cases are summarized in the Table (see online). All but 1 case has been observed in K pneumoniae, the most common CRE species worldwide. Remarkably, ceftazidime-avibactam resistance has emerged within varying clonal backgrounds of KPC K pneumoniae, including sequence type (ST) 258, the predominant international clone; ST307, an emerging clone; and ST1519, a rare clone in Europe. Resistance also differs by a single amino acid at Ambler position 273 (H273Y). Resistance among patients. Recently, 2 cases of resistance were reported among K pneumoniae isolates carrying KPC-2 variants with characteristic D179Y substitutions.

### Clinical and Laboratory Considerations

Susceptibility testing should be performed routinely when ceftazidime-avibactam is being considered for treatment. Of the commercially available methods, testing by disk diffusion may overcall resistance at the currently proposed cutoff values. Gradient strip testing, on the other hand, has been shown to reliably correlate with the gold-standard broth microdilution method. Importantly, clinicians and microbiologists now have a better understanding of the nuances in detecting ceftazidime-avibactam resistance. Because automated susceptibility testing systems tend to lag behind FDA approval of new antibiotics, routine surveillance for resistance is rarely employed. Testing ceftazidime-avibactam through reflex algorithms or by clinician request may fail to trigger testing against KPC-variant isolates with restored carbapenem susceptibility. In such cases, clinicians and laboratories must work collaboratively to recognize relevant phenotypes against isolates collected from patients with a history of CRE infection and recent ceftazidime-avibactam exposure.

In conclusion, clinical development of ceftazidime-avibactam has marked a major advance for treatment of CRE infections. The emergence of resistance following treatment is concerning, but not surprising given the fate of other antibiotics after regulatory approval. Clinicians should be particularly vigilant in monitoring for resistance among CRE-infected patients with deep-seated sources of infection and other predisposing factors, such as immunosuppression and receipt of RRT. The most common mechanisms by which resistance is mediated are mutations within the bla_KPC gene that encodes variant KPC enzymes with altered spectra of activity, that may include reverted susceptibility to carbapenems. As use of ceftazidime-avibactam expands, it is likely that other mechanisms of resistance will be identified. Future research efforts are needed to define effective dosing regimens and combination strategies that will preserve the effectiveness of ceftazidime-avibactam and limit resistance. Taking everything into consideration, the real-world experience with ceftazidime-avibactam has helped to shift CRE treatment paradigms away from older, less effective strategies while setting the bar for other new agents to be measured by. Ongoing reporting of the real-world experiences for each of these agents will be essential in further defining their therapeutic niche in the landscape of CRE management.

References and table are available at ContagionLive.com.
Twitter is useful for searching for up-to-date information, sharing stories and information related to antibiotic-resistant infections and treatment, and communicating principles of antibiotic stewardship to medical professionals, but its uptake among medical professionals has been slow, said John Nosta, BA, and Debbie Goff, PharmD, in a recent Contagion® Peer Exchange panel.

According to Dr. Goff, the real-time aspect of Twitter makes it a unique platform for communicating information about infectious disease and antibiotic stewardship and connecting with others outside her immediate circle, such as Mr. Nosta. "To be a great steward, you've got to learn more than infectious disease," Dr. Goff said. "It's the social aspect of connecting with people to convince them they need to change [what] they're doing. Following [Mr. Nosta's] Twitter feed empowered me to learn a different type of knowledge that really helped me be a better clinician."

USING HASHTAGS AS A SEARCH TOOL

According to Mr. Nosta, common reasons physicians cite for not using Twitter include the perception that they have "nothing to say" and "have no followers." However, he pointed out that the ability to search hashtags enables clinicians to identify pertinent up-to-date information.

"If I Google 'American Heart Association,' I'm going to get reams of data that I can't make heads or tails of," Mr. Nosta said. "But if I hashtag AHA [#AHA], I know what's going on right now, and I can even prioritize my search by the top-trending tweet. If you use Google, you should be using Twitter."

Dr. Goff cited World Antibiotic Awareness Week as a prime example of how the coordinated efforts around hashtags enable users to reach a worldwide audience. During the awareness week in November 2018, groups around the world—including the US Centers for Disease Control and Prevention, the Society of Infectious Disease Pharmacists, and the Infectious Disease Society of America—communicated relevant information that was searchable via hashtags. She said that having a strategy for reaching an audience larger than her immediate circle is important for spreading her message about the importance of antibiotic stewardship.

"By knowing [Mr. Nosta], I now reach a whole different avenue of people, and a lot of them are not in health care," Dr. Goff said. "[Those individuals are] exactly who we're trying to reach, and [Mr. Nosta is] the one who has the voice."

RELAYING STORIES OF ANTIBIOTIC RESISTANCE TO THE PUBLIC

Mr. Nosta and Dr. Goff agreed that Twitter also provides broad-based dissemination of information to individuals who have a large following. Mr. Nosta added that he often asks nonexperts to retweet information about medical topics because these individuals have a diverse audience.

"Imagine I tweet something about a MRSA [methicillin-resistant Staphylococcus aureus] infection...and Mark Cuban, his son, happens to have MRSA," Dr. Goff said. "All of a sudden Mark Cuban, [whom] I've never met and don't know, might retweet my tweet because now it's personal to him."

Using Twitter to share stories of individuals affected by antibiotic-resistant bacteria may also help communicate the widespread problem of antibiotic resistance, especially among individuals who do not feel that the topic is personally relevant. "When I see a patient, and sometimes it's as
simple as a 23-year-old college student with her first urinary tract infection...and I have to tell them, 'We actually have no oral effective agents to treat you with, so we’ve got to admit you to get IV [intravenous] therapy...and then their parents go, 'How did my daughter get this?' That’s the moment we’re living in right now,” Dr. Goff explained. “To me, Twitter provides me a voice to get the story out there, and [Mr. Nosta is] a vehicle to help me spread that story.”

Mr. Nosta added that bridging the gap between medical professionals and individuals outside of the medical field often requires Twitter posts to be “a little poetic,” as original articles may not be as effective for engaging the general public. He described a recent example of how he altered the language of a Twitter post highlighting a story he wrote about a study that investigated mutation patterns of MRSA in microgravity.

"[The original headline about] bacterial mutation MRSA...it was a yawn. Most people didn’t want to read that," Mr. Nosta said. "[Instead of using the original headline] I said, 'Elon Musk just launched a lethal pathogen into space and it might save your life.' All of a sudden everyone wanted to know about the mutation patterns of MRSA."

COMMUNICATING WITH OTHER MEDICAL PROFESSIONALS

By contrast, Dr. Goff stated that providing the original data source and reliable scientific evidence is important for appealing to medical professionals outside of the infectious disease field, such as surgeons, who need clinically relevant information on antibiotic stewardship. "They’re not infectious disease experts," she said. "That’s my job as a steward to [say a] Klebsiella pneumoniae carbapenemase [KPC] [infection] means none of these antibiotics will work. I link it to a PubMed abstract that’s scientific and factual."

Dr. Goff described a study in which she, along with surgical and clinical pharmacists at Ohio State University, analyzed the best ways to communicate relevant infectious disease topics to participating surgeons at the university using Twitter. “Surgeons are one of the highest users of antibiotics,” Dr. Goff explained. “I can’t give a lecture to 100 surgeons in real time. Twitter is the vehicle.”

Although a common belief is that Twitter is primarily used by younger generations, Dr. Goff stated that she was able to recruit surgeons of all ages, ranging from a new surgical attending physician in his early 30s to the chair of surgery at Ohio State, who is 71 years old. “We had 4 generations to dispel that [Twitter] is just [for] the young,” Dr. Goff said. “They all understood the power of using Twitter as a communication tool in real time.”

Dr. Goff said that the tweet that resonated the most in her study was the one that included a link to a medical article on management of KPC infections during a well-publicized outbreak from contaminated duodenoscopes at the University of California, Los Angeles. "That was the most retweeted tweet," she said. "That 1 tweet was retweeted by [Dr.] Ben Nwomeh [pediatric surgeon at the Ohio State University Wexner Medical Center in Columbus, Ohio] and reached 15,800 people, most of them surgeons. That’s the power of Twitter.”

Mr. Nosta also noted that “power tweeters” who attend large conferences, such as IDWeek, can disseminate the breaking news to professionals who are unable to attend the meeting. "I can attend IDWeek virtually because I’ve got power tweeters doing all the hard work to consolidate 2 or 3 hours of talks into 1, 2, or 3 key points," he said.

Dr. Goff agreed that tweeting the key points from a presentation provides a larger audience for the studies and increases exposure for the presenters. "If I’m presenting breaking work, I want my work to be known and recognized," she said. "It allows me to have someone tweet my work, and now all of a sudden, a much bigger audience is seeing my research, not just the attendees.”

Dr. Goff and Mr. Nosta concluded that Twitter provides a “cognitive hierarchy” for physicians that is independent of age and clinical experience. "If you have knowledge, it doesn’t matter what your age is,” Dr. Goff said. "If you have something that can be shared to help others, you can really become well respected on Twitter and get recognized by your own peers as an expert.”

However, she cautioned that medical professionals need to avoid presenting their knowledge as medical advice. "You never know how people will [interpret it],” Dr. Goff advised. “You can’t give a dissertation on Twitter, so you have to be very careful you’re not giving medical advice.”

INSIGHTS

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PWID Infected With Hepatitis C Virus Can Achieve SVR Despite Imperfect Adherence to Treatment

BY DANIELLE MROZ, MA

(continued from cover)

Maryland, set out to evaluate adherence in this population and determine if PWID are able to achieve cure of HCV infection.

For the open-label, nonrandomized, observational ANCHOR study (NCT03221309), Dr. Rosenthal and her team evaluated a model of care for the treatment of HCV infection in PWID with chronic HCV infection. All patients in the ongoing trial are receiving treatment with direct-acting antivirals (sofosbuvir/velpatasvir for 12 weeks, dispensed monthly in 28-pill bottles) and are offered pre-exposure prophylaxis for HIV prevention, as well as buprenorphine for treatment of opioid use disorder, when clinically indicated, according to the study design.

A total of 160 patients were screened for the trial and 100 were enrolled. The majority of the patients were male (n = 76, 76%), with a median age of 57 years (interquartile range, 53-62 years), and black (n = 93, 93%) and about half (n = 51, 51%) were unstably housed. More than half (n = 58, 58%) reported daily injection drug use.

Three of the participants were infected with HIV, and all 3 were not on treatment for HIV when they started treatment for their HCV coinfection. According to Dr. Rosenthal, these patients were linked with care for their HIV infection. Two of the patients initiated treatment for HIV; the patient who did not have a CD4 count >500 c/mm³.

"[The patients who had] HIV and HCV coinfection and [were] in HIV care had already been preferentially treated early on [for their HCV coinfection],” Dr. Rosenthal explained in an interview with Contagion’s sister publication, MD Magazine. "The coinfected people that we saw were not in HIV care. Some of our patients had very low CD4 counts, and so we prioritized HIV treatment in those patients.”

After 24 weeks of treatment, Dr. Rosenthal and her team found that even with imperfect adherence to treatment, the majority of the participants were able to achieve cure and had completed all 3 bottles of the treatment (n = 87, 87%). Twenty-one patients completed the treatment on time (at week 12), and 46 patients completed treatment after week 12.

The team found that having a suppressed viral load (<200 IU/mL) at week 4 was significantly associated with achieving SBR, and about 84 patients achieved this goal. Interestingly, an interruption in treatment did not impact their SVR. Furthermore, although completing the full course of treatment (3 bottles) was associated with SVR (n = 87), so was completing 2 or more bottles (n = 7). The participants who completed less than 2 bottles did not achieve SVR (n = 6). Thirteen participants had an interruption in treatment at varying time points in the study period, and these ranged from 3 to 70 days.

"The most surprising result we had was the number of patients who cured, despite significant nonadherence,” Dr. Rosenthal said. “I had 1 patient who completed his medication 5 weeks after week 12, and he still cured. I had a patient who disappeared for 8 weeks and then came back to treatment. He cured. I had a patient with a 70-day interruption. He cured.”

"Our per-protocol SVR was 89%, and I think that is probably more reflective of the SVR in reality because when I look at the patients who are lost to follow-up, 7 had [an] undetectable viral load at week 4, 2 had [an] unknown viral load at week 4, and 1 had a detectable viral load at week 4. This leads me to believe that the majority of people who were lost to follow-up were also cured,” Dr. Rosenthal continued.

MD Magazine asked Dr. Rosenthal if the participants’ age had an impact on the results.

"I don’t think patients’ ages impacted the results because we did not really find different outcomes between the men and the women in the study,” she explained. "We were treating patients in Washington, DC, and so [in this region], there are different subgroups of the opioid epidemic. The opioid epidemic that we are seeing now in more rural and suburban areas tends to be a white, younger population. A lot of the patients we are treating [in DC] tend to be from the ‘original’ opioid epidemic that started in the 1970s and 1980s, and that tends to be made up of individuals from more urban areas who are ethnic minorities. The people we are seeing are people who have been using heroin for 20, 30, and 40 years already.”

According to Dr. Rosenthal, the biggest takeaway from this study is that PWID should not be excluded from treatment for their HCV infection because of concerns regarding treatment adherence. She explained that their findings indicate that there is not a clear factor at the beginning of treatment that should result in a patient being excluded from access to HCV infection treatment purely because they are a person who injects drugs.

"The individuals who we were treating in this study were facing so many challenging socioeconomic and demographic factors that, if they can be cured, anyone can be cured,” Dr. Rosenthal said. "I think the biggest distinction [among this population] is going to be interest. If patients are not interested in getting treated, it is unlikely that they are going to take the treatment. However, in anyone who is coming to you and wants to get treated for HCV infection, I don’t think having opioid use disorder or ongoing injection drug use should preclude them from being treated and achieving cure. If patients are interested in taking treatment, they can take treatment.”

Data on any reinfections in the population treated are forthcoming; however, Dr. Rosenthal explained that if the team ends up seeing reinfections in this population, that indicates they are treating the right population.

“Our goal was to find the people who are actively transmitting [HCV]. When you see reinfection, it means you are treating a patient population who continues to transmit the virus,” she explained. "That was critical for us: We were not just treating people with HCV infection, but we were curing their infection to interrupt transmission to others and helping to eliminate the epidemic.”

Dr. Rosenthal and her colleagues explained that an important component of treating HCV infection in PWID and have opioid use disorder is understanding why they have HCV infection, and that is their opioid use disorder. Therefore, it is important to address this underlying cause of infection during treatment for their HCV infection to improve their overall outcomes.

"High SVR in PWID With HCV Despite Imperfect Medication Adherence: Data From The Anchor Study,” was presented at the American Association for the Study of Liver Disease annual meeting, November 9-13, 2018, in San Francisco, California. ▲

References available at ContagionLive.com.

This article originally appeared on MDMagazine.com/link/2028.
C Difficile Infection Is Associated With Higher Mortality Rates in Patients With Cirrhosis

BY SAMANTHA HITCHCOCK

(continued from cover)

2009 to 2013. To be included in the analysis, patients must have had an International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code consistent with cirrhosis or its complications, including ascites, esophageal varices, hepatic encephalopathy, and hepatocellular carcinoma. Patients who underwent prior liver transplant were excluded from the study. The primary endpoint was hospital readmission within 30 and 90 days, with secondary endpoints of total inpatient mortality and multiple readmission.

Of the 123,546 patients meeting the criteria for eligibility, 1827 (1.5%) had C diff infection and 121,719 (98.5%) did not. The study identified notably higher rates of mortality among patients with C diff at index admission than those without C diff infection (17.9% vs 7.4%; P<.001).

For patients who did not die or who were transplanted at index admission, those with C diff infection had higher admission rates within 30 days compared with those without C diff infection (21.1% vs 19.3%; P = .03). However, the percentage of patients readmitted within 90 days of index admission were similar between the 2 arms (31.7% and 30.2%, respectively).

“Index and subsequent admissions for C diff infection [have] significant consequences for patients with cirrhosis,” the investigators wrote.

The readmission rate with C diff infection at 30 days was 17.2% for patients who presented with the infection at index admission compared with 0.8% for those who did not (P<.001). Similar rates were noted at 90 days (21.7% vs 1.1%, respectively; P<.001) and inpatient death during readmission.

Higher overall mortality was seen for patients with C diff infection at index admission (24.0% vs 13.1%; P<.001); however, there were no significant differences noted in overall readmission rates.

“Prevention, early recognition, and aggressive treatment strategies need to be reexamined for those patients with cirrhosis and C diff infection to prevent deleterious consequences,” the investigators concluded.

“The Effect of Clostridium Difficile Infections on Readmissions in Patients with Cirrhosis” was presented at the American Association for the Study of Liver Disease annual meeting held November 9-13, 2018, in San Francisco, California. ▲

References available at ContagionLive.com.

This article originally appeared on MDMagazine.com/link/2029.

SOF/VEL/VOX Is Successful for Hepatitis C Virus Retreatment in Patients With and Without HIV

BY DANIELLE MROZ, MA

A fixed-dose combination therapy of sofosbuvir, velpatasvir, and voxilaprevir (SOF/VEL/VOX, Vosevi, Gilead) was highly effective after 12 weeks in retreating direct-acting antiviral-experienced patients with hepatitis C virus (HCV) infection, with and without HIV co-infection, including those with prior noncompletion of treatment or poor adherence, according to results of a new study.

HCV infection can be successfully treated with the use of direct-acting antiviral agents. In rare cases, patients can relapse; however, they can still be retreated successfully. SOF/VEL/VOX is one such treatment for HCV infection that has shown success in patients who are treatment-experienced; however, many studies have not assessed the success of retreatment in patients with HIV or hepatitis B virus (HBV) co-infection.

“I think many people expect that the drugs will work the same in HIV-positive patients as in HIV-negative patients because of the early data in ledipasvir/sofosbuvir (Harvoni, Gilead) especially showing similar efficacy like in the ERADICATE study,” study lead investigator Eleanor MP Wilson, MD, MHS, assistant professor of medicine at the University of Maryland School of Medicine in Baltimore, explained in an email to Contagion®’s sister publication MD Magazine. “[However,] some recent data [have] shown that in real-world studies, patients with HIV may be less likely to succeed because of drug interactions, immunologic effects, or other factors.”

A team of investigators led by Wilson pulled data from the RESOLVE trial, an open-label phase 2b study on the safety and efficacy of 12 weeks of a fixed dose of SOF/VEL/VOX (sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg) in HCV-infected patients with early and advanced liver disease, including those with HIV or HBV infection, who failed previous combination direct-acting antiviral therapy. The primary endpoint was the proportion of patients who achieve sustained viral response at 12 weeks, as well as the incidence of grade 3 or grade 4 adverse events during treatment or within 30 days of treatment completion.

Seventy-seven subjects were enrolled in the study at 3 sites in Baltimore and Washington, DC. Three-quarters of the patients (n = 58, 75%) were infected with HCV genotype 1a, 17 patients (22%) had HIV, and 2 (3%) were co-infected with HIV and HBV.

Sustained viral response at 12 weeks was achieved by 70 of the 77 patients (90.9%). “Our study shows that SOF/VEL/VOX is a good option, in terms of both safety and efficacy, for retreatment of hepatitis C virus infection in patients with HIV, those with hepatitis B virus infection on treatment, and in those patients who had previously not completed their initial direct-acting antiviral regimen (with either poor adherence or treatment interruption),” Wilson said.

The study, “Retreatment Eth SOF/VEL/VOX in Treatment-Experienced Patients With and Without HIV: The Resolve Study,” 4 was presented at the 2018 American Association for the Study of Liver Diseases annual meeting, November 9-13, 2018, in San Francisco, California. ▲

References available at ContagionLive.com.
Analyses Support Rezafungin for Prevention of Aspergillosis Following Bone Marrow Transplant

BY MICHAELA FLEMING

(continued from cover)

To evaluate an appropriate dosing regimen for the echinocandin in the prevention of A. fumigatus infection among BMT recipients, a team of investigators conducted pharmacokinetic (PK)/pharmacodynamic simulations in which they compared a PK model to observed data. The investigators refined a previously developed PK population model using intravenous (IV) data from additional phase 1 and phase 2 studies. The investigators studied the ability of "covariates such as body size, age, albumin, markers of liver and renal function, and infection status to explain a portion of the interindividual variability on select PK parameters...using stepwise forward selection and backward elimination."

The model was validated by comparison to baseline demographic data that were available from 100 patients who underwent a BMT at Stanford Medical Center. Using the dataset, and the developed population PK model, the investigators conducted a Monte Carlo simulation to explore "expected rezafungin concentration-time profiles" in BMT recipients following administration of rezafungin, according to the study. The participants received a single dose of 400 mg of rezafungin intravenously at week 1, followed by 200 mg once weekly for the remaining 11 weeks. From surveillance data collected in 2016, free-drug concentration-time profiles were evaluated relative to the maximum observed A. fumigatus minimum effective concentration (MEC) to inhibit 100% of isolates tested (MEC<sub>100</sub>) using a human protein-binding value of 97.4%.

In the final population PK model, a linear, 4-compartment model with zero order IV input, the investigators noted that albumin was an important predictor of the interindividual variability, because there were observed relationships between serum albumin concentration and clearance and volume of peripheral compartment. Relationships were observed between the parameters and sex, body surface area, presence of cirrhosis, and infection status.

In the demographic data set, the median baseline body surface areas were 1.84 m<sup>2</sup> and the median albumin was 3.35 g/dL. Additionally, there were no patients with infection or cirrhosis at baseline.

The authors wrote that at weeks 1, 2, and 12, 98.4%, 93.3%, and 91.9% of simulated patients, respectively, had rezafungin free–drug concentrations above the MEC<sub>100</sub> value for the week. The result was ≥99.9% for all 12 weeks when based on the MEC<sub>100</sub> (0.015 mg/L).

The authors of the analyses also indicated that the favorable PK profile of the candidate provides the opportunity to mitigate challenges of the administration of prophylaxis for invasive fungal infections in recipients of BMTs and other immunocompromised patients.

Low Microbiota Diversity Prior to BMT Linked With Higher Risk of Complications

BY MICHAELA FLEMING

(continued from cover)

of Memorial Sloan Kettering’s (MSK) Division of Hematologic Malignancies and senior author of the study, said in a recent statement:“The thing that we keep coming back to is that preserving the commensal flora in the microbiome is good for transplant patients.”

In a multicenter analysis, international investigators led by a team at MSK hypothesized that the microbiota configuration prior to transplant could be an important determinant of posttransplant complications. To investigate their hypothesis, the investigators examined 1922 stool samples from 991 individuals undergoing allogeneic BMTs. The participants were all adults undergoing transplants at MSK; Duke University School of Medicine in Durham, North Carolina; Hokkaido University in Sapporo, Japan; or University Hospital Regensburg in Germany.

The investigators found that, on average, prior to transplant, the participants had a gut microbiota that was 1.7- to 2.5-fold lower in diversity compared with healthy volunteers. Additionally, the strains of bacteria that were present and more common in the transplant patients were different than those of the healthy volunteers. The participants with the lowest microbial diversity showed lower overall survival and a higher risk for graft-versus-host disease.

*Before someone has a BMT to treat their cancer, we do a lot of screening tests to make sure they are otherwise healthy. We look at things like their heart, lung, and kidney functions,” Dr. van den Brink added. “This study suggests that we should also screen the microbiota. If we find out that it’s in bad shape, we could do something to repair it.”

The authors noted that the study did not examine how gut microbes might influence the process of the transplant or lead to complications. They are studying the relationship between microbes and the activation of T cells in transplants, but more research is needed to understand if the relationship can lead to a decrease in protective bacteria or increased harmful species.

However, the team also indicated that this particular study further supports evidence that there is a connection between microbiota and patient outcomes that starts prior to the transplantation process. This information provides the opportunity for clinicians to work to repair the microbiota prior to transplant. Possible interventions to improve microbiota health could include avoidance of certain antibiotics, changes in diet or calorie intake, or fecal transplants of healthy gut microbes.

This “Multicenter Microbiota Analysis Indicates That Pre-HCT Microbiota Injury Is Prevalent across Geography and Predicts Poor Overall Survival” study was presented at the 60th Annual American Society of Hematology Annual Meeting, which was held December 1-4, 2018, in San Diego, California. ▲

References available at ContagionLive.com.

According to a statement issued by Cidara, the company plans to launch the phase 3 ReSPECT prophylaxis trial evaluating rezafungin in patients undergoing allogenic BMTs in the first quarter of 2019.2

The "Pharmacokinetic-Pharmacodynamic Analyses to Provide Rezafungin Prophylaxis Dose Selection for Prevention of Invasive Fungal Infections for Bone Marrow Transplant Patients” study was presented at the 60th Annual American Society of Hematology Annual Meeting, which was held December 1-4, 2018, in San Diego, California. ▲

References available at ContagionLive.com.
Pharmacists Play a Role in Responding to Drug Shortages

BY KRISTEN COPPOCK, MA

(continued from cover)

from Baxter Healthcare Corporation, centered on best practices that pharmacists can use to respond to ongoing drug shortage issues.

Drug shortages have a tremendous impact on the health care system; in the United States, $209 million was spent in 2013 for the purchase of more expensive substitutes, according to ASHP estimates. This estimate does not include other significant costs, such as the added labor required to identify available alternative products.

Data from the Drug Information Service, which provides drug shortage content to ASHP, show that the top 5 drug classes with active shortages on September 30, 2018, were antimicrobials, chemotherapy products, cardiovascular and central nervous system medications, and E-lytes, nutrition, and fluids. The data presented by Dr. Fox showed that many of these active shortages were injectable.

In her presentation, Dr. Fox said some of most basic products required for patient care are often subject to shortage. She noted bupivacaine, lidocaine, morphine, fentanyl, ketamine, ondansetron, saline, and sterile water as examples.

Many drug shortages are related to quality issues at manufacturing facilities, Dr. Fox said. Although most factories are running at capacity, some also are utilizing aging facilities or producing medications “just in time.” In addition, business decisions impact drug availability, she explained.

“Over the years, manufacturing has become more lean,“ Dr. Fox said. “It’s expensive to add manufacturing lines, and it takes time. It may not be worth the money to keep those factories up to date.”

Meanwhile, a lack of transparency can pose a problem for ensuring quality, Dr. Fox told the audience. Often, companies hire other companies to make their products, and “they just put a label on it,” she said.

For injectables, there is also a fragile supply chain to consider, Dr. Fox said. Often, a single firm is producing 90% of the total supply and it is common for that firm to have a sole source of raw materials, she added. Competition for manufacturing these drugs is low, especially when companies consider a low return on investment for certain products.

During her presentation, Dr. Fox acknowledged challenges pharmacists face with drug shortages, but said the goal should be to minimize the impact of drug shortages on patients. These shortages may not be seen by other professionals on a patient’s health care team, she emphasized, so it is imperative that pharmacists take on this role.

Citing the ASHP’s Guidelines on Managing Drug Product Shortages, which she developed, Dr. Fox said a key strategy for pharmacists is to plan for drug availability challenges. “Do as much work ahead as you can,” she explained. “If you can be well prepared and make your checklist, you’re already ahead of the game.”

Planning ahead includes having a team in place, assessing operational and therapeutic needs, conducting impact analysis, and devising an action plan, Dr. Fox said. Having that plan in place extends to disaster response, such as preparedness and recovery.

Gathering data, monitoring a shortage, and maintaining contact with local representatives of the manufacturer are part of the pharmacy team’s work to mitigate the impact of less drug availability, she added. Making decisions for purchasing and rationing drugs, and communicating the information to patients also are crucial for managing a drug shortage.

In situations when there is not enough product, Dr. Fox urged pharmacists not to ration alone and suggested having a resource allocation committee in place. “There might be days where you lose your entire supply. You have to have a plan for dealing with that,” she said.

Overall, coping with drug shortages comes down to communication. Every team member should know his or her role and be proactive in sharing that information.

The presentation, “Current State of Drug Shortages,” was made during the “Current Issues in IV Injectable Safety: Continuing the Conversation,” symposium at the ASHP Midyear Clinical Meeting held December 2-6, 2018, in Anaheim, California.

Reference available at ContagionLive.com.
Final Diagnosis: Disseminated Kaposi Sarcoma With Tonsillar and Pulmonary Involvement

A shocking find on a CT scan leads to an unexpected diagnosis.

BY ERIN TUTTLE, MD; REBECCA HOPPE, MD; ALEXANDER CUBBERLEY, MD; GINNY MARMOLEJOS, MD; AND ANITA KO, MD

HISTORY OF PRESENT ILLNESS:
A 29-year-old Brazilian man was sent to the emergency department (ED) for an incidental finding of a pneumothorax. The pneumothorax was discovered on a CT scan ordered by his ear, nose, and throat (ENT) physician to evaluate a left necrotic tonsillar mass. Five months prior, he presented at an outside hospital with a dry cough and was found to have pneumocystis pneumonia (PCP), HIV (CD4 count, 23 c/mm³; viral load unknown), and syphilis. He was treated successfully with trimethoprim-sulfamethoxazole and antiretroviral therapy (ART), and single-tablet tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat was initiated at that time. Three months later, he had his initial occurrence of a tonsillar lesion, which progressed to a mass the following month. In addition to seeing an ENT specialist, he had been following up with a provider at a city health center where his ART was subsequently switched to single-tablet abacavir/lamivudine/dolutegravir. Upon arrival in the ED, a chest tube was placed and the patient was admitted to the hospital where the infectious disease, ENT, pulmonary, and hematology-oncology teams were all consulted.

PAST MEDICAL HISTORY:
The patient was diagnosed with HIV, PCP, and syphilis 5 months prior. He had no surgical history.

MEDICATIONS:
Abacavir/lamivudine/dolutegravir (Triumeq, ViiV Healthcare) and trimethoprim-sulfamethoxazole for PCP prophylaxis.

EPIDEMIOLOGICAL HISTORY:
The patient was born in Brazil and is currently in the United States to attend school. He had no travel history except to Brazil (none recently) and no pets. He lives alone. He denies any recent sexual activity, but stated he has sex with women only. He also denied any tobacco, alcohol, or drug use.

PHYSICAL EXAM:
The patient’s vital signs were within normal limits. He was awake and alert and not in acute distress. On oral inspection, he had a large dark red lesion on his left palatine tonsil. His neck was supple, and he had bilateral bulky cervical lymphadenopathy. His heart sounds were regular, with normal S1 and S2. He had coarse breath sounds bilaterally, but louder over the right lung with normal work of breathing. He had a left-sided chest tube. His abdomen was soft with no rebound or guarding. His complete neurological exam was nonfocal.

STUDIES:
On admission, the patient’s labs were significant for a CD4 count of 154. His HIV viral load was not tested.

Left: Chest x-ray showing diffuse severe extensive bilateral infiltrates and opacities as well as a moderate to large left-sided pneumothorax.

Center top to bottom: Chest CT, axial view and coronal view, shows multilobar dense alveolar consolidation with areas of soft tissue attenuation and numerous surrounding flame-shaped nodular opacities with perilymphatic distribution.

Right: CT of the neck shows an exophytic, heterogeneously enhancing mass arising from the left palatine tonsil with numerous cervical lymph nodes.
Rapid plasma reagin was positive at 1:4. A hepatitis C virus (HCV) antibody test was positive, and his HCV viral load was undetectable. Urine gonorrhea and chlamydia tests were negative by nucleic acid amplification testing. His chemistries and comprehensive blood count were unimpressive.

A head-and-neck CT scan showed an exophytic, heterogeneously enhancing left palatine tonsillar mass and incidentally found a moderate to large left apical pneumothorax. Further imaging with CT of the chest revealed a multilobular dense alveolar consolidation with areas of soft tissue attenuation and numerous surrounding flame-shaped nodular opacities with perilymphatic distribution.

DIAGNOSTIC PROCEDURES AND RESULTS:
Tonsillectomy with biopsy was performed, showing numerous unoriented irregular fragments of red-purple, soft, glistening to cauterized tissue admixed with a blood clot measuring 3.5 x 2.8 x 1.4 cm in aggregate, consistent with Kaposi sarcoma (KS). Immunohistochemical stains for CD34, CD31, and HHV8 were positive, confirming the KS diagnosis. K67 immunostaining showed 50% positive staining. Bronchoscopy was unrevealing for endobronchial lesions; however, it showed friable mucosa with erythema. Bronchoalveolar lavage (BAL) was negative for Pneumocystis jirovecii, acid fast bacilli, or fungal infection. Absolute CD4 count of 154 cells/μL (16%) and serum HHV-8 polymerase chain reaction were positive. Additionally, herpesvirus 8 IgG antibody was positive 1:7320.

Clinically, the patient appeared to have disseminated KS in the setting of paradoxical immune reconstitution inflammatory syndrome (IRIS). Chest imaging indicated pulmonary KS, with the characteristic flame-shaped nodules, although BAL was negative. He was discharged 6 days after admission, with outpatient hematology–oncology follow-up for port placement to begin doxorubicin therapy for treatment of disseminated KS caused by IRIS.

DISCUSSION:
KS, first described in 1872 by Moriz Kaposi, is a multicentric neoplasm that presents as vascular tumors of the skin, mucus membrane, and viscera.1 KS is the most common neoplasm associated with HIV infection. It predominantly affects the skin in 80% to 90% of cases and is the most common initial manifestation. Visceral organs can also be affected. Visceral KS most frequently affects the lungs and gastrointestinal (GI) tract; however, it has been documented in almost every visceral site.

There are 4 clinical types of KS: classic, endemic, transplant-related, and AIDS-associated. AIDS-associated KS, the most prevalent form, is associated with infection from HHV-8, also known as the KS-associated herpesvirus.2 The mechanism of transmission of HHV-8 is not well understood, although it is possible the virus could be sexually transmitted, as it is seen almost exclusively in men who have sex with men.3 KS, an AIDS-defining illness, can be seen at any stage of HIV infection, even if the CD4 count is normal;4 however, incidence is highest among patients with CD4 counts <200.5 KS is typically seen in patients with a low CD4 count (<150 cells/mm3) and a high viral load (>10,000 c/mL); however, more recent study findings are showing increased incidence in patients with CD4 counts >350 c/mm3.6 Treatment always consists of ART and can include systemic chemotherapy.

Initial manifestations of AIDS-associated KS include erythematous, violaceous cutaneous lesions (macular, papular, or nodular) involving the face, oral mucosa, upper trunk, and lower extremities, with increasing involvement of visceral organs, including lymph nodes, GI tract, and lungs as the disease progresses.7 Pulmonary involvement is preceded by skin lesions 80% of the time and presents as shortness of breath.8 Other pulmonary manifestations include dyspnea, fever, cough, hemoptysis, and chest pain. Radiographic findings are nonspecific and demonstrate pleural effusion, lymphadenopathy, and nodules, as well as interstitial and alveolar infiltrates. Dyspnea, cough, hemoptysis, stridor, nodular infiltrates, pleural effusion, low diffusion capacity, and absence of arterial desaturations are more likely to be due to pulmonary KS than to opportunistic infections.9 However, among persons at high risk for AIDS, the etiology of spontaneous pneumothorax has been more commonly associated with Pneumocystis carinii infections.7

Clinical diagnosis alone is not sufficient for KS; it requires tissue examination for confirmation. Pulmonary KS diagnosis is made based on physical exam findings, CT features, and endobronchial lesions. Classical CT chest findings show hilar densities along peribronchovascular pathways and a nodular pattern accompanied by pleural effusions.10 Bronchoscopy and BAL are often performed in HIV-infected patients with pulmonary symptoms and parenchymal abnormalities on imaging. Endobronchial lesions appear violaceous or bright red and are macular and papular, often located at airway bifurcations. Transbronchial biopsies are not common, as hemorrhage can occur in up to 30% of patients.9 The mainstay of treatment is ART, although there are no definitive treatment guidelines. In the majority of cases, ART alone will cause regression of lesions; however, KS has also been known to appear as a form of IRIS. ART with chemotherapy is indicated in visceral disease, rapid progression of disease, or disseminated skin or mucosal involvement. If there is single lesion, then radiation or cryotherapy may be introduced. For extensive or disseminated disease, interferon alpha or chemotherapy is considered. The response rate of initial therapy is dependent on CD4 count. If the count is <150 cells/mm3, then interferon alpha is given; otherwise, treatment is with chemotherapy. The response rate for interferon alpha in patients with CD4 <150 c/mm3 is less than 10%. The US Food and Drug Administration has approved 4 chemotherapy agents for treatment that have been shown to have activity against KS: liposomal daunorubicin, liposomal doxorubicin, vincristine, and paclitaxel.10 In patients with pulmonary KS, the median survival time has increased from 4 months to 1.6 years due to the initiation of ART.11 Patients presenting with KS already on ART typically have a less aggressive presentation compared with those not receiving treatment.

IRIS-KS is seen with improvement of immune status by a decrease in the viral load and an increase in CD4 count after initiating ART, with the greatest risk of development within the first 3 months. There is no difference in initial presentation or location of involvement in those with AIDS-associated KS compared with IRIS-KS. Early initiation of chemotherapy with continuation of ART remains the most effective treatment for reducing mortality.12 With the increase in HIV awareness and increased use of ART, the incidence of KS has significantly declined, increasing the likelihood of alternative diagnoses in patients with pulmonary symptoms that resemble KS.

References available at ContagionLive.com.
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