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NEWS & BREAKTHROUGHS

The Shingrix Vaccine: What You Should Know

By Jennifer Gershman, PharmD, CPh

(continued on page 10)

Infectious Diseases Today

2018 BMT Tandem Meetings

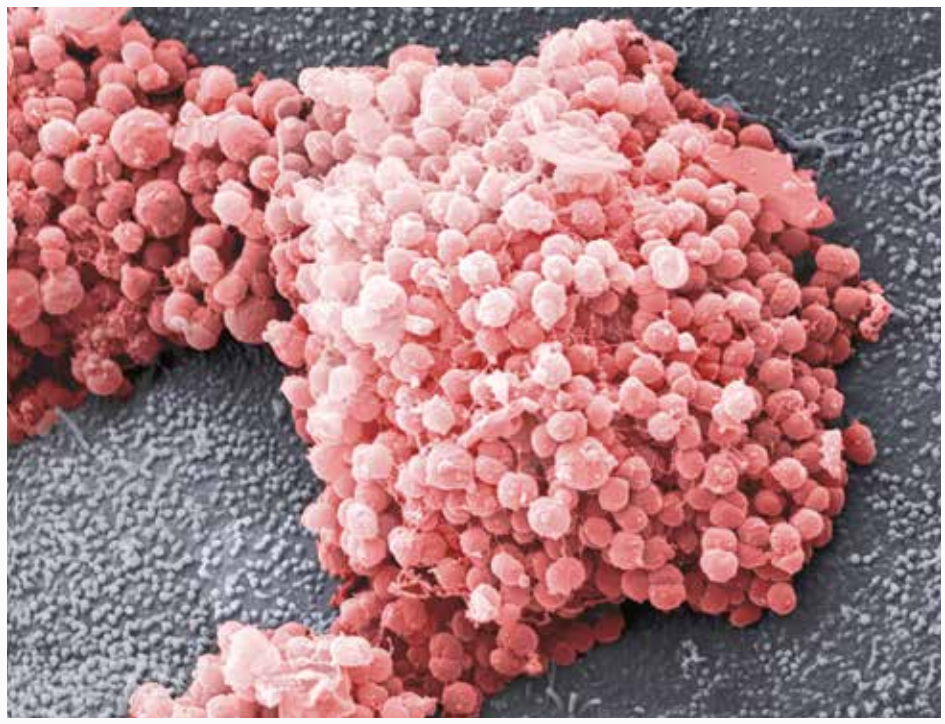
Considerations for CMV in Allogeneic HSCT Recipients

Two poster presentations at the 2018 BMT Tandem Meetings of the Center for International Blood & Marrow Transplant Research and the American Society for Blood and Marrow Transplantation held in Salt City, Utah, provided a compelling extension of the recent phase 3 clinical trial[1] that demonstrated the efficacy of prophylactic therapy with letermovir (Prevymis) for the prevention of cytomegalovirus (CMV) infection in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT).

Roy F Chemaly, MD, MPH, FACP, FIDSA

Immunosuppression is necessary for the success of HSCT, but it carries the danger of lessened resistance to potentially lethal infections like CMV, one of the most common infections

(continued on page 38)



Neisseria gonorrhoeae © Juergen Berger/ Science Source

EMERGING & RE-EMERGING DISEASES

Drug-Resistant Gonorrhea and Other Emerging Issues in STIs

By Nicola M. Parry, BVSc, MRCVS, MSc, DACVP, ELS

Previous downward trends in the rates of sexually transmitted infections (STIs) have reversed in recent years, and their incidence is on the rise in both men and women in the United States.[1] In particular, the 3 most common reportable STIs—gonorrhea, chlamydia, and syphilis—represent a growing health threat, according to the US Centers for Disease Control and Prevention (CDC).[1]

(continued on page 14)

CROI 2018

D/C/F/TAF Performs Well in Treatment-Experienced Patients

Although significant advances have been made in the treatment of HIV, certain patient populations continue to face barriers to viral suppression. Treatment-experienced patients from diverse backgrounds who may have struggled with adherence in the past are facing the issue of drug resistance.

Gregory D. Huhn, MD

Therefore, new treatment options for these patients need to be developed and made available. The 48-week results of a post hoc analysis of clinical trial testing of one of these new agents in treatment-experienced patients—the EMERALD trial—were recently presented at the 25th Annual Conference on Retroviruses and Opportunistic Infections (CROI), and they look promising.

(continued on page 40)

Shingrix Prevents Herpes Zoster Episodes Following HSCT

A herpes zoster (HZ) subunit vaccine (Shingrix) effectively prevented episodes of HZ and other related complications among patients who had recently underwent autologous hematopoietic stem cell transplant (HSCT), according to the results of the phase 3 ZOE-HSCT trial presented at the 2018 BMT Tandem Meetings.

The vaccine reduced the risk of HZ by 68.2% (95% CI, 55.6%-77.5%; P <.0001) in high-risk recipients of HSCT. Improvements were also noted in cases of postherpetic neuralgia, HZ-related hospitalizations, and other complications, noted lead author Javier de la Serna, MD, PhD, of the Hospital Universitario in Madrid, Spain. "Administered to adults early after autologous

(continued on page 39)

47th Critical Care Congress

Procalcitonin-Guided Antibiotic Cessation Reduces Mortality

Since the discovery of the biomarker procalcitonin (PCT) as a proven marker of an individual's response to a bacterial infection, investigators have been actively pursuing how best to use it to guide antibiotic therapy. They have been researching the safety and efficacy of PCT-guided treatments for a multitude of infections, including acute respiratory infections. In fact, in early 2017, the US Food and Drug Administration cleared the expanded use of a PCT test to guide initiating or ceasing antibiotic treatment

(continued on page 42)

SEP-1 Bundle Compliance Leads to Reduced Readmissions

As the leading cause of unplanned 30-day hospital readmissions,[1] sepsis affects more than 1.5 million individuals in the United States each year.[2] Although numerous studies have been conducted to address improving sepsis mortality, studies on methods to reduce readmissions are lacking. To this end, investigators from the Cleveland Clinic Health Center located in Cleveland, Ohio, sought to determine whether there was an association between Early Management bundle Severe Sepsis

(continued on page 43)

Vaginal Microbiome May Influence Effectiveness of PrEP

Over 1 million women are infected with HIV on an annual basis. To reduce this number, more understanding is needed. Even after decades of research, not much is known about the biological mechanisms that lead to HIV acquisition in this population.

This lack of knowledge was addressed in the Tuesday Plenary Lecture of the 25th Conference on Retroviruses and Opportunistic Infections (CROI), during which Nichole Klatt, PhD, from the University of Washington, provided an overview of what is known about vaginal microbial dysbiosis and its association with HIV infection as well as how vaginal bacteria may influence transmission in women.

(continued on page 41)

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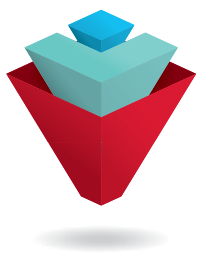

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BIKTARVY® (bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx only.

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

DOSAGE AND ADMINISTRATION

Also see ***Warnings and Precautions*** and ***Use in Specific Populations***.

Testing Prior to or When Initiating: Test patients for HBV infection.

Testing Prior to or When Initiating, and During Treatment: As clinically appropriate, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Dosage: One tablet taken once daily with or without food.

Renal Impairment: BIKTARVY is not recommended in patients with CrCl <30 mL/min.

Hepatic Impairment: BIKTARVY is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS

Also see ***Drug Interactions***.

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY

WARNINGS AND PRECAUTIONS

Also see ***BOXED WARNING, Contraindications, Adverse Reactions,*** and ***Drug Interactions***.

Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV: Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating ARV therapy. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: Coadministration of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions; this may lead to loss of efficacy and development of resistance to BIKTARVY or clinically significant adverse reactions from greater exposures of concomitant drugs. Consider the potential for drug interactions and review concomitant medications prior to and during therapy. Monitor for adverse reactions associated with concomitant drugs.

Immune Reconstitution Syndrome (IRS): IRS has been reported in patients treated with combination ARV therapy. During the initial phase of treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; the time to onset is variable, and can occur many months after initiation of treatment.

New Onset or Worsening Renal Impairment: Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs in animal studies and human trials. In clinical trials of BIKTARVY in subjects with no antiretroviral treatment history with eGFRs >30 mL/min, and in virologically suppressed subjects switched to BIKTARVY with eGFRs >50 mL/min, renal serious adverse events were encountered in less than 1% of subjects treated with BIKTARVY through Week 48. BIKTARVY is not recommended in patients with CrCl <30 mL/min. Patients taking tenofovir prodrugs who have renal impairment and/or are taking nephrotoxic agents including NSAIDs are at increased risk of developing renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. ***Renal Monitoring:*** Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC and TDF. Treatment with BIKTARVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

ADVERSE REACTIONS

Also see ***BOXED WARNING*** and ***Warnings and Precautions***.

In Adults with No ARV Treatment History:

The safety assessment of BIKTARVY is based on Week 48 data from two randomized, double-blind, active-controlled trials: 1489 (n=314) and 1490 (n=320), in HIV-1 infected, ARV treatment-naïve adults. Through Week 48, 1% of subjects discontinued BIKTARVY due to adverse events, regardless of severity.

Adverse Reactions: Adverse reactions (all Grades) reported in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 and 1490, respectively were: diarrhea (6%, 3%), nausea (5%, 3%), headache (5%, 4%), fatigue (3%, 2%), abnormal dreams (3%, <1%), dizziness (2%, 2%), and insomnia (2%, 2%). Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression. Suicidal ideation, suicide attempt, and depression suicidal occurred in <1% of subjects administered BIKTARVY; all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

Laboratory Abnormalities: Laboratory abnormalities (Grades 3–4) occurring in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 or 1490, respectively were: amylase >2.0 x ULN (2%, 2%), ALT >5.0 x ULN (1%, 2%), AST >5.0 x ULN (2%, 1%), Creatine Kinase ≥10.0 x ULN (4%, 4%), Neutrophils <750 mm^3 (2%, 2%), and fasted LDL-cholesterol >190 mg/dL (2%, 3%).

Changes in Serum Creatinine: Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Trials 1489 and 1490, median serum creatinine increased by 0.10 mg/dL from baseline to Week 48 in the BIKTARVY group and was similar to the comparator groups.

Continued on next page.

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Changes in Bilirubin: In Trials 1489 and 1490, total bilirubin increases were observed in 12% of subjects administered BIKTARVY through Week 48.

In Virologically Suppressed Adults: The safety of BIKTARVY in HIV-1 infected, virologically suppressed adults is based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial in which virologically suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY.

Adverse Reactions: Overall, the safety profile in virologically suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

DRUG INTERACTIONS

Also see ***Indications and Usage, Contraindications,*** and ***Warnings and Precautions***.

Other Antiretroviral Medications: BIKTARVY is a complete regimen for the treatment of HIV-1 infection, BIKTARVY coadministration with other ARV medications for treatment of HIV-1 infection is not recommended. Complete information regarding potential drug interactions with other ARV medications is not provided.

Potential for BIKTARVY to Affect Other Drugs: BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations.

Potential Effect of Other Drugs to Affect BIKTARVY: BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of efficacy and development of resistance. The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC. TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of efficacy and development of resistance.

Drugs Affecting Renal Function: Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs, which may increase the risk of adverse reactions.

Established and Potentially Significant Drug Interactions: The listing of established or potentially clinically significant drug interactions with recommended prevention or management strategies described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY. **An alteration in regimen may be recommended.**

- Antiarrhythmics: dofetilide. Coadministration is contraindicated due to potential for serious and/or life-threatening events.
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Coadministration with alternative anticonvulsants should be considered.
- Antimycobacterials: rifampin. Coadministration is contraindicated due to the effect on BIKTARVY. Rifabutin, rifapentine. Coadministration is not recommended.
- Herbal Products: St. John's wort. Coadministration is not recommended.
- Medications/oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Antacids containing Al/Mg or Calcium: BIKTARVY can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium. Routine administration of BIKTARVY simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended. Supplements containing Calcium or Iron: BIKTARVY and supplements containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended.
- Metformin: Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

Consult the full Prescribing Information prior to and during treatment with BIKTARVY for important drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS

Also see *Dosage and Administration, Warnings and Precautions,* and *Adverse Reactions*.

Pregnancy: *Pregnancy Exposure Registry:* There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. *Risk Summary:* There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. BIC and TAF use in women during pregnancy has not been evaluated; however, FTC use during pregnancy has been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Based on published data, FTC has been detected in human milk; it is not known whether BIKTARVY or all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is unknown if TAF is present in animal milk. Because of the potential for HIV transmission in HIV-negative infants, developing viral resistance in HIV-positive infants, and adverse reactions in nursing infants, mothers should be instructed not to breastfeed.

Pediatric Use: Safety and effectiveness of BIKTARVY in pediatric patients less than 18 years of age have not been established.

Geriatric Use: Clinical studies of BIKTARVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment: BIKTARVY is not recommended in patients with severe renal impairment (CrCl <30ml/min). No dosage adjustment of BIKTARVY is recommended in patients with CrCl >30ml/min.

Hepatic Impairment: No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) as BIKTARVY has not been studied in these patients.

OVERDOSAGE:

If overdose occurs, monitor the patient for evidence of toxicity. Treatment consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

210251-GS-000 February 2018

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EDITOR-IN-CHIEF'S LETTER

Spring(ing) Into Action on Drug-Resistant STIs and Recruiting New Professions on Antimicrobial Stewardship Teams


JASON C. GALLAGHER, PHARMD,FCCP, FIDSA, BCPS

Spring has finally sprung. New guidelines for *Clostridium difficile* infection have been published, and the April issue of *Contagion*® is here with a bevy of interesting content. In this edition's featured article, "**Drug-Resistant Gonorrhea and Other Emerging Issues in STIs**" (page 14) by Nicola M. Parry, BVSc, MRCVS, MSc, DACVP, ELS. Dr. Parry discusses how trends of decreasing sexually transmitted infections (STIs) in the United States have recently reversed. Current first-line drugs are largely effective, although the US Centers for Disease Control and Prevention's listing of drug-resistant *Neisseria gonorrhoeae* as 1 of the 3 most urgent threats in antibiotic-resistant bacteria in the United States is a reminder that further drug development and research in this area are sorely needed.

The new In the Literature and Case Study sections are providing fresh material for *Contagion*® readers and their section editors have more in the queue. This issue's case study concerns an intriguing case of *Aspergillus* infection of implanted cardiac defibrillator leads (page 44). Other therapeutic content includes articles on HIV and hepatitis C co-infection, treatment options for carbapenem-resistant Enterobacteriaceae infections, and a discussion on how to use long-acting agents for methicillin-resistant *Staphylococcus aureus* infection. In Stewardship and Prevention, we have an article on involving nurses in antimicrobial stewardship. Sometimes I feel that antimicrobial stewardship has become such as buzzword that it gets mentioned with every health profession that has ever been associated with the word "antibiotic." I admit that I was ignorant about the role that nurses can play before attending the most recent IDWeek conference, when a presenter turned on a lightbulb in my head about how much these most-visible colleagues can add. One example that was given, on teaching nurses in skilled nursing facilities when not to call prescribers for urinalyses, can significantly decrease the number of patients treated for asymptomatic bacteriuria. David R. Ha, PharmD, and Mary Bette Forte, MSN-Ed, RN, write about this type of collaboration from a hospital perspective.

This issue also contains information gleaned from recent conferences, namely CROI 2018, the 47th Critical Care Congress, and the 2018 BMT Tandem Meetings. Moving forward, you can look forward to coverage from the upcoming conferences of the Society for Healthcare Epidemiology of America and the American Society for Microbiology.

Jason C. Gallagher, PharmD, FCCP, FIDSA, BCPS
Editor-in-Chief

CHAIRMAN'S LETTER

Arming Health Care Providers Against Growing Antimicrobial Resistance

Antibiotic resistance continues to grow, and it's plaguing health care providers and patients alike. Despite initiatives from the US Centers for Disease Control and Prevention's Antibiotic Resistance Solutions Initiative,[1] and the commitment of multiple organizations to the World Health Organization's Global Antimicrobial Resistance Surveillance System to assemble data on antimicrobial resistance around the world, a startling 2 million individuals become infected with resistant bacteria and 23,000 die from resistant infections each year.[1] New antibiotics are continually being developed, but only a handful of those pipeline therapies are reported to be effective against resistant priority pathogens.[2] As fast as new antibiotics are being developed, bacteria are evolving even faster, and infections that were once treatable are quickly on their way to becoming incurable.


MIKE HENNESSY, SR

It should come as no surprise, then, that many of the articles in this issue focus on the problem of antimicrobial resistance. Health care providers are now faced with these once-rare infections every day—they must be equipped with best practices on how to handle them. From "**Treatment Options to Address the Threat of Carbapenem-Resistant Enterobacteriaceae**" (page 27) to "**Long-Acting Anti-MRSA Agents: One Dose to Cure?**" (page 22), the expert contributions in this issue provide timely and relevant information to help providers battle these superbugs.

Furthermore, with organizations such as the Center for Disease Dynamics, Economics & Policy in Washington, DC, purporting that by the year 2030, antibiotic consumption will increase by as much as 200% if health care providers keep moving forward with their current prescribing practices,[3] we need to ensure that all members of the health care team, such as nurses, are actively involved in stewardship (page 29). The war on antimicrobial resistance will not be won alone, but with the commitment of every player in the game, we might just live to fight another day.

I trust you will learn from the expert-contributed reporting, built on smart insights and in-depth stories, in this magazine. I also recommend you visit our website, ContagionLive.com, for real-time updates on the shifts rippling through the world of infectious disease.

Stay informed and thanks for reading.

Mike Hennessy, Sr
Chairman and CEO

References are available at ContagionLive.com

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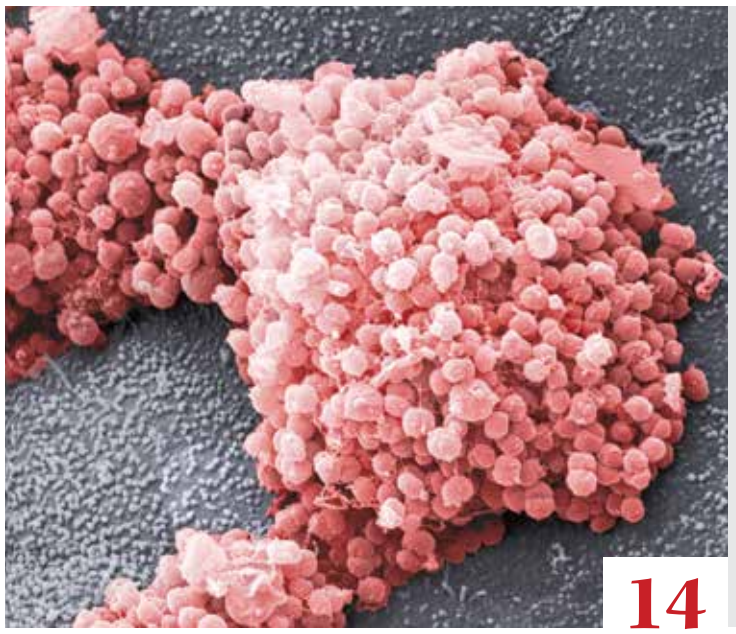

14

EMERGING & RE-EMERGING DISEASES

FEATURE

Drug-Resistant Gonorrhea and Other Emerging Issues in STIs

Sexually transmitted infections are increasing in the United States.

BY NICOLA M. PARRY, BVSC, MRCVS, MSC, DACVP, ELS

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Cover Image: Juergen Berger/ Science Source | © Illustrator: Patrick Welsh

ACIP Releases Updated Adult Immunization Recommendations

By *Contagion*® Editorial Staff

Overall vaccination rates in this population remain low.

The US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) voted to approve the updated vaccination recommendations for adults 19 years or older for 2018.

Changes to the schedule include new guidelines for the use of recombinant zoster vaccine (RZV) for adults over 50 years as well as for additional doses of the measles, mumps, and rubella (MMR) vaccine when in an outbreak setting.

RZV, GlaxoSmithKline's Shingrix vaccine, received approval from the US Food and Drug Administration for the treatment of adults 50 years or older to prevent herpes zoster (shingles) along with its complications. Updated recommendations fo herpes zoster vaccines include the following:

- Adults 50 years and older should be given 2 doses of RZV, 2 to 6 months apart, regardless of a past episode of herpes zoster or having received zoster vaccine live (ZVL).
- Adults who have previously received ZVL should be given 2 doses of RZV, 2 to 6 months apart, at least 2 months after having received ZVL.
- Adults 60 years and older should be given either RZV or ZVL, although RZV is preferred.

There is no recommendation for the use of RZV for pregnant women and recommendations for adults with immunocompromising conditions are pending. RZV can be used in adults who are "receiving low-dose immunosuppressive therapy, are anticipating immunosuppression, or have recovered from an immunocompromising illness," according to the paper.

The updated recommendations for the MMR vaccine include:

- Adults who have received 2 or fewer doses of mumps-containing vaccine and are considered to be at increased risk during a mumps outbreak by a public health authority should receive 1 dose of MMR.
- Adults who do not have evidenced immunity to the disease should receive 1 dose of MMR routinely; if they are students in postsecondary educational institutions, international travelers, or household members in contact with individuals who are immunocompromised, they should receive 2 MMR doses at least 28 days apart.
- In outbreak settings, those identified to be at increased risk should receive 1 MMR dose regardless of whether they received 0, 1, or 2 doses of a mumps-containing vaccine in the past.

"Although modest increases in vaccination coverage rates were observed in several groups of [the] adult population in 2015, the overall vaccination coverage rates for adults in the United States have remained low," the authors wrote.

Multiple factors can lead to low vaccination rates among this population. Adult patients may not be aware of the vaccines recommended for them, incomplete vaccination records can make it difficult for providers to ascertain which vaccines are needed, and providers may prioritize other tasks during the visit over reviewing vaccinations.

To address the issue, the National Vaccine Advisory Committee has updated the standards for adult immunization practice, encouraging the "integration of vaccinations as a part of routine clinical care for adults."

According to the paper, the standards serve as a call to action for health care providers to:

- Assess the vaccination status of adult patients at every clinical encounter.
- Strongly recommend needed vaccines to patients.
- Offer vaccines recommended to patients (providers who do not stock vac- cines should refer patients to another provider or pharmacist who stocks and administers vaccines).
- Document vaccines administered in the state or local immunization information system. ▲

FDA Warns of Potential Long-Term Risks of Clarithromycin in Patients With Heart Disease

By Kristi Rosa

A safety announcement released by the US Food and Drug Administration (FDA) urged health care providers to practice caution before prescribing clarithromycin (Biaxin) for patients with heart disease, as it could put these individuals at increased risk for heart problems or death in later years.

"Our recommendation is based on our review of the results of a 10-year follow-up study of patients with coronary heart disease from a large clinical trial that first observed this safety issue," shared the FDA in an announcement.

The large clinical trial CLARICOR found "an unexpected increase in deaths among patients with coronary heart disease" who had been given a 2-week course of the antibiotic; the increase in deaths became apparent after the patients were followed for 1 year or longer, according to the FDA. However, investigators have been unable to pinpoint an exact explanation for this. The FDA noted that "of the 6 observational studies published to date in patients with or without coronary artery disease, 2 found evidence of long-term risks for clarithromycin, and 4 did not."

These findings have also led the FDA to add a new warning regarding the increased risk of death in this patient population. Because of the potentially fatal long-term risks, the FDA advises that prescribers consider the use of other antibiotics in these patients. The study's results have been added to clarithromycin drug labels as well.

Clarithromycin is used to treat a wide variety of mild to moderate bacterial infections, according to the PubChem Open Chemistry Database from the National Institute of Health (NIH); these include pneumonia, pharyngitis, acute sinus infections. In addition, the antibiotic can also be used off label to treat opportunistic infections of HIV, according to the NIH.

This is not the first time the FDA has called attention to this safety issue; the agency also released an announcement regarding similar concerns in December 2005, prior to the 10-year follow-up results yielded by CLARICOR.

"Health care providers should be aware of these significant risks and weigh the benefits and risks of clarithromycin before prescribing it to any patient, particularly in patients with heart disease and even for short periods, and consider using other available antibiotics," the FDA recommended. "Advise patients with heart disease of the signs and symptoms of cardiovascular problems, regardless of the medical condition for which you are treating them with clarithromycin."

Providers should report any clarithromycin-associated adverse effects to the FDA MedWatch program. ▲

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Senate Proposes $1B for Universal Flu Vaccine Research

By Einav Keet

After the US Centers for Disease Control and Prevention (CDC) reported overall flu vaccine effectiveness to be at 36%, US Food and Drug Administration (FDA) Commissioner Scott Gottlieb, MD, followed up with a statement on the FDA's ongoing effort to improve the vaccine's effectiveness. On the issue of the vaccine's low rate of 25% effectiveness overall against influenza A (H3N2), which has predominated this year's difficult flu season, Dr. Gottlieb noted that the vaccine was found to be 51% effective against H3N2 in children ages 6 months to 8 years.

"There are a number of theories on why this season's vaccines produced reduced effectiveness against H3N2. We're taking steps to investigate each of these potential causes, rule out possible reasons for the variation in effectiveness and improve vaccine efficacy against H3N2," Dr. Gottlieb said in a statement. "We don't think it was a question of getting the particular H3N2 strain wrong when we set out to produce this season's flu vaccines. Although adapting circulating virus strains for manufacture can lead to differences between the circulating strain and the one used for manufacturing that could affect effectiveness, so far, the data we have suggests that the viruses provided by reference laboratories to manufacturers to make this year's vaccines do reasonably match the circulating flu strains that are causing most of the illnesses, including H3N2."

Looking ahead to the 2018-2019 flu season, the World Health Organization recently announced its recommendations to change 2 of the 4 vaccine components, including the H3N2 and the influenza B Victoria lineage components. The new H3N2 vaccine strain will be A/Singapore/INFIMH-16-0019/2016, though public health experts worry that low vaccine effectiveness will persist as long as the H3N2 components continue to be egg-grown and prone to mutation. Dr. Gottlieb noted in a recent tweet that the FDA is reviewing improved flu vaccine efficacy in cell-based vaccines, and how this may impact decisions regarding next season's flu vaccine components in the United States.

Meanwhile, a group of US senators introduced a bill on February 15, 2018, in support of more comprehensive research on the development of a universal flu vaccine. The Flu Vaccine Act, introduced by Ed Markey (D, Massachusetts), aims to invest $1 billion over the next 5 years, allocating $200 million each year from 2019 through 2023 to the National Institutes of Health (NIH). In 2017, the NIH's National Institute of Allergy and Infectious Diseases spent $64 million on universal flu vaccine research.

"America's scientists and clinicians are gold medalists in health and disease research, and it is up to the United States to lead the world in the response to the flu," said Sen. Markey in a press release. "We must enhance our ability to predict the right strain for the next season, produce a more optimal vaccine, and protect all Americans against all strains of this virus. The Flu Vaccine Act will help provide dedicated, consistent resources so that we can perform the basic science research necessary to improve upon our current vaccine and ultimately develop a universal one." ▲

Aromatherapy in Health Care Settings—A Source of Drug-Resistant Bacterial Infections?

By Saskia v. Popescu, MPH, MA, CIC

Hospitalization and medical care can be stressful, and many patients are trying to find ways to reduce the anxiety. For example, requests from women to incorporate aromatherapy through the use of essential oils into their birthing experience are increasing. Although there is some evidence that using aromatherapy prior to and during delivery can result in a reduction in anxiety, fear, and/or pain in labor, there are challenges with this practice in terms of infection control. Indeed, reviews are mixed regarding the medical applications of aromatherapy; however, the fact remains that the popularity of essential oils remains high. Sadly, a recent outbreak of an extensively drug-resistant *Pseudomonas aeruginosa* (XDR-PA) infection has revealed how aromatherapy can pose a high risk to patient safety.

Aromatherapy can be administered 2 ways: through a diffusing machine, which requires water, or direct application of the oil onto parts of the body. Understandably, from an infection prevention perspective, there is concern that diffusers may pose a challenge for disinfection and put patient(s) at risk for waterborne infections with pathogens such as *Legionella* or *P. aeruginosa*. The quick and rising popularity of aromatherapy use in health care settings means that these institutions may not have processes in place to ensure patient safety.

This may have been the case at the University Hospital of Innsbruck in Austria, which is a tertiary care facility that houses 1600 beds. The hospital staff maintain patient screening on admission—oropharyngeal, rectal, and nasal—as a way to maintain active infection prevention; however, when they began to see an increase in infections with XDR-PA from multiple sites across 7 patients in the surgical intensive care unit (SICU), the infection prevention staff knew something was afoot.

In their quest to find the source of this increased rate of XDR-PA, they found several infection control failures, such as the fact that patient wash water was discharged directly into the basins in the patient's room instead of within a dedicated sink to avoid splash-back and contamination, and medical devices were placed within the splash-contaminated zone. Although these are actions likely to occur in all hospitals, 1 particular observation raised a red flag. Patients had been using oil for an aromatherapy body treatment and the same bottle was used across 7 of the patients who were positive (either colonized or infected) for XDR-PA.

When the staff took additional environmental samples to identify the source of the infection, they found that of the 145 samples, 4.1% had XDR-PA present. The highly resistant pathogen was found in the wash basins and the patient aromatherapy oil.

To decipher whether or not the aromatherapy bottles arrived contaminated, the team tested an unopened bottle, which came back negative.

The staff then implemented infection prevention practices to reduce the transmission. They separated the patients into cohorts and discontinued putting wash water into the basin. In addition, they no longer allowed the sharing of aromatherapy oil.

The outbreak of XDR-PA across these 7 patients lasted for 24 days and was ultimately deemed nosocomial. What pointed to the aromatherapy was that all 7 patients received the care oil, which had been directly applied by nurses. Further investigation suggested that the patients likely contaminated the environment (ie, basins) rather than the oil, and that the oil was contaminated directly by a patient via a health care worker or the discharge of the basin water contaminated the area where the oil was stored. Improper storage and sharing of the oil is a likely risk factor for contamination and thus transmission, meaning that hospitals should use single-patient containers if they allow aromatherapy.

Overall, the risks of diffusers are considerable and if patients are requesting essential oils, topical application with single-patient bottles should be considered; however, ultimately, each facility should ensure they have a designated policy and plan in place. ▲

Kratom Likely Responsible for 132 *Salmonella* Infections in 38 States, CDC Says

By Kristi Rosa

The FDA considers kratom to be an opioid substitute.

The US Centers for Disease Control and Prevention (CDC) announced the launch of an investigation into a multistate outbreak of *Salmonella* infections that have been linked with the botanical substance kratom.

Native to Thailand, Malaysia, Indonesia, and Papua New Guinea, kratom, or *Mitragyna speciosa*, is a plant typically crushed and made into a tea as a means to treat pain; it can also be chewed, smoked, or ingested in capsule form. Known for its stimulant effects, the plant has been considered by governmental agencies as an opioid substitute, a concern that hits home as the United States struggles with an ongoing opioid crisis.

To this end, the US Food and Drug Administration (FDA) issued a public health advisory in November 2017, warning consumers not to use kratom because, "[the] FDA is concerned that kratom, which affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependence." Since then, the FDA has set out to better understand kratom's safety profile. Commissioner Scott Gottlieb, MD, has also released statements on the additional associated adverse events and further evidence on kratom's opioid properties.

Now the botanical substance has been linked with another troubling effect: *Salmonella* infection.

CDC officials are currently investigating outbreaks of *Salmonella* I 4,[5],12:b:-61, *Salmonella* Javiana, *Salmonella* Okatie, and *Salmonella* Thompson infections linked with 132 infections across 38 states. Thirty-eight of the affected individuals have been hospitalized as a result of the infection. Washington has reported the highest number of cases (13).

The CDC estimates that illnesses began on January 11, 2017. Those who have fallen ill range in age from 1 to 73 years. No deaths have been reported thus far.

The CDC identified kratom as the likely source of the outbreak when 57 of 78 individuals reported consuming the plant via pills, powder, or tea. However, the CDC has not pinpointed a common brand or supplier. ▲

Bystander Activation of T Cells May Be Cause of Persistent Arthritis in Lyme Disease

By Jared Kaltwasser

Investigators from the University of Utah Health believe they have found the reason why some patients with Lyme disease have persistent arthritis even after antibiotic treatment. The news could pave the way to an effective treatment for a painful and confounding complication of the disease.

"One of the clinical problems with Lyme disease infection is that there's a small group of patients who continue to display symptoms, including arthritis symptoms, following what should be an effective treatment of antibiotics," said Janis J. Weis, PhD, a professor of pathology at University of Utah Health and a study author.

Dr. Weis said these symptoms persist in some patients even if there's no longer evidence of an active infection with *Borrelia burgdorferi (B. burgdorferi)*, the bacterium that causes Lyme disease.

The investigators now think they know how it's happening. They have identified a T cell receptor that interacts with surface molecules on *B. burgdorferi*. According to the study, this interaction causes bystander activation of T cells, which in turn causes the T cells to produce inflammatory molecules that lead to arthritis symptoms around the joints.

Those activated T cells can continue to interact with residual bacteria long after the initial tick bite, causing some patients to continue to feel symptoms like arthritis.

To arrive at those results, Dr. Weis and colleagues first had to find a suitable animal model because reliable animal markers to study the inflammatory response had not existed. However, Dr. Weis stated that students in her lab realized that a specific set of mice—those lacking the anti-inflammatory molecule IL-10—had the same kinds of sustained inflammatory responses that were so troublesome in the small subset of patients with Lyme disease and persistent arthritis.

Graduate student Sarah Whiteside, the study's first author, monitored these IL-10–deficient mice for more than 4 months post infection with *B. burgdorferi*.

"Sarah demonstrated that even 18 weeks after infection, the arthritis was still severe and there was a tremendous amount of joint inflammation in the joint tissue but no evidence of bacteria in the joint tissue," Dr. Weis told *Contagion®*.

They discovered that T cells in the mice were undergoing bystander activation. "Instead of activating a very small, specific set of T cells, it causes this global activation of immune cells," Ms. Whiteside said. Once activated, those T cells can interact with residual bacteria to generate continued inflammation long after the initial infection.

The study has multiple implications. Ms. Whiteside said a next step will be to test the theory in humans to confirm whether bystander activation is also contributing to lingering symptoms in human patients with Lyme disease.

At the same time, identification of the IL-10 deficiency in the mouse model could spark additional research and new therapies, such as one to short-circuit T-cell activation to mitigate the risk of persistent arthritis.

Further research may look into whether it is possible to identify patients who are most likely to have persistent symptoms. There is currently no way to reliably identify those patients, Dr. Weis stated, but she noted that results from research by Allen Steere, MD, of Massachusetts General Hospital, have suggested that certain genetic markers seem to be more common in patients who develop persistent arthritis with Lyme disease. Those markers are similar to the markers associated with rheumatoid arthritis (RA), she continued. However, that connection doesn't appear to be found 100% of the time.

"It's not an all-or-nothing kind of association," stated Dr. Weis.

Still, the potential combination could suggest therapeutic options. "Maybe drugs that are used to treat RA or drugs that can temporarily suppress the immune response could be applicable for this persistent arthritis," added Whiteside. ▲

South Africa Hit With Largest-Ever *Listeria* Outbreak

By Kristi Rosa

South Africa has been struggling with a deadly *Listeria* outbreak for over a year.

As of March 14, 2018, laboratory-confirmed cases of listeriosis had risen to 978. A total of 674 patients have been traced for outcome of illness and 183 have died, indicating a 27% case fatality rate.

Since the outbreak began, health officials have been working doggedly to identify a potential source. Officials from the National Institute for Communicable Diseases interviewed 109 of the infected individuals to glean information on foods they consumed in the month prior to falling ill, according to a statement from Aaron Motsoaledi, MBBS, the minister of health of South Africa. The majority of those interviewed (85%) reported consuming ready-to-eat processed meat products—polony, sausages, and other cold meats.

This *Listeria* outbreak is believed to be the largest-ever outbreak to date, according to the United Nations. Prior to this outbreak, the second largest outbreak of listeriosis was in 2011 and was linked with whole cantaloupes from Jensen Farms in Colorado—that outbreak had 147 confirmed cases across 28 states; 33 individuals died.

After 9 children under the age of 5 presented with febrile gastroenteritis at the Chris Hani Baragwanath Hospital in South Africa, the pediatrician suspected that they may have been infected with a food-borne illness. Environmental health practitioners (EHPs) were informed of the situation, and on the same day, they collected samples from 2 unrelated polony brands (Enterprise and Rainbow Chicken Limited) and submitted the samples for laboratory testing. Whole genome sequencing found that 91% of the 9 sequence types of *Listeria monocytogenes* isolated from the samples were sequence type 6 (ST6)—this outbreak is driven by ST6, according to Dr. Motsoaledi.

EHPs visited all food processing, packaging, and production sites, including the Enterprise factory located in Polokwane, where they conducted an extensive food product and environmental sampling. *Listeria* was isolated in upwards of 30% of the environmental samples collected. Whole genome sequencing found that at least 16 environmental samples collected from the site were of the outbreak strain, ST6.

"The conclusion from this is that the source of the present outbreak can be confirmed to be the Enterprise food-production facility in Polokwane," Dr. Motsoaledi stressed.

Furthermore, officials found that other ready-to-eat meat products from the Enterprise facility located in Germiston also contained *Listeria*, however, the sequence type is not yet known.

Meanwhile, officials are also investigating the RCL Wolwehoek production facility, where already, polony products have come back positive for *Listeria*. However, the isolates are not ST6. Regardless, the contaminated food product still poses a public health risk as upwards of 10% of environmental samples collected from the site were positive for *Listeria*.

In light of this information, Dr. Motsoaledi stressed that all consumers should avoid eating processed meat products that are sold as ready-to-eat. ▲

Europe Responds to Recent Measles Outbreaks With Tougher Vaccination Laws

By Einav Keet

A recent 4-fold increase in measles cases in Europe has been linked with declining vaccination rates, prompting several European countries and nations to pass legislation making more types of vaccinations mandatory and penalizing parents who refuse to vaccinate their children.

The European Center for Disease Prevention and Control (ECDC) says vaccine hesitancy has led to significant outbreaks of diseases such as measles, rubella, and polio in undervaccinated communities, despite the remarkable reductions seen in morbidity and mortality from vaccine-preventable diseases in recent decades.

Of the 21,315 measles cases that occurred in Europe in 2017, 5,006 of these cases were reported in Italy. Measles vaccination coverage for children in Italy was 85% in 2015, below the target goal of 95% needed to achieve herd immunity. In response, Italy's Parliament passed a law for mandatory vaccinations for children being registered for school. Under the law, which took effect in September 2017, children up to the age of 16 are required to have vaccinations for chickenpox, diphtheria, Haemophilus B, hepatitis B, meningitis B and C, measles, mumps, polio, rubella, tetanus, and whooping cough. In addition, parents in Italy who don't have their children vaccinated will face penalties, including being prohibited from enrolling their children in public or private schools and fines of €500 to €7500 (US $559 to $8380).

"The international scientific community unanimously recognizes that vaccines are one of the safest and most effective public health tools of all time," Italy's Ministry of Health said in a statement.

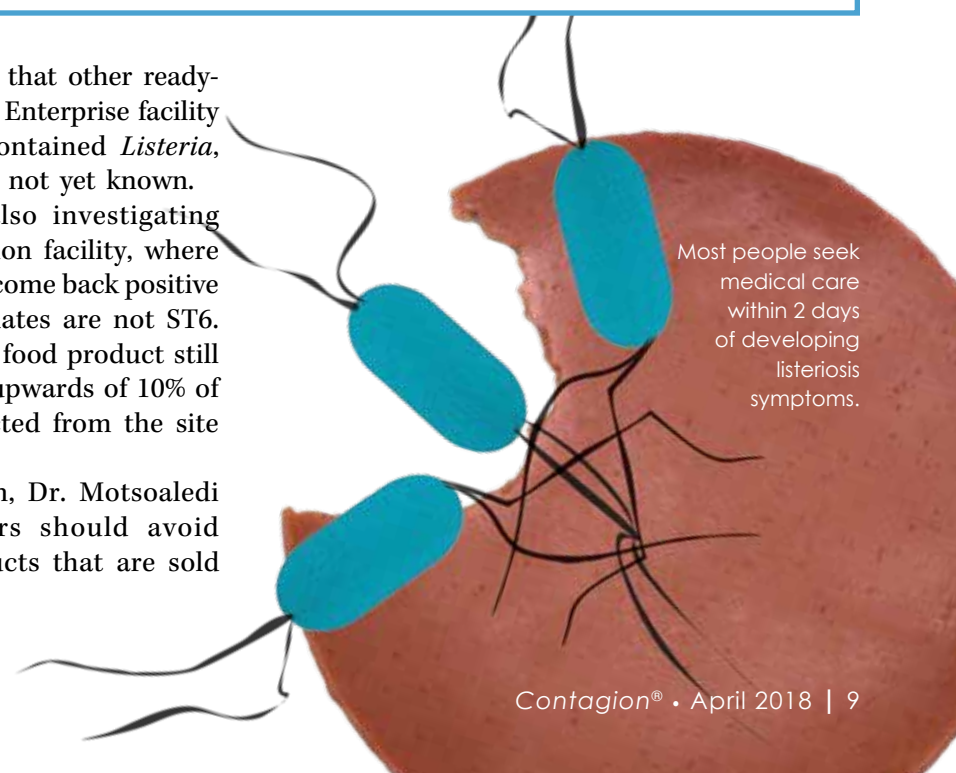
The ECDC says that outbreaks of measles are still occurring in a number of countries. In Romania, which reported 5562 measles cases in 2017, health ministry officials said that there are more than 224,200 children between the ages of 9 months and 9 years who have not been vaccinated for measles. On August 9, 2017, Romanian lawmakers adopted a draft bill obligating parents and legal guardians to vaccinate their children, with the state funding and organizing vaccinations.

Germany, which saw 927 measles cases last year, has also fought against declining vaccination rates by passing a law calling for kindergartens to report to authorities any parents who fail to provide documentation of vaccination. Parents who fail to follow health ministry requirements on vaccination face penalties of up to €2500 (US $2800).

In 2015, Australia's government announced that it was seeking to limit immunization requirement exemptions, and, as such, proposed a "No Jab, No Play" measure aimed at improving vaccination rates. The measure eliminated the conscientious objector exemption while maintaining certain medical and religious exemptions, and extended immunization requirements to children of all ages.

New South Wales and Victoria have gone further, passing legislation banning unvaccinated children from enrolling in schools and child care centers and imposing fines on centers that admit unvaccinated children. In 2017, the state of South Australia (SA) proposed a similar bill. "The new 'No Jab, No Play' laws will mean children must be appropriately immunized, on an immunization catch-up program, or be exempt for medical reasons, in order to attend early childhood care services," according to the Government of South Australia.

The hope is that these efforts to get more children vaccinated will work to quell the ongoing vaccine-preventable disease outbreaks running rampant throughout Europe. ▲



Most people seek medical care within 2 days of developing listeriosis symptoms.

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About 1 in 3 individuals in the United States will develop shingles.

The Shingrix Vaccine: What You Should Know

This breakthrough vaccine is quickly becoming an integral part of the adult immunization arsenal.

BY JENNIFER GERSHMAN, PHARMD, CPH

JENNIFER GERSHMAN, PHARMD, CPH

Jennifer Gershman, PharmD, CPh, is a medical writer and a *Pharmacy Times*® contributor who resides in South Florida.

The adjuvanted zoster vaccine recombinant, Shingrix, was approved for adults 50 years and older for the prevention of herpes zoster (shingles) in October 2017.[1] Shingles, which develops after the reactivation of the varicella-zoster virus (VZV), is a painful rash that generally occurs on 1 side of the body, usually the face or torso. Complications may include postherpetic neuralgia (PHN), ophthalmic involvement, and bacterial infection. These complications can lead to hospitalization or even death. The risk of shingles and PHN increases with age, and about 1 of every 3 individuals in the United States will develop shingles, leading to about 1 million cases each year.

DOSAGE AND ADMINISTRATION

Shingrix is administered through intramuscular (IM) injection as a 2-dose (0.5 mL each) vaccine series.[2] The second dose should be administered anytime between 2 and 6 months after the first dose. The vaccine series does not need to be restarted if more than 6 months have passed since the first dose.[3]

PHARMACOLOGY

The vaccine has been shown to boost VZV-specific immune response with the adjuvant known as ASO1B, which is thought to protect against shingles.[2] Additionally, VZV glycoprotein E is essential for viral replication and cell-to-cell spread and is the primary target of VZV-specific immune responses. Shingrix does not contain preservatives.

METHOD OF SUPPLY

Shingrix is supplied as 2 components, including the adjuvant and antigen (see **TABLE 1** available at contagionlive.com).[2]

STORAGE

Before reconstitution, both vials should be refrigerated between 36°F and 46°F and protected from light.[2] The vials should be discarded if they have been frozen. Shingrix should be used immediately after reconstitution or stored refrigerated between 36°F and 46°F and used within 6 hours.[2]

DRUG INTERACTIONS AND CONTRAINDICATIONS

Immunosuppressive therapies may reduce the effectiveness of Shingrix. The vaccine is contraindicated in patients with a history of a severe allergic reaction to any vaccine component or after a previous dose of Shingrix.

WARNINGS AND PRECAUTIONS

Health care providers should review patients' immunization history for possible sensitivity and previous vaccination-related adverse reactions. Epinephrine should be administered in the event of an anaphylactic reaction.

ADVERSE REACTIONS

Clinical studies have demonstrated that Shingrix is safe, with the most common adverse effects being mild to moderate in severity (see **TABLE 2** available at contagionlive.com).[2] Adverse reactions should be reported to the Vaccine Adverse Events Reporting System of the US Centers for Disease Control and Prevention (CDC).

PREGNANCY AND LACTATION

There are no available human data to establish any risks associated with administering Shingrix to pregnant women, and it is unknown whether it is excreted into human milk.

PEDIATRIC POPULATION

The safety and efficacy of Shingrix have not been evaluated in patients younger than 18 years of age.

CONCOMITANT VACCINE ADMINISTRATION

During clinical studies, patients could receive the inactivated influenza vaccine up to 8 days before each Shingrix dose or at least 14 days after the vaccine.[4,5] The influenza vaccine did not affect the immune response. The influenza vaccine can be administered on the same day as Shingrix as separate injections.

CLINICAL STUDIES

Shingrix appears to be more effective than Zostavax; however, there are no head-to-head trials comparing both. Two phase 3 placebo-controlled trials were the basis of US Food and Drug Administration approval and demonstrated the safety and efficacy of Shingrix.[4,5] One study evaluated the safety and efficacy of Shingrix in 15,411 adults 50 years and older in 18 countries in Europe, North America, Latin America, and Asia–Australia.[4]

Study participants received 2 IM doses of Shingrix or placebo 2 months apart. The primary objective was to evaluate the efficacy of the vaccine compared with placebo in reducing the risk of herpes zoster in older adults. Secondary end points included assessing the vaccine efficacy in each age group (50 to 59 years, 60 to 69 years, and at least 70 years).

During the average follow-up of 3.2 years, there were 6 herpes zoster cases in the Shingrix group and 210 in the placebo group. The overall vaccine efficacy against herpes zoster was 97.2% (P <.001) and was between 96.6% and 97.9% for all age groups. The demographics were similar in the 2 study groups, and the average age was 62 years. The most common reported adverse reaction was pain at the injection site.[4]

The second trial was conducted at the same sites as those in the study involving adults 50 years and older.[5] This was a randomized, placebo-controlled, phase 3 study conducted in 18 countries and involved 13,900 adults 70 years and older. Patients received 2 doses of Shingrix administered intramuscularly 2 months apart. Study participants were followed for at least 30 months after the second dose through monthly contacts and yearly clinic visits. The primary objective was to evaluate the efficacy of Shingrix compared with placebo in reducing the risk of shingles in adults 70 years and older. The average age of the study participants was 75.6 years. The average follow-up time was 3.7 years, and herpes zoster occurred in 23 patients who were administered Shingrix and 223 in the placebo group. Overall vaccine efficacy against herpes zoster was 89.8% (P <.001) and for PHN was 88.8%.[5]

Evidence has demonstrated that the Zostavax vaccine reduces the overall incidence of shingles by 51% and the incidence of PHN by 67% for patients 60 years or older. Zostavax vaccine efficacy decreases with age and is only about 38% effective for individuals older than 70 years of age.[4]

VACCINE RECOMMENDATIONS

The Advisory Committee on Immunization Practices (ACIP) voted that Shingrix is recommended as the preferred vaccine for healthy adults 50 years and older to prevent shingles and related complications.[3] This is a change from the previous recommendations that individuals 60 years and older receive the Zostavax vaccine and will likely result in more patients being vaccinated. Evidence indicates that an individual's risk of developing shingles increases after 50 years of age. Patients who have previously received the Zostavax vaccine should still receive 2 doses of Shingrix.[3] It is important to note that Shingrix is not indicated for chicken pox prevention.

Because Shingrix is not a live vaccine like Zostavax, issues should not be expected with administering it to patients who may be immunocompromised. However, the studies excluded patients with confirmed or suspected immunosuppressive conditions (eg, cancer or HIV infection) or immunosuppressive therapy (eg, chemotherapy, organ transplantation medications, or autoimmune disorder treatment).[4,5] Data regarding administration of Shingrix to immunocompromised patients are being gathered and should be published by the ACIP.[3] Individuals who are immunocompromised with the following conditions have an increased risk of developing shingles: cancer, HIV, bone marrow or solid organ transplantation, or taking immunosuppressive medications. The ACIP states that Shingrix be administered to patients taking low-dose immunosuppressive therapy (eg, less than 20 mg/day of prednisone or equivalent or using inhaled or topical steroids) and individuals anticipating immunosuppression or those who have recovered from an immunocompromising condition.[3] Patients with chronic medical conditions should receive Shingrix.

VACCINE COST AND AVAILABILITY

The vaccine cost is expected to be $280 for 2 doses.[6] Shingrix is available for ordering, and pharmacies are starting to receive the vaccine. Because the recommendations were just published in the CDC's *Morbidity and Mortality Weekly Report*, insurance companies will likely begin to cover Shingrix. It is also expected that Shingrix will be covered under Medicare Part D. Billing codes are available for administering and prescribing Shingrix (see **TABLE 3** available on contagionlive.com).[6]

PATIENT COUNSELING

Health care providers can play an important role in educating patients about the importance of completing the vaccine series. There is little information available regarding the efficacy of just 1 dose of Shingrix. Compliance may be increased by follow-up reminder phone calls and counseling during refill pickups, in the case of pharmacists who administer the vaccine. Patients may inquire about whether they can develop shingles from Shingrix. Health care providers should explain that because Shingrix is not a live vaccine, individuals cannot develop shingles from the vaccine.

It is also important to educate patients who have experienced shingles to still receive the vaccine to prevent future recurrences. Two to 3 repeat shingles episodes can occur in someone's lifetime.[1] Patients should generally wait until the shingles rash has disappeared before being vaccinated with Shingrix.

Health care providers should encourage patients who have already received Zostavax to still get vaccinated with Shingrix, as the efficacy for shingles prevention is greater with Shingrix. A recent study examined the safety of Shingrix in patients who received the Zostavax vaccine at least 5 years ago.[8] The study found that Shingrix produced a strong immune response and was safe in patients previously vaccinated with Zostavax.[8] In fact, protection from Zostavax is lost after about 5 years, so it is important to target these patients for Shingrix vaccination.[8] Health care providers should recommend that patients wait at least 8 weeks after Zostavax administration to receive Shingrix.[3,9]

Patients may inquire about how long it takes for Shingrix to become effective after the second vaccine dose. Studies have generally evaluated the immune response 4 weeks after the second dose demonstrating the vaccine's efficacy.[4,5]

Pain and redness are the most common injection site adverse reactions for patients to expect with Shingrix, but these should last for only a few days.[2]

Health care providers should discuss with patients how Shingrix can help prevent PHN, which is the most common complication of shingles.[10] Individuals are at a greater risk of experiencing PHN if they are over 50 years of age, have a severe case of shingles, or have a chronic disease such as diabetes. ▲

References available at ContagionLive.com.

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Should Early FMT Be First-Line Treatment for Severe CDI?

By Payal K. Patel, MD, MPH

Given the impressive efficacy of fecal microbiota transplantation (FMT) on decreasing recurrence of *Clostridium difficile* infection (CDI), the next logical step is seeing how it works for hospitalized patients with CDI.[1] A recent *Clinical Infectious Diseases* article by Hocquart et al describes a retrospective study of patients who received either medical treatment for CDI or treatment plus FMT in their hospital over 3 years.[2]

PAYAL K. PATEL, MD, MPH

After work had shown that FMT improved survival in patients with CDI of the ribotype O27[3] and decreased recurrence and duration of symptoms, the infectious disease team at a hospital in Marseille, France, began to recommend early FMT for all hospitalized patients with CDI. They used this patient population for the retrospective study, which included 111 patients—66 who received FMT and medical therapy and 45 who received therapy alone. None had surgical intervention. The primary outcome was 3-month mortality. Severe colitis was defined to be leukocytes >15 g/L, albumin <30 g/L, serum creatinine >130 µmol/L or >1.5 times the baseline, peritonitis, occlusive syndrome, megacolon, or signs of shock. The 2 patient groups were largely similar, except all those in the FMT group received oral vancomycin for medical treatment, whereas some in the non-FMT group received metronidazole or fidaxomicin. The investigators found that early FMT reduced mortality in patients with severe CDI (odds ratio, 0.08; 95% CI, 0.016-0.34; P = .001) but not in cases classified as nonsevere.

With these conclusions, the authors recommended that early FMT should be first-line treatment in severe CDI. An accompanying editorial[4] asked the question on most readers' minds: Is it too early to recommend FMT without further trials? Hocquart et al provide a compelling argument that patients with severe CDI have a poor prognosis, FMT has a good safety profile (as far as we know), benefit of this therapy could be vast, and surgery in a potential trial would be a poor control because certain patients would not be surgical candidates. However, it is still too early in FMT research to know what the long-term effects of FMT may be, and there is good reason that double-blind, randomized controlled multicenter trials should be considered before widely changing practice. The hope is that researchers will build off this work and hospitals will begin to add early FMT to the arsenal of weapons against CDI, along with improving antibiotic stewardship practices to avoid CDI altogether. For clinicians who have faced the tough situation of having a patient in the intensive care unit with severe CDI and few treatment options that seem to be working, this article serves as promising news. The literature awaits the next trial of early FMT in severe CDI patients. ▲

References are available at ContagionLive.com.

Meta-Analysis On the Utility of Nasal Swabs to Rule Out MRSA Pneumonia

By Tiffany Lee, PharmD

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasingly common and potentially deadly pathogen seen in cases of hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP). Risk factors for invasive *S. aureus* infection include nasal colonization.[1,2] This can carry significant clinical impact given that nasal colonization of *S. aureus* occurs in about 25% to 30% of the population, with varying proportions of methicillin-resistant isolates.[3,4] As a result, many patients presenting with pneumonia are empirically treated with anti-MRSA therapy, leaving antimicrobial stewardship programs (ASPs) faced with the challenge of identifying patients who truly warrant continuation of anti-MRSA therapy.

Tiffany Lee, PharmD

Although the role of MRSA nasal swabs to rule out MRSA pneumonia has been of particular interest to a number of researchers, Dr. Parente and colleagues are the first to consolidate the available data describing the predictive value of the nares screen. This recently published meta-analysis included 22 relevant studies that described the relationship between rates of positive MRSA nasal swabs and diagnosed MRSA pneumonia.[5] The primary outcome was diagnostic performance described through pooled sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios, and diagnostic odds ratios.

Most of the included studies were retrospective in nature (18/22, 81.8%) and performed at teaching hospitals (16/22, 72.7%), and of those reporting types, ventilator-associated pneumonia (VAP, 8/11, 72.7%) predominated. Diagnostic criteria and MRSA screening processes were similar across all reported studies.

The diagnostic performances of MRSA nasal swabs across different classifications of pneumonia are reported in **TABLE 1**. Overall, MRSA nasal swabs demonstrate a 96.5% NPV, 90.3% specificity, and 0.32 negative likelihood ratio in the combined analysis. Of note, the low sensitivity rate in patients with VAP suggests that the benefit of the MRSA nasal swabs may not be applicable in this population due to iatrogenic sources of MRSA from intubation. As reflected by its relatively low PPV, positive MRSA nasal swabs cannot distinguish between colonization versus true infection. The authors concluded that nares screening can prove valuable in ruling out MRSA pneumonia, especially in CAP and HCAP, and aiding in de-escalation off of empiric antibiotics.

TABLE 1: Diagnostic Performances of MRSA Nasal Swabs Across Pneumonia Classifications

	ALL	VAP	CAP/HCAP
Sensitivity, % (95% CI)	70.9 (58.8-80.6)	40.3 (17.4-68.4)	85.0 (59.7-95.6)
Specificity, % (95% CI)	90.3 (86.1-93.3)	93.7 (77.1-98.4)	92.1 (81.5-96.9)
PPV, %	44.8	35.7	56.8
NPV, %	96.5	94.8	98.1
Positive likelihood ratio (95% CI)	7.28 (5.3-10.1)	6.34 (1.94-20.8)	10.8 (5.1-23.0)
Negative likelihood ratio (95% CI)	0.32		
Diagnostic odds ratio (95% CI)	24.6 (13.6-37.5)	9.96 (2.63-37.6)	66.4 (28.5-154.6)

CAP indicates community-acquired pneumonia; HCAP, health care-associated pneumonia; NPV, negative predictive value; PPV, positive predictive value; VAP, ventilator-associated pneumonia

Streamlining empiric antibiotics continues to be a challenge for clinicians, particularly in the absence of microbiologic data. This meta-analysis further drives home the value of MRSA nasal swabs for ASPs to quickly and safely de-escalate patients off anti-MRSA therapy while curbing rates of side effects, need for lab monitoring, and costs. Although the findings of this study question their utility in patients with VAP, MRSA nasal swabs can be leveraged as a powerful de-escalation tool in patients presenting with CAP and HCAP. With the next iteration of the CAP guidelines soon to be released, it is anticipated that the rapidly growing body of literature supporting the MRSA nasal swab will be incorporated and its use will be encouraged. ▲

References are available at ContagionLive.com.

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SOLSTICE is a clinical research study designed to explore an investigational drug—maribavir—for transplant recipients whose CMV infections are not responding to current treatments.

The goal of the SOLSTICE study is to see if maribavir works (at 400 mg twice-daily), compared to the study doctor's treatment of choice, to clear CMV infection from the blood. Participants will be randomly assigned to receive either the investigational drug or the study doctor's treatment of choice for 8 weeks. The study will also assess participants for an additional 12 weeks after treatment to evaluate if they remain free of CMV infection.

To refer a patient who may be eligible, or for further information on the study, please contact the study physician, Shailesh Chavan at 781-482-2184 or shailesh.chavan@shire.com, or visit **www.StudyCMV.com**.

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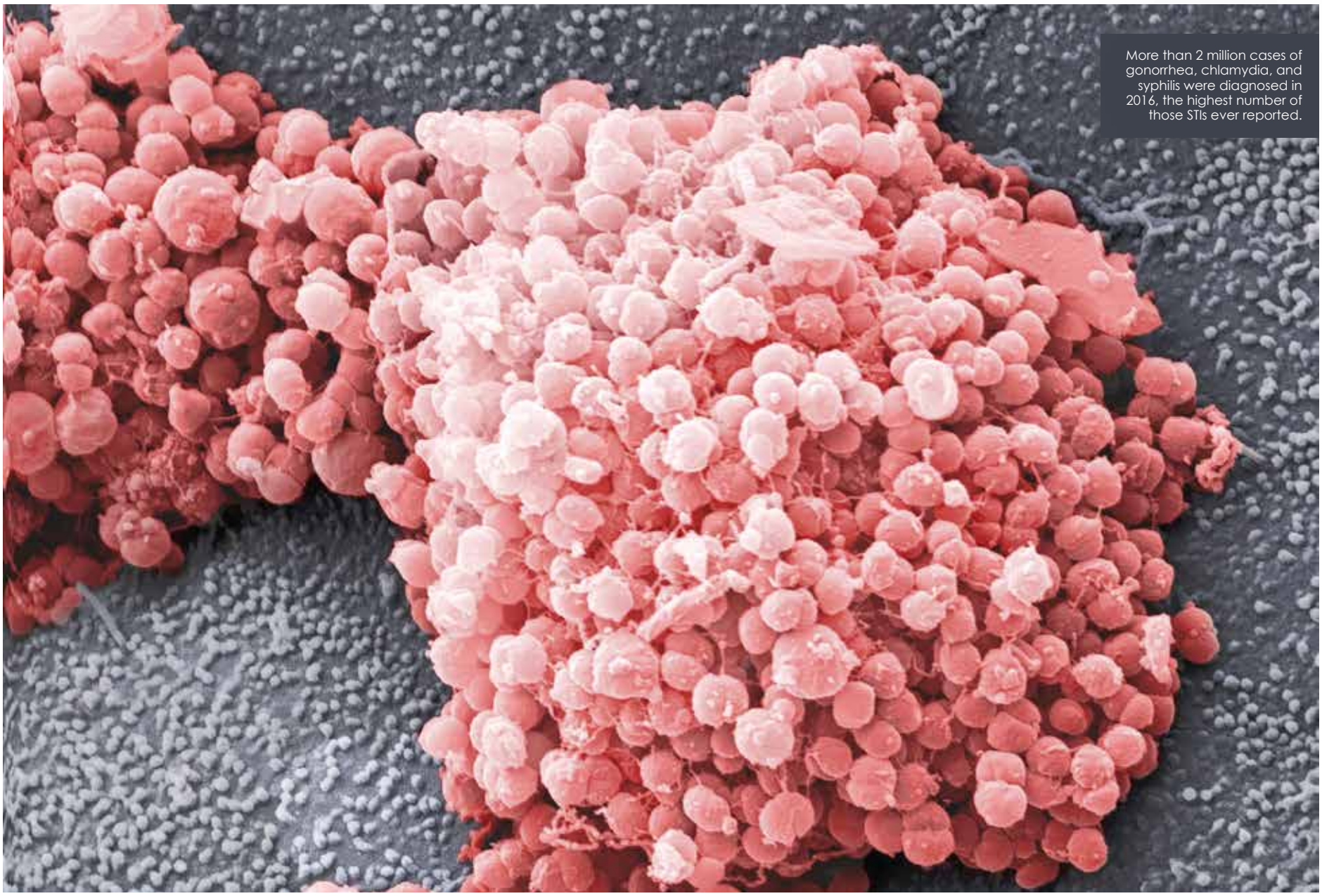


Drug-Resistant Gonorrhea and Other Emerging Issues in STIs

Sexually transmitted infections are increasing in the United States.

BY NICOLA M. PARRY, BVSC, MRCVS, MSC, DACVP, ELS

NICOLA M. PARRY, BVSC, MRCVS, MSC, DACVP, ELS

Dr. Parry is a veterinarian and is board-certified in veterinary pathology. After 13 years in academia, she now works as a private pathology consultant, and is an active member of the American Veterinary Medical Association and the American College of Veterinary Pathologists.

(*continued from cover*)

CDC surveillance data showed that more than 2 million cases of gonorrhea, chlamydia, and syphilis were diagnosed in 2016, the highest number of these STIs ever reported. Most of these new cases were due to chlamydia infection.[1]

Although all three of these STIs remain treatable with antibiotics in the majority of cases (**Table 1**), without timely diagnosis, they may lead to deleterious consequences such as infertility, stillbirth, and neonatal mortality.[2] And, adding to the public health threat associated with these infections, antibiotic resistance is making gonorrhea increasingly harder to treat.[3]

GONORRHEA

Gonorrhea is caused by infection with the bacterium *Neisseria gonorrhoeae* (*N. gonorrhoeae*). Complications associated with gonorrhea disproportionately affect women, and include pelvic inflammatory disease (PID), ectopic pregnancy, and infertility.[3] Studies have also shown that gonococcal infections facilitate the transmission of HIV infection.[3]

Gonorrhea is the second most commonly reported notifiable disease in the United States.[4] Although its rates dropped to an all-time national low in 2009, 470,000 new cases were reported to CDC in 2016—an increase of more than 18% from 2015.[1,5] The greatest increase in cases was seen among men, particularly men who have sex with men (MSM).[5]

Although gonorrhea is treatable with antibiotics, therapy has been complicated by the ability of the bacterium to develop resistance to most of the antibiotics recommended to treat it: first the sulfonamides, then tetracycline and penicillin, and, most recently, the fluoroquinolones.[6] Indeed, a 2013 CDC report listed antibiotic-resistant gonorrhea among the 3 most urgent threats of its kind in the United States.[7,8]

"Our first-line drugs, combination cephalosporins and azithromycin, are still effective for gonorrhea (Table 1)," said Christine Johnston, MD, MPH, FIDSA, an associate professor in the Division of Allergy & Infectious Diseases, University of Washington, Seattle, and medical director of the University of Washington STD Prevention Training Center, part of the

Juergen Berger/ Science Source

CDC-funded National Network of STD Clinical Prevention Training Centers. "But we are seeing emergence of case reports of resistance to these drugs, which is of huge concern," she emphasized.

"In my clinical practice, I have not been seeing resistance to the combination therapy recommended by CDC for gonorrhea[9]—yet. But, the main concern is that we are marching through classes of antibiotics for treatment. Several drugs have been available, but gonorrhea has rapidly acquired resistance with use of these drugs."

Surveillance is critical for identifying and monitoring gonococcal resistance. According to Dr. Johnston, surveillance for antibiotic resistance in *N. gonorrhoeae* in the United States is conducted through the Gonococcal Isolate Surveillance Project (GISP).[10-12] In GISP, participating regional laboratories collect *N. gonorrhoeae* specimens each month from STI clinics throughout the country. "This has provided a good picture of resistance to the drugs and how it's developing, and has really helped to inform treatment strategies for gonorrhea," said Dr. Johnston.

"A few new drugs are in the pipeline for gonorrhea," said Dr. Johnston. These include solithromycin,[13] zoliflodacin,[14] and gepotidacin.[15] "And, we need to stay ahead of the resistance by developing new antibiotics."

CHLAMYDIA

Infection with *Chlamydia trachomatis* is the most frequently reported STI in the United States.[5] Almost 1.6 million new cases were reported in 2016, and most of these diagnoses continue to be in adolescent and young adult women.[5]

Because treatment delays can be associated with reproductive health complications, prompt treatment for chlamydia infections is essential for all individuals who test positive for infection.[16] But, asymptomatic chlamydia infections are also common and frequently go undetected.[16]

"We are seeing historically high rates of infection with chlamydia," said Dr. Johnston, "especially in young women, and in MSM." However, she explained that the rise in rate of chlamydia infections is not associated with antimicrobial resistance. "It is likely to be associated with increased transmission of infection, as well as with improved rates of screening," she said.

Although azithromycin (Table 1) is an effective treatment for chlamydia infection, Dr. Johnston expressed concern about treatment failure when managing some specific chlamydia infections.[17] Because of reduced drug penetration, rectal chlamydia infections can be challenging to treat, and treatment failure rates of up to 22% have been reported.[17] For this reason, other regimens, including using doxycycline (Table 1), have been investigated for rectal chlamydia infections.[18]

SYPHILIS

Syphilis, caused by the bacterium *Treponema pallidum,* can also lead to significant complications if left untreated.[19,20] In addition to potentially causing reproductive problems and neonatal mortality, untreated syphilis can persist for many years, and can progress to become a systemic infection, affecting many organ systems, including the brain.[19,20]

Although rates of syphilis reached an all-time low in 2000, they have steadily increased since then, with almost 28,000 cases of primary and secondary syphilis—the most infectious stages of the disease—reported in 2016 in the United States.[5] This represented a 17% rise in the number of cases from 2015, with increases seen in both men and women. However, most cases of syphilis in the United States continue to occur among MSM.[5]

"We are seeing historically high rates of syphilis infection in the United States," stressed Dr. Johnston. Although this is concerning, she noted that, much like the situation with chlamydia infections, this increase is also not associated with antimicrobial resistance. "Syphilis is still very susceptible to first-line penicillins (Table 1)." However, she stressed the need for improved control programs to reduce the incidence of this infection.

NONREPORTABLE SEXUALLY TRANSMITTED INFECTIONS

Although common, some other STIs, including those due to herpes simplex virus (HSV) or human papilloma virus (HPV), are not required to be reported and may not cause noticeable symptoms.[21,22] This makes their incidence difficult to determine.

Genital herpes results from infection with predominantly HSV2 but is increasingly due to HSV1.[23] Infections with HSV are among the most common human diseases,[23] and an estimated 1 in 8 individuals in the United States aged 14 to 49 years has genital herpes.[24] However, most HSV infections are subclinical,[22] and most infected individuals have not received a diagnosis.

Data from the most recent National Health and Nutrition Examination Survey from 2015 to 2016 show that the prevalence of HSV1 and HSV2 decreased from the 1999 to 2000 survey, from 59.4% to 48.1% for HSV1, and from 18.0% to 12.1% for HSV2.[25] However, although rates are decreasing in all racial groups, substantial racial disparities persist in HSV1 and HSV2 prevalences.[25]

Genital herpes is treated with antiviral agents within the nucleoside analog class (Table 1).[23] However, long-term treatment with acyclovir and its derivatives may lead to drug resistance, the mechanism of action of which is related to viral thymidine kinase or DNA polymerase mutations.[23] Nevertheless, Dr. Johnston noted that resistance to these drugs is uncommon in immunocompetent hosts, and is almost exclusively seen in immunocompromised individuals, such as AIDS patients with low CD4 counts and transplant recipients. Reported prevalence rates for HSV resistance to acyclovir typically range from 3.5% to 10%.[23]

Several new strategies are emerging for treating drug-resistant HSV infections. These include development of new drug targets (such as the DNA helicase/primase complex), new antiviral strategies (such as lethal mutagenesis), and new drugs.[23] In a recent study, researchers found that a novel small drug molecule, a TANK-binding kinase 1 inhibitor known as BX795, suppressed HSV1 infection in cell cultures as well as in mice.[26] The researchers say it may also hold promise in treating HSV2 infections.[26]

HPV is the most common STI, affecting an estimated 79 million Americans, with about 14 million new infections arising each year.[27,28] Although some HPV types can cause genital warts and are considered low risk for causing cancer, others are considered high risk for causing cancer, including of the cervix and vagina in women, penis in men, and anus and oropharynx in men and women.[29]

Latest estimates of HPV prevalence indicate that, from 2013 to 2014, the prevalence of any genital HPV among adults aged 18 to 59 years was 42.5% in the total population, 45.2% among men, and 39.9% among women; the prevalence of high-risk genital HPV was 22.7% in the total population, 25.1% among men, and 20.4% among women. And, the prevalence of any oral HPV was 7.3% in the total population, 11.5% among men, and 3.3% among women; the prevalence of high-risk oral HPV was 4.0% in the total population, 6.8% among men, and 1.2% among women.

"We don't usually treat HPV with antiviral medications," said Dr. Johnston, "because the virus is often cleared by the immune response. In addition, effective vaccines against the most common strains of the virus are available." Indeed, HPV vaccination has been shown to be effective in reducing the prevalence of HPV infection among young men and women in the United States.[30,31] One US study showed substantial reductions in national vaccine-type HPV prevalence among young women aged 14 to 19 years (64%) and 20 to 24 years (34%) within 6 years >>

TABLE 1: Antimicrobial Therapies Commonly Used for STIs

	CURRENT RECOMMENDED FIRST-LINE THERAPY	ALTERNATIVE THERAPY
Gonorrhea	Single dose of 250 mg IM ceftriaxone in combination with 1 g of oral azithromycin	Two alternative dual-treatment regimens are available for patients with cephalosporin allergy: Single dose of 320 mg oral gemifloxacin plus 2 g of oral azithromycin OR Single dose of 240 mg IM gentamicin plus 2 g of oral azithromycin
Syphilis • Primary, secondary, or early (<1 year) latent syphilis	2.4 million units of IM long-acting benzathine penicillin G as a single dose	100 mg of oral doxycycline 2 x daily for 14 days OR 500 mg of oral tetracycline 4 x daily for 14 days
• Late (>1 year) latent syphilis or latent syphilis of unknown duration	3 doses of 2.4 million units of IM long-acting benzathine penicillin G at weekly intervals	100 mg of oral doxycycline 2 x daily for 28 days OR 500 mg of oral tetracycline 4 x daily for 28 days
Chlamydia	Single dose of 1 g oral azithromycin OR 100 mg of oral doxycycline twice daily for 7 days	500 mg of oral erythromycin base 4 times daily for 7 days OR 800 mg of oral erythromycin ethylsuccinate 4 times daily for 7 days OR 500 mg of oral levofloxacin once daily for 7 days OR 300 mg of oral ofloxacin twice daily for 7 days
HSV • First clinical episode	400 mg of oral acyclovir 3 x daily for 7–10 days OR 200 mg of oral acyclovir 5 x daily for 7–10 days OR 1 g of oral valacyclovir twice daily for 7–10 days OR 250 mg of oral famciclovir 3 x daily for 7–10 days	None at this time.
• Episodic therapy for recurrent genital herpes	400 mg of oral acyclovir 3 x daily for 5 days OR 800 mg of oral acyclovir twice daily for 5 days OR 800 mg of oral acyclovir 3 x daily for 2 days OR 500 mg of oral valacyclovir twice daily for 3 days OR 1 g of oral valacyclovir once daily for 5 days OR 125 mg of oral famciclovir twice daily for 5 days OR 1 g of oral famciclovir twice daily for 1 day OR 500 mg of oral famciclovir once, followed by 250 mg twice daily for 2 days	
• Suppressive therapy for recurrent genital herpes	400 mg of oral acyclovir twice daily OR 500 mg of oral valacyclovir once daily OR 1 g of oral valacyclovir once daily OR 250 mg of oral famciclovir twice daily	
HPV	Specific antiviral therapy is not recommended to eradicate infection.	Prevention of infection is key, and vaccines are licensed in the United States to protect against the most common strains of HPV that cause cancer.

HPV indicates human papillomaviruses; HSV, herpes simplex; IM, intramuscular.

of the vaccine being introduced.[30] And, a more recent study also confirmed a reduction in vaccine-type oral HPV prevalence among young adults in the United States. In particular, the prevalence of oral HPV types 16, 18, 6, and 11 infections was significantly decreased in vaccinated men compared with unvaccinated men (0.0% vs 2.13%; P_{adj} = .007). However, the population-level effect of HPV vaccination on the burden of these oral infections was only modest and was especially low in men, the authors say, because of low vaccine uptake.[31]

Despite improvements in public awareness, treatment, and prevention, the incidence of many common STIs, thus, continues to rise, and these infections persist as a public health problem and a major cause for morbidity and mortality worldwide.[32]

In the United States, many cases of gonorrhea, chlamydia, and syphilis continue to go undiagnosed and unreported, and data on other STIs—such as HSV and HPV, are not routinely reported to CDC. Consequently, national surveillance data fails to highlight the true burden of STIs in this country. A collaborative effort is required to address this problem.[33] Heightened efforts are critical to combating drug resistance, especially for gonorrhea.[34] Screening and prevention are also key, and health care providers should incorporate STI screening and prompt treatment into standard practice, especially for pregnant women and MSM. Providers should also educate patients about STIs, how to prevent them, and the need for screening.[35] In addition, state and local health departments must receive additional funding to improve existing technical infrastructure, to increase efficiency and quality of laboratory diagnostic capabilities, in order to facilitate prompt detection and treatment of STIs.[35] ▲

References are available at ContagionLive.com

For virologically suppressed* adult patients with HIV-1

The ART of Two

The only single-pill, 2-drug regimen with
the power of dolutegravir at the core

*HIV-1 RNA <50 copies/mL on a stable antiretroviral therapy for at least 6 months.

Indication and Usage for JULUCA

JULUCA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for ≥6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of JULUCA.

Important Safety Information

CONTRAINDICATIONS

JULUCA is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir or rilpivirine.
- receiving dofetilide, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, systemic dexamethasone (>1 dose), St. John's wort, and proton pump inhibitors (e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole).

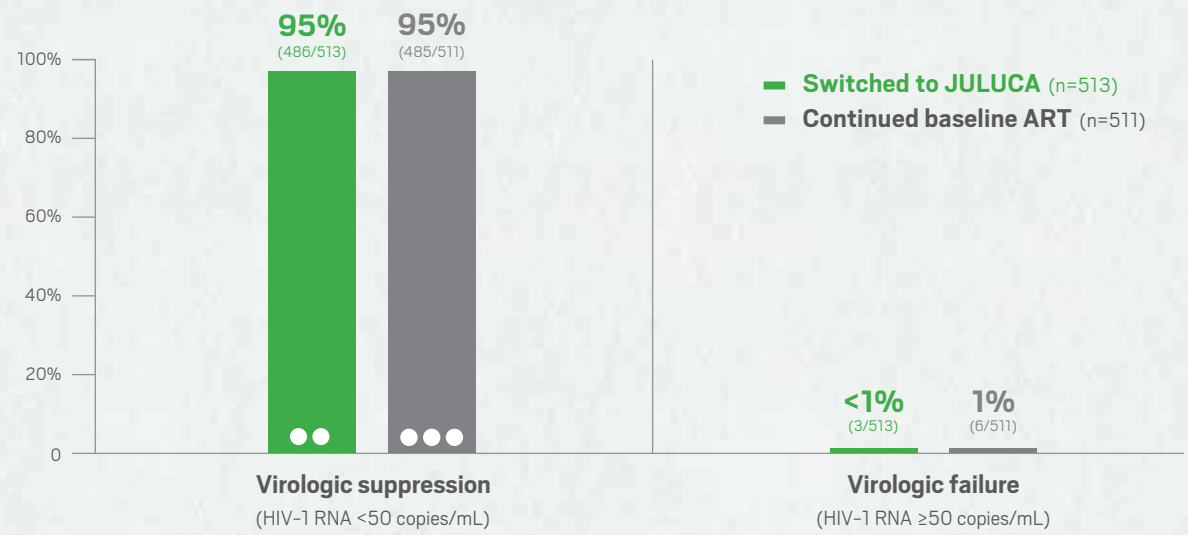
Please see additional Important Safety Information for JULUCA on the following pages.

Please see Brief Summary of Prescribing Information for JULUCA on the following pages.

Juluca
dolutegravir 50 mg/
rilpivirine 25 mg tablets

For virologically suppressed adult patients with HIV-1

JULUCA maintained virologic suppression as effectively as traditional 3-drug regimens at 48 weeks*



- Treatment difference was –0.2% (95% CI; –3.0%, 2.5%); assessed using a noninferiority margin of –8%
- Treatment difference was –0.6% (95% CI; –1.7%, 0.6%); assessed using a noninferiority margin of –4%

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

Skin and Hypersensitivity Reactions:

- Hypersensitivity reactions have been reported with dolutegravir and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in <1% of subjects receiving dolutegravir in Phase 3 clinical trials.
- Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens and have been accompanied by fever and/or organ dysfunctions including elevations in hepatic serum biochemistries.
- Discontinue JULUCA immediately if signs or symptoms of severe skin or hypersensitivity reactions develop (such as severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, mucosal involvement, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, and difficulty breathing), as a delay in stopping treatment may result in a life-threatening reaction. Clinical status, including laboratory parameters with liver aminotransferases, should be monitored and appropriate therapy initiated.

Hepatotoxicity:

- Hepatic adverse events have been reported, including cases of hepatic toxicity, in patients without pre-existing hepatic disease or other identifiable risk factors.
- Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation, particularly in the setting where anti-hepatitis therapy was withdrawn.
- Monitoring for hepatotoxicity is recommended.

Depressive Disorders:

- Depressive disorders (including depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, and suicidal ideation) have been reported.
- Promptly evaluate patients with severe depressive symptoms.

Please see additional Important Safety Information for JULUCA on the previous page.
Please see Brief Summary of Prescribing Information for JULUCA on the following pages.

Is it time to rethink virologic suppression?

As effective as traditional **THREE**-drug regimens*

With only **TWO** ARVs

In **ONE** small pill

A complete, once-daily regimen in the smallest single pill†

Actual size of tablet.

Grades 1 to 4 adverse reactions of ≥2% frequency were diarrhea, 2% vs <1%, and headache, 2% vs 0% (JULUCA vs continued baseline ART, respectively). Discontinuations due to adverse events were 4% for patients who switched to JULUCA and <1% for patients who continued baseline ART in the pooled analyses.

*Based on a pooled analysis of the SWORD 1 and SWORD 2 trials, 2 identically designed, randomized, multicenter, open-label, parallel-group, noninferiority trials comparing JULUCA (n=513) vs continuation of current stable ART (INSTI, NNRTI, or PI + 2 NRTIs; n=511) in treatment-experienced, virologically suppressed (HIV-1 RNA <50 copies/mL; on stable suppressive uninterrupted therapy for ≥6 months prior to screening) adults (≥18 years) with HIV-1. At baseline, 11% of patients had $CD4^+$ T-cell counts <350 cells/mm^3 and 11% were CDC Class C (AIDS). Baseline third agents were: 54% NNRTIs, 26% PIs, and 20% INSTIs. Patients were excluded if they had a history of treatment failure, known substitutions associated with resistance to dolutegravir or rilpivirine, any degree of hepatic impairment, positive for hepatitis B virus (HBV), or with an anticipated need for hepatitis C virus (HCV) therapy during the study.
Primary endpoint was proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 using FDA snapshot analysis.

†Pill size is not intended to convey efficacy, safety, or treatment adherence. Approximate pill size is 14 mm x 7 mm.

ART=antiretroviral therapy; CI=confidence interval; ARVs=antiretrovirals; INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; NRTIs=nucleoside reverse transcriptase inhibitors; CDC=Centers for Disease Control and Prevention.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:

- The concomitant use of JULUCA and other drugs may result in known or potentially significant drug interactions, see Contraindications and Drug Interactions sections. Rilpivirine doses 3 and 12 times higher than the recommended dose can prolong the QTc interval. Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes. Consider the potential for drug interactions prior to and during therapy with JULUCA and monitor for adverse reactions.

ADVERSE REACTIONS: Most common adverse reactions with JULUCA (incidence ≥2%, all Grades) were diarrhea (2%) and headache (2%).

DRUG INTERACTIONS

- Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.
- Drugs that induce or inhibit CYP3A or UGT1A1 may affect the plasma concentrations of the components of JULUCA.
- Drugs that increase gastric pH or containing polyvalent cations may decrease plasma concentrations of the components of JULUCA.
- Consider alternatives to prescribing JULUCA with drugs with a known risk of Torsade de Pointes.
- Consult the full Prescribing Information for JULUCA for more information on potentially significant drug interactions, including clinical comments.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There are insufficient prospective pregnancy data to adequately assess the risk of birth defects and miscarriage. An Antiretroviral Pregnancy Registry has been established.
- **Lactation:** Breastfeeding is not recommended due to the potential for HIV-1 transmission and the potential for adverse reactions in nursing infants.

DOSAGE AND ADMINISTRATION

- **Dosage:** 1 tablet taken orally once daily with a meal for adult patients.
- **Recommended Dosage of JULUCA with Rifabutin Coadministration:** Take an additional 25-mg tablet of rilpivirine with JULUCA once daily with a meal for the duration of the rifabutin coadministration.

Juluca
dolutegravir 50 mg/
rilpivirine 25 mg tablets

Visit **www.julucahcp.com** to learn more.

BRIEF SUMMARY

JULUCA (dolutegravir and rilpivirine) tablets

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS

JULUCA is contraindicated in patients: with previous hypersensitivity reaction to dolutegravir or rilpivirine; receiving the following coadministered drugs for which elevated plasma concentrations are associated with serious and/or life-threatening events or that significantly decrease rilpivirine plasma concentrations:

Drug Class	Clinical Comment
Antiarrhythmic: Dofetilide	Potential for serious and/or life-threatening events due to the potential for increased dofetilide plasma concentrations.
Anticonvulsants: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	Potential for significant decreases in rilpivirine plasma concentrations due to CYP3A enzyme induction, which may result in loss of virologic response.
Antimycobacterials: Rifampin, Rifapentine	
Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)	
Herbal Products: St John's wort (*Hypericum perforatum*)	
Proton Pump Inhibitors: e.g., Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.

WARNINGS AND PRECAUTIONS

Skin and Hypersensitivity Reactions: Hypersensitivity reactions have been reported with dolutegravir and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase 3 clinical trials of rilpivirine, treatment-related rashes with at least Grade 2 severity were reported in 3% of subjects. No Grade 4 rash was reported. Discontinue JULUCA immediately if signs or symptoms of severe skin or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, mucosal involvement [oral blisters or lesions], conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including laboratory parameters with liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with JULUCA after the onset of hypersensitivity may result in a life-threatening reaction. **Hepatotoxicity:** Hepatic adverse events have been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations. Additionally, in some patients receiving dolutegravir-containing regimens, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity including elevated serum liver biochemistries and hepatitis have also been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to acute liver failure has been reported with dolutegravir-containing products, including liver transplant with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended. **Depressive Disorders:** Depressive disorders (including depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, and suicidal ideation) have been reported with rilpivirine. For information regarding depressive disorders reported in patients taking dolutegravir, *see Adverse Reactions*. Promptly evaluate patients with severe depressive symptoms to assess whether the symptoms are related to JULUCA and to determine whether the risks of continued therapy outweigh the benefits. **Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:** The concomitant use of JULUCA and other drugs may result in known or potentially significant drug interactions, some of which may lead to: Loss of therapeutic effect of JULUCA and possible development of resistance; Possible clinically significant adverse reactions from greater exposures of concomitant drugs. In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QTc interval of the electrocardiogram. Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes. See the Drug Interactions section for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with JULUCA; review concomitant medications during therapy with JULUCA; and monitor for the adverse reactions associated with the concomitant drugs.

ADVERSE REACTIONS

The safety assessment of JULUCA in HIV-1–infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine is based on the pooled primary Week 48 analyses of data from 2 identical, international, multicenter, open-label trials, SWORD-1 and SWORD-2. A total of 1,024 adult HIV-1–infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 nucleoside reverse transcriptase inhibitors [NRTIs] plus either an integrase strand transfer inhibitor [INSTI], a non-nucleoside reverse transcriptase inhibitor [NNRTI], or a protease inhibitor [PI]) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine, were randomized and received treatment. Subjects were randomized 1:1 to continue their current antiretroviral regimen or be switched to dolutegravir plus rilpivirine administered once daily. In the pooled analyses, the proportion of subjects who discontinued treatment due to an adverse event was 4% in subjects receiving dolutegravir plus rilpivirine once daily and was <1% in subjects who remained on their current antiretroviral regimen. The most common adverse events leading to discontinuation were psychiatric disorders: 2% of subjects receiving dolutegravir plus rilpivirine and <1% on their current antiretroviral regimen. The most common adverse reactions (grades 1 to 4) reported in at least 2% of virologically suppressed subjects with HIV-1 infection in SWORD-1 and SWORD-2 trials (week 48 pooled analyses) in either treatment arm – JULUCA (n=513) vs current antiretroviral regimen (n=511), respectively: diarrhea (2%, <1%), headache (2%, 0). Less Common Adverse Reactions occurred in less than 2% of subjects receiving dolutegravir plus rilpivirine or are from studies described in the prescribing information of the individual components, TIVICAY (dolutegravir) and EDURANT (rilpivirine). Some events have been included because of their seriousness and assessment of potential causal relationship. *General Disorders:* Fatigue. *Gastrointestinal Disorders:* Abdominal pain, abdominal discomfort, flatulence, nausea, upper abdominal pain, vomiting. *Hepatobiliary Disorders:* Cholecystitis, cholelithiasis, hepatitis. *Immune System Disorders:* Immune reconstitution syndrome. *Metabolism and Nutrition Disorders:* Decreased appetite. *Musculoskeletal Disorders:* Myositis. *Nervous System Disorders:* Dizziness, somnolence. *Psychiatric Disorders:* Depressive disorders including depressed mood; depression; suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Other reported psychiatric adverse reactions include anxiety, insomnia, sleep disorders, and abnormal dreams. *Renal and Urinary Disorders:* Glomerulonephritis membranous, glomerulonephritis mesangioproliferative, nephrolithiasis, renal impairment. *Skin and Subcutaneous Tissue Disorders:* Pruritus, rash. Laboratory Abnormalities: Selected laboratory abnormalities with a worsening grade from baseline (grades 2 and 3 to 4; week 48 pooled analyses) and representing the worst-grade toxicity in at least 2% of subjects in SWORD-1 and SWORD-2 trials were – JULUCA (n=513) vs current antiretroviral regimen (n=511), respectively: ALT Grade 2 (>2.5-5.0 x Upper Limit of Normal [ULN]) 2%, <1%; Grade 3 to 4 (>5.0 x ULN) <1%, <1%; AST Grade 2 (>2.5-5.0 x ULN) <1%, 2%; Grade 3 to 4 (>5.0 x ULN) <1%, <1%; Total Bilirubin Grade 2 (1.6-2.5 x ULN) 2%, 4%; Grade 3 to 4 (>2.5 x ULN) 0, 3%; Creatine kinase Grade 2 (6.0-9.9 x ULN) <1%, <1%; Grade 3 to 4 (≥10.0 x ULN) 1%, 2%; Hyperglycemia Grade 2 (126-250 mg/dL) 4%, 5%; Grade 3 to 4 (>250 mg/dL) <1%, <1%; Lipase Grade 2 (>1.5-3.0 x ULN) 5%, 5%; Grade 3 to 4 (>3.0 x ULN) 2%, 2%. *Changes in Serum Creatinine:* Dolutegravir and rilpivirine have been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred within the first 4 weeks of treatment with dolutegravir plus rilpivirine and remained stable through 48 weeks. A mean change from baseline of 0.093 mg per dL (range: -0.30 to 0.58 mg per dL) was observed after 48 weeks of treatment with dolutegravir plus rilpivirine. These changes are not considered to be clinically relevant. *Serum Lipids:* At 48 weeks, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol to HDL ratio were similar between the treatment arms. Bone Mineral Density Effects: Mean bone mineral density (BMD) increased from baseline to Week 48 in subjects who switched from an antiretroviral treatment (ART) regimen containing tenofovir disoproxil fumarate (TDF) to dolutegravir plus rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a TDF-containing antiretroviral regimen (0.05% total hip and 0.15% lumbar spine) in a dual-energy X-ray absorptiometry (DXA) substudy. BMD declines of 5% or greater at the lumbar spine were experienced by 2% of subjects receiving JULUCA and 5% of subjects who continued their TDF-containing regimen. The long-term clinical significance of these BMD changes is not known. Fractures (excluding fingers and toes) were reported in 3 (0.6%) subjects who switched to dolutegravir plus rilpivirine and 9 (1.8%) subjects who continued their current antiretroviral regimen through 48 weeks. Adrenal Function: In the pooled Phase 3 trials results analysis of rilpivirine, at Week 96, there was an overall mean change from baseline in basal cortisol of -0.69 (-1.12, 0.27) micrograms/dL in the rilpivirine group and of -0.02 (-0.48, 0.44) micrograms/dL in the efavirenz group. The clinical significance of the higher abnormal rate of 250 micrograms ACTH stimulation

(cont'd on next page)

tests in the rilpivirine group is not known. **Postmarketing Experience:** The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or rilpivirine-containing regimen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Musculoskeletal Disorders: Arthralgia, myalgia. Hepatobiliary Disorders: Acute liver failure, hepatotoxicity. Renal and Genitourinary Disorders: Nephrotic syndrome. Skin and Subcutaneous Tissue Disorders: Severe skin and hypersensitivity reactions including DRESS.

DRUG INTERACTIONS

Concomitant Use with Other Antiretroviral Medicines: Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. **Potential for JULUCA to Affect Other Drugs:** Dolutegravir, a component of JULUCA, inhibits the renal organic cation transporters (OCT)2 and multidrug and toxin extrusion transporter (MATE)1, thus it may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide and metformin. **Potential for Other Drugs to Affect the Components of JULUCA:** Dolutegravir: Dolutegravir is metabolized by uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations. Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir. Rilpivirine: Rilpivirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of rilpivirine. Coadministration of JULUCA and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Coadministration of JULUCA and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Coadministration of JULUCA with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. *QT-Prolonging Drugs:* In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QTc interval of the electrocardiogram. Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes. **Established and Other Potentially Significant Drug Interactions:** Information regarding potential drug interactions with dolutegravir and rilpivirine are provided below. These recommendations are based on either drug interaction trials of individual components or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. Alterations in dose or regimen may be recommended based on drug interaction trials or predicted interactions with JULUCA:

- Antacids: e.g., aluminum or magnesium hydroxide, calcium carbonate - administer JULUCA 4 hours before or 6 hours after taking antacids.
- Antiarrhythmic: dofetilide - coadministration is contraindicated with JULUCA.
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- Antidiabetics: metformin - with concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or JULUCA. When starting or stopping JULUCA, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of JULUCA is recommended.
- Antimycobacterials: rifampin, rifapentine - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- Antimycobacterials: rifabutin - an additional rilpivirine 25-mg tablet should be taken with JULUCA once daily with a meal when rifabutin is coadministered.
- Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment) - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- H_2-Receptor Antagonists: Famotidine, cimetidine, nizatidine, ranitidine - JULUCA should only be administered at least 4 hours before or 12 hours after taking H_2-receptor antagonists.
- Herbal Products: St John's wort (*Hypericum perforatum*) - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- Macrolide or ketolide antibiotics: clarithromycin, erythromycin, telithromycin - Where possible, consider alternatives, such as azithromycin.
- Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing products or laxatives, sucralfate, or buffered medications - Administer JULUCA 4 hours before or 6 hours after taking products containing polyvalent cations.
- Narcotic analgesics: methadone - No dose adjustments are required when starting coadministration of methadone with JULUCA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
- Oral calcium and iron supplements, including multivitamins containing calcium or iron (non-antacid) - administer JULUCA and supplements containing calcium or iron together with a meal or take these supplements 4 hours before or 6 hours after taking JULUCA.
- Proton Pump Inhibitors: e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.

Consult the full Prescribing Information for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JULUCA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. There is insufficient prospective pregnancy data from the APR to adequately assess the risk of birth defects and miscarriage. Given the limited number of pregnancies exposed to dolutegravir-containing regimens reported to the APR, no definitive conclusions can be drawn on the safety of dolutegravir in pregnancy, and continued monitoring is ongoing through the APR. Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population. **Lactation:** The Centers for Disease Control and Prevention recommend that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether JULUCA or components of JULUCA are present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir and rilpivirine were present in milk. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving JULUCA. **Pediatric Use:** The safety and efficacy of JULUCA have not been established in pediatric patients. **Geriatric Use:** Clinical trials of JULUCA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in administration of JULUCA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Renal Impairment:** No dosage adjustment is necessary for patients with mild or moderate renal impairment (creatinine clearance greater than or equal to 30 mL/min). In patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, increased monitoring for adverse effects is recommended. **Hepatic Impairment:** No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir or rilpivirine is unknown.

OVERDOSAGE

There is no known specific treatment for overdose with JULUCA. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required, including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance. As both dolutegravir and rilpivirine are highly bound to plasma proteins, it is unlikely that either would be significantly removed by dialysis.

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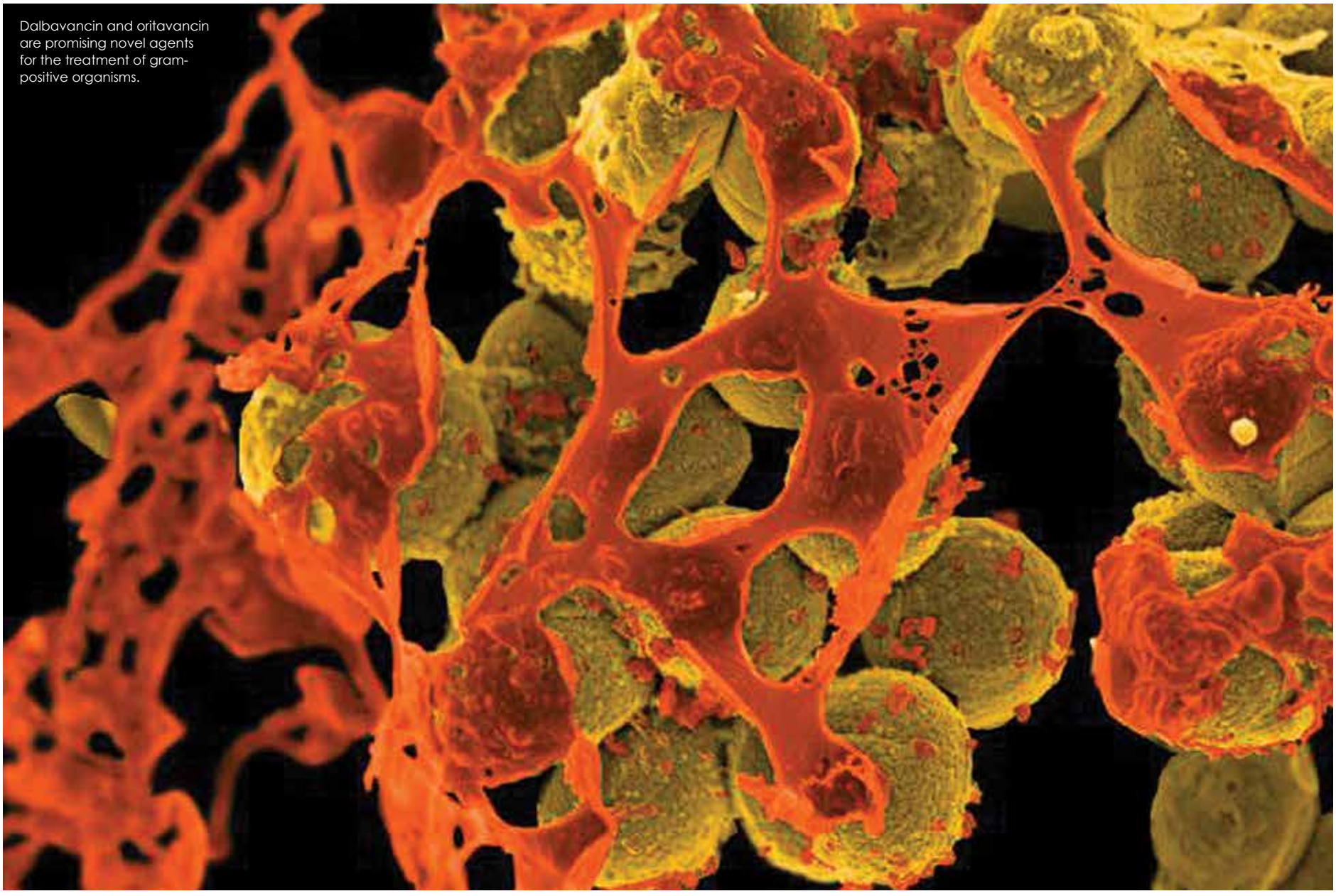

Dalbavancin and oritavancin are promising novel agents for the treatment of gram-positive organisms.

Long-Acting Anti-MRSA Agents: One Dose to Cure?

A review of the current literature and future directions.

BY LOUISE DE SOUZA, PHARMD; MICHAEL KENT, PHARMD; MARILYN MOOTZ, PHARMD; AND MARGUERITE L. MONOGUE, PHARMD

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant cause of both health care–associated and community-associated infections.[1] The most common types of infections caused by MRSA are skin and soft-tissue infections, bacteremia, infective endocarditis, pneumonia, and osteomyelitis.[2] Per current guidelines, oral antimicrobials for the treatment of mild-to-moderate MRSA skin infections include trimethoprim/ sulfamethoxazole, clindamycin, doxycycline, minocycline, and linezolid.[1] Alternatively, vancomycin tends to be the most common intravenous (IV) agent for empiric coverage of a potentially serious MRSA infection.[1] Serious infections caused by MRSA have a high morbidity and mortality, with estimates for mortality as high as 30% to 37% with endocarditis.[1] Treatment durations for MRSA infections can vary widely based on the site and source of infection.[1] Because of growing resistance and the need for a single-dose treatment option to help patients avoid hospitalization, facilitate their earlier discharge, or eliminate their need for continued outpatient parenteral antimicrobial therapy (OPAT), long-acting anti-MRSA agents have been developed.

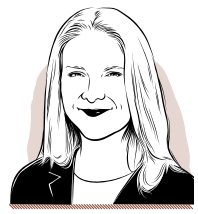
Dalbavancin (Dalvance) and oritavancin (Orbactiv) are semi-synthetic lipoglycopeptides with potent in vitro activity against multidrug-resistant gram-positive organisms, including MRSA.[3] Both agents inhibit transglycosylation and transpeptidation, thus inhibiting cell-wall synthesis. Dalbavancin and oritavancin exhibit concentration-dependent, bactericidal activity. The presence of a lipophilic side chain in each molecule prolongs the half-life of the drug and permits 1-time dosing (see **Table 1**).[2] Currently, dalbavancin and oritavancin are US Food and Drug Administration (FDA) approved for the treatment of acute bacterial skin and skin structure infections (ABSSIs).[4,5] Advantages and disadvantages of using long-acting anti-MRSA agents are described in **Table 2**.[6]

Source: CDC / Digitally colorized, SEM image MRSA bacteria surrounded by cellular debris.

Table 1. Administration Considerations for Dalbavancin and Oritavancin

DRUG	DALBAVANCIN (DALVANCE)	ORITAVANCIN (ORBACTIV)
Half-life dosing	147-258 hours	393 hours
Dosing	Single dose: 1500 mg IV x 1 Two doses: 1000 mg IV x 1 initially, followed by 500 mg IV x 1, 1 week later	Single dose: 1200 mg IV x 1
Dose adjustment for renal impairment	If CrCl <30 mL/min: Single dose: 1225 mg IV x 1 Two doses: 750 mg IV x 1, followed by 375 mg IV x 1, 1 week later ESRD on iHD: No dose adjustment necessary; administer without regard to timing of hemodialysis	No dose adjustment for renal impairment Not studied for CrCl <30 mL/min Not removed by hemodialysis
Dose adjustment for hepatic impairment	No dose adjustment for mild hepatic impairment Not studied in moderate to severe hepatic impairment	No dose adjustment for Child-Pugh class A or B Not studied in Child-Pugh class C
Contraindications	Hypersensitivity	Hypersensitivity Use of IV unfractionated heparin should not occur for 120 hours (5 days) after oritavancin administration
Warnings/Precautions	Hypersensitivity Infusion reactions: Red man syndrome Superinfection: CDAD or pseudomembranous colitis Hepatic effects: Patients may have ALT elevation >3x ULN during therapy	Hypersensitivity Infusion reactions: Red man syndrome Superinfection: CDAD or pseudomembranous colitis Osteomyelitis
Common adverse drug events	Headache, pyrexia, nausea, vomiting, diarrhea, constipation	Phlebitis at injection site, fever, nausea, vomiting, diarrhea
Administration	Infuse over 30 minutes*	Infuse over 3 hours*

ALT indicates alanine transaminase; CDAD, *Clostridium difficile*–associated diarrhea; CrCl, creatinine clearance; ESRD, end stage renal disease; iHD, intermittent hemodialysis; IV, intravenous; ULN, upper limit of normal.
*If infusion-related reaction occurs, consider slowing or interrupting infusion.



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The cited clinical scenarios of use for oritavancin and dalbavancin include patients seen in the emergency department (ED) who do not require hospital monitoring; completion of inpatient therapy to allow for earlier hospital discharge; patients in whom medical compliance would be an issue; and certain parenteral home-therapy cases.[7] These potential therapeutic niches have been explored via cross-sectional studies and meta-analysis.

A recent systematic review, network meta-analysis, and cost analysis comparing the new lipoglycopeptides with standard care and with each other for the treatment of complicated skin and soft-tissue infections (cSSTIs) found that dalbavancin and oritavancin demonstrate efficacy and safety as compared with standard of care in randomized controlled trials (RCTs) (odds ratio [OR], 1.09; 95% CI, 0.90-1.33).[8] Seven RCTs were included in the analysis. Moreover, no difference in clinical response between oritavancin and dalbavancin was seen (OR, 1.36; 95% CI, 0.85-1.18].[8]

Since the approval of these novel agents, hospital-based protocols have been initiated to evaluate their potential role in a clinical setting. Health care providers from many disciplines have been utilized to screen patients to the use of dalbavancin in the treatment of ABSSIs. At 1 site, patients were identified via an ED-initiated guideline for dalbavancin use. Of the 22 patients assessed for inclusion, 7 received dalbavancin. Patient follow-up was pursued and only 1 patient of the 7 required hospital readmission due to further complications. Such results demonstrate the potential for such a program and for the use of the agent with restricted guidelines.[9]

A similar study assessing the use of dalbavancin in EDs was completed via a retrospective cohort study describing the site's experience with dalbavancin in the ED. All adult patients diagnosed with cellulitis and treated with dalbavancin over the span of 2 years had their medical records reviewed for patient characteristics, comorbidities, cellulitis severity classification, and length of stay. The average length of stay was 180 minutes for patients treated and discharged from the ED, and 1902 minutes for patients placed in observation. The researchers found that of the 23 patients included, 2 returned to the ED within 1 week for cellulitis-related complications. The use of this agent was not associated with frequent return to the ED or treatment failure.[10]

With regard to pharmacoeconomic outcomes, cost analyses demonstrated that, when compared with standard of care, dalbavancin and oritavancin were less costly in the scenarios evaluated.[7] Per cSSTI, third-party payers saved between $1442 and $4830 and between $3571 and $6932 with the use of dalbavancin and oritavancin, respectively.[8] Furthermore, with increasing pressure to reduce avoidable hospitalizations and the associated costs of inpatient care, these agents serve as an attractive treatment option.[10]

With increasing pressure to reduce avoidable hospitalizations and the associated costs of inpatient care, these agents serve as an attractive treatment option.

Regardless of the great potential these agents can provide, the ultimate future of oritavancin and dalbavancin is yet to be determined. Both the pharmacokinetics and the convenient 1-time dosing of these drugs make them alluring options for the treatment of gram-positive infections that otherwise require prolonged courses of antibiotics, such as osteomyelitis, endocarditis, and even bacteremia. However, recent literature searches mostly yield case reports of these drugs being used as alternative therapy for infections.

Intermittent dosing with oritavancin could potentially be a convenient addition for the treatment of osteomyelitis, but efficacy and safety data for this indication are lacking. Patients with osteomyelitis were excluded from the original phase 2 and phase 3 studies. One successful case study with the use of oritavancin was described in a patient with documented allergies to penicillin, cephalosporin, and erythromycin who developed a methicillin-sensitive *Staphylococcus aureus* (MSSA) right tibial infection. The patient received a preoperative dose of oritavancin >>

2 days prior to surgical debridement, then standard perioperative vancomycin during the surgery. After the surgery, the patient was treated with IV oritavancin 1200 mg per week for a total of 6 weeks. The patient was free of signs of infection on follow-up visits at 1, 4, 8, 12, 24, and 40 weeks after the end of therapy.[11-13]

The use of oritavancin was further tested in a case series of 10 patients in which the most common indication was MSSA bacteremia. Other indications included MRSA bursitis, group B *Streptococcus* bacteremia with native tricuspid valve endocarditis, coagulase-negative *Staphylococcus* bacteremia, MSSA deep-tissue infection, and enterococcal bacteremia. Oritavancin was well-tolerated and led to successful treatment of 70% of patients.[14]

Reported reasons for using long-acting MRSA agents over a more traditional OPAT regimen were history of IV drug use, patient refusal to participate in OPAT, patient desire to avoid OPAT, and history of noncompliance with OPAT.[17]

Similarly, promising results were indicated by 1 case report with the use of dalbavancin in a patient with a history of recurrent MRSA bacteremia who had failed multiple courses of vancomycin and daptomycin. The patient was treated with dalbavancin 1000 mg IV weekly for 2 weeks followed by 500 mg IV weekly for 6 weeks. The original infection was shown to be cleared after therapy completion; however, the patient eventually developed MRSA bacteremia once more, showing that dalbavancin did not prevent recurrence.[15]

Dalbavancin has been compared with vancomycin in the setting of catheter-related bloodstream infections. A phase 2, open-label, randomized, controlled, multicenter study compared dalbavancin 1000 mg followed by 500 mg 1 week later with vancomycin administered twice daily for 14 days; the results indicated that the success rate of dalbavancin at 87% was significantly higher than that of vancomycin at 50%. Most frequently isolated bacteria were *Staphylococcus* spp., including coagulase-negative *Staphylococcus* and MRSA.[16] Studies assessing dalbavancin's role in osteomyelitis treatment are currently ongoing (NCT03426761; NCT02685033).

In addition to certain disease states, there are specific patient populations that may benefit from the reduced burden of administration of these longer-acting agents. Advances in the infrastructure for OPAT have been made, due to the increasing integration of home health care and infusion clinics. However,

Table 2. Advantages and Disadvantages of the Use of Long-Acting Anti-MRSA Agents[5]

ADVANTAGES	DISADVANTAGES
• 1-dose administration assures compliance • Targets common organisms in ABSSSI • Convenience: no hospital admission and fewer pharmacy visits • No drug-level monitoring • Central catheter not needed • Safety and efficacy levels comparable with those of vancomycin	• Expensive • Delayed hypersensitivity reactions • Only compatible with 5% dextrose in water • Limited data for oritavancin in patients with severe renal insufficiency • Use of IV heparin is contraindicated within 120 hours of oritavancin use

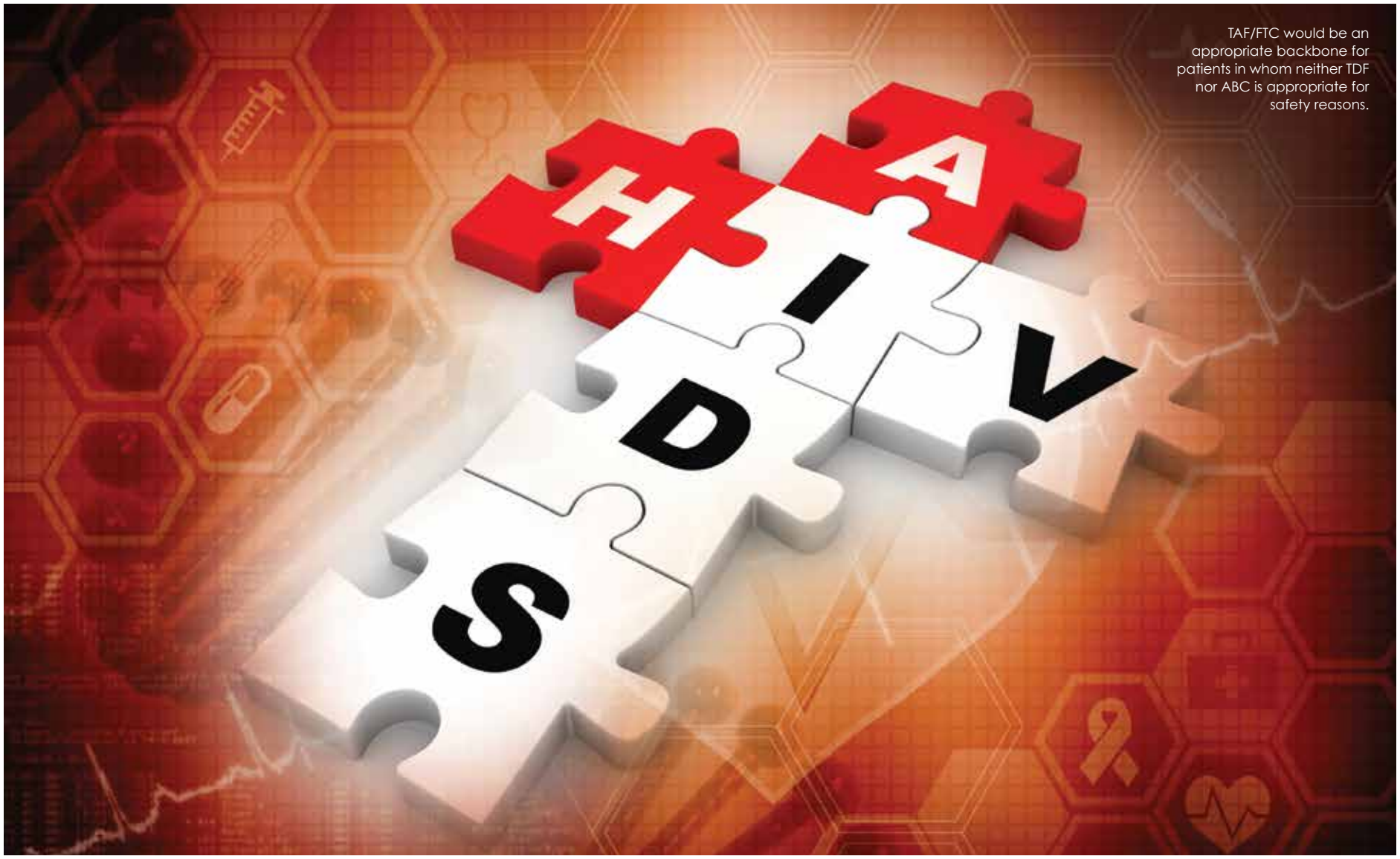
ABSSSI indicates acute bacterial skin and skin structure infection; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.
Adapted from: Stanton M. Orbactiv and dalbavancin: one and done. *Pharmacy Times* website, pharmacytimes.com/link/183. March 22, 2016. Accessed February 15, 2018.

OPAT's limitations still include cost, availability of services, the patient's ability to be compliant with OPAT, and the potential need for in-dwelling catheters. Reported reasons for using long-acting MRSA agents over a more traditional OPAT regimen were history of IV drug use, patient refusal to participate in OPAT, patient desire to avoid OPAT, and history of noncompliance with OPAT.[17]

Another patient population in which long-acting anti-MRSA agents have been used are those who are attempting to transition to hospice care. One study outlined 3 case reports of oritavancin used in hospice care in which all 3 patients had advanced terminal cancer; had developed methicillin-resistant, gram-positive bacteremia (*Streptococcus gallolyticus*, *Granulicatella adiacens*, or MRSA); and were experiencing delay in hospice placement due to continued IV antibiotic therapy. Each patient received a single dose of oritavancin, then transitioned to hospice care. The patients died in hospice care between 2 and 5 weeks after administration of oritavancin.[18]

In conclusion, dalbavancin and oritavancin are promising novel agents for the treatment of gram-positive organisms. Although they are currently FDA approved only for the treatment of ABSSIs, they have potential use in the treatment of other infections, such as osteomyelitis and endocarditis. However, further studies, including randomized controlled trials, are still needed. ▲

References are available at ContagionLive.com



TAF/FTC would be an appropriate backbone for patients in whom neither TDF nor ABC is appropriate for safety reasons.

Source: sheelamohanachandran/ Adobe Stock, HIV and AIDS puzzle crossword

HIV Drug Tenofovir Alafenamide Offers Safety, Noninferiority to Abacavir

Study results confirm both drug regimens are solid choices for many patients with HIV.

BY LAURIE SALOMAN, MS

The array of streamlined drug regimens that treat HIV has been nothing short of lifesaving. As more options become available, patients and providers need to weigh the pros and cons of particular regimens based on the needs of each patient. One frequently prescribed drug, tenofovir disoproxil fumarate (TDF), can have serious adverse effects (AEs) such as kidney and liver toxicity, as well as bone softening or thinning,[1] so several years ago, scientists introduced an alternative drug, tenofovir alafenamide (TAF). According to numerous studies, TAF has a safer profile. Both of these drugs are nucleoside analog reverse-transcriptase inhibitors (NRTIs), which typically form the backbone of an HIV regimen.

Although research compared TAF with TDF, a group of scientists noted a dearth of data regarding the safety of TAF compared with abacavir (ABC), another commonly prescribed NRTI. After an online search confirmed that no such studies had been conducted, they decided to launch their own.

The double-blind study began in 2015 and continues today, run by scientists at universities and medical centers in England, France, Ireland, Spain, and the United States. Initially, it enrolled 556 individuals screened at 79 sites in Belgium, Canada, Denmark, France, Germany, Ireland, Italy, Spain, Sweden, the United Kingdom, and the United States. Those participants, described in a recent report in *The Lancet HIV*,[2] were followed from 2015 to 2016. All were HIV positive, on a 3-drug regimen including ABC plus lamivudine (3TC), and had achieved viral suppression. Roughly half (280) were randomly assigned to switch from ABC plus 3TC to TAF plus emtricitabine (FTC), and 276 continued taking ABC plus 3TC. (The third drug in the regimens was not changed.) Participants agreed to in-person visits at weeks 4, 8, 12, 24, 36, and 48, at which numerous lab tests measured the efficacy of the regimens. After 48 weeks, participants were assessed for viral suppression, measured as an RNA level less than 50 copies per mL.

During the first 48 weeks, some individuals dropped out for various reasons, including AEs, noncompliance, and death, and not all participants were assessed for all possible outcomes. Therefore, the number of participants in the outcomes data varies. >>

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The results showed virtually no difference in virological suppression between the 2 groups—90% of 253 participants in the TAF/FTC group achieved virological suppression by week 48, compared with 93% of 248 in the ABC/3TC group. There also was almost no difference between the groups regarding changes in hip and lumbar spine bone mineral density. By week 48, spine density decreased in 8 of 213 in the TAF/FTC group compared with 8 of 217 in the ABC/3TC group, and hip density decreased in 3 of 212 versus 4 of 212, respectively.

Clinicians should not necessarily rush to prescribe TAF plus FTC—the key takeaway is that this regimen offers another option.

To measure renal function, the investigators recorded the levels of creatinine clearance at week 48 and found that both groups experienced minimal issues, with a decrease of 25% or more in just 2 of 279 participants taking TAF/FTC and 4 of 275 taking ABC/3TC. There was a slight difference in protein levels in the urine between the 2 groups right after treatment began, with 6 of 279 in the TAF/FTC group and 20 of 275 in the ABC/3TC group experiencing grade 2 proteinuria or higher. By week 48, tubular proteinuria levels between the groups were much more similar. In general, the authors reported, any AEs experienced were mild or moderate—and those did not occur often.

The results were welcome news to the study authors, who knew that both drug regimens were solid choices for many patients with HIV, but were unsure if 1 was inherently inferior to the other. "Both TAF/FTC and ABC/3TC have displayed high rates of efficacy in previous studies," Alan Winston, MD, professor of HIV and genitourinary medicine at Imperial College London in England and the lead author of the study, told *Contagion*®. "[Therefore,] our expectation was that virological efficacy would be similar in both arms as observed. Differences in safety between these 2 strategies were less well understood prior to our study, and we were pleased to observe similar safety profiles for both strategies," he said. "The double-blind design of our study makes the safety results unbiased and more interpretable."

DECIDING WHICH MEDICATION TO PRESCRIBE

The increased understanding of the safety and efficacy of both pairings gives patients with HIV options for treatment. "We think that TAF/FTC would be an appropriate backbone for patients in whom neither TDF nor ABC is appropriate for safety reasons, such as those at high risk [of] renal or bone toxicities or cardiovascular events, respectively," Dr. Winston said. "Initiation of TAF/FTC does not require HLA-B*5701 testing to rule out concerns for ABC hypersensitivity. Also, in people living with both HIV and HBV [hepatitis B virus] coinfection, TAF/FTC is an appropriate backbone."

Should people living with HIV who take ABC plus 3TC switch to TAF plus FTC? "We think that the decision to switch from ABC/3TC to TAF/FTC should be based on the unique clinical circumstances of an individual person living with HIV," said Dr. Winston, noting that the results point to TAF/FTC as a noninferior choice for some patients. "Our data suggest that after switching from ABC/3TC to TAF/FTC, there should be no safety concerns from a renal, bone, and lipid standpoint. In people living with HIV with high cardiovascular risk, switching from ABC/3TC may have clinical benefits, and our study reassures people living with HIV—and their physicians—that no safety concerns emerge."

However, clinicians should not necessarily rush to prescribe TAF plus FTC—the key takeaway is that this regimen offers another option. "Today, in the HIV world, we have a whole mess of magic bullets," Sharon Nachman, MD, chief of the Division of Pediatric Infectious Diseases at Stony Brook University in New York, who was not affiliated with the study, told *Contagion*®. "Some drugs work better on some patients, some drugs work better on other patients, and some patients can no longer tolerate drugs they once did. There's no 1 right choice for everybody. There's a bunch of right choices."

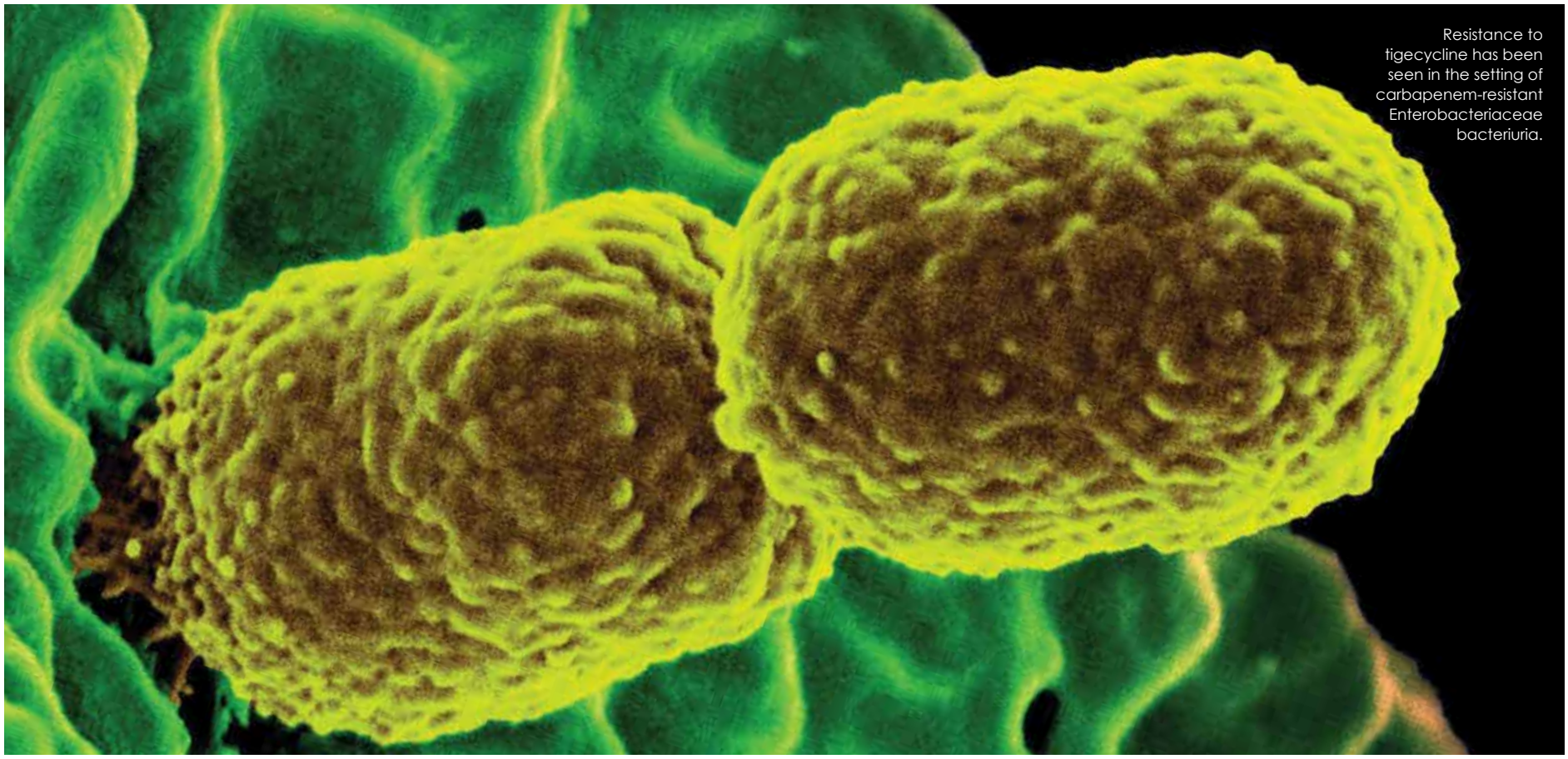
Although the study evaluated patients who already were doing well on ABC plus 3TC, Dr. Nachman said, plenty of other people with HIV have never taken an HIV drug and might respond differently. She recommends that a clinician test a patient for resistance to HIV drugs, do HLA-B*5701 testing to determine if the patient can take any regimen containing ABC, and then consult guidelines to learn which drugs may be off limits due to contraindications such as heart disease and high cholesterol. Other considerations include cost, insurance coverage, and how often a medication needs to be taken. Ideally, the physician and patient will be able to choose from several first-line HIV drugs.

FURTHER STUDY NEEDED TO ADDRESS LIMITATIONS

More years of study are needed to confirm this trial's promising results. "The hope behind TAF was that it would do the trick that Truvada [TDF/FTC] did in a way that was less toxic to the kidneys," said Payal Patel, MD, MPH, a *Contagion*® editorial advisory board member and an assistant professor at the University of Michigan Health System in Ann Arbor, who was not involved in the study. "I think this is a reassuring trial [showing] that what HIV providers wanted in the drug seems to be true in the short term, though they only followed patients for less than a year. The long term is really where the question lies, and since TAF is new, we won't know the answer to this for a while. Many people who had [adverse] effects with Truvada would not manifest issues in the first year of treatment."

The authors agreed regarding the study's limitations. "The sample size was not large enough, nor was the duration of follow-up long enough, to evaluate rare events such as cardiovascular events," Dr. Winston said. "However, our objective was not to evaluate the rate of such rare events but rather to evaluate the general safety of switching from ABC/3TC to TAF/FTC, particularly from a renal and bone standpoint. [This] can be evaluated with clinical markers [such as] serum creatinine or bone mineral density." The authors also noted in their report a few additional limitations, such as an underrepresentation of women and a disproportionate percentage of white men who have sex with men. ▲

References are available at ContagionLive.com



Resistance to tigecycline has been seen in the setting of carbapenem-resistant Enterobacteriaceae bacteriuria.

Source: NIAID. Digitally colorized SEM image of carbapenem-resistant *Klebsiella pneumoniae* and a neutrophil.

Treatment Options to Address the Threat of Carbapenem-Resistant Enterobacteriaceae

New agents are in development, but none represent a magic bullet for the problems that CRE infections present.

BY ANN MARIE PORRECA, PHARMD, BCPS; AND JASON C. GALLAGHER, PHARMD, FCCP, FIDSA, BCPS

The global emergence of resistant Enterobacteriaceae that produce carbapenemases has furthered the development of serious, difficult-to-treat infections associated with significant morbidity and mortality.[1,2] Antimicrobial agents currently used for treatment of infections caused by carbapenem-resistant Enterobacteriaceae (CRE) include carbapenem combinations, polymyxins, fosfomycin, tigecycline, aminoglycosides, ceftazidime–avibactam, and meropenem–vaborbactam. Trials supporting their clinical use are scarce, and many of the agents are limited by toxicities and pharmacokinetics disadvantages. New beta-lactamase combinations have been made available within the last few years, and early results suggest they are safer and more efficacious for the treatment of CRE infections compared with some of the older agents, particularly polymyxin regimens. Furthermore, new treatments with activity against CRE are currently being studied to help mitigate the threat of resistance.

Combinations of carbapenems have been utilized for the treatment of CRE infections, generally when administered as prolonged or continuous infusions and in combination with other agents.[3-7] Although carbapenem-based regimens for the treatment of infections caused by CRE have demonstrated some utility, evidence is limited. If such a regimen is used, the pharmacodynamics of the carbapenem used must be maximized through prolonged or continuous infusions.

The polymyxins, colistin and polymyxin B, have been revitalized for the treatment of resistant Gram-negative infections, including those caused by CRE. However, in vitro studies suggest that polymyxin monotherapy may lead to emergence of resistance; therefore, a polymyxin should be administered in conjunction with other agents, including carbapenems.[8-10] Appropriate dosing is also a concern for these agents, since the results of modern pharmacokinetic and pharmacodynamic studies indicate that dosing recommendations in both polymyxin B and colistin package inserts are inaccurate.[11,12] Also, both agents have the potential to cause nephrotoxicity and neurotoxicity, but several comparisons have shown a significantly higher risk of acute kidney injury in patients who received colistin compared with polymyxin B.[13-15] Trial results also show that beta-lactamase inhibitor combinations have more favorable safety and efficacy results than do polymyxin-containing regimens.

Fosfomycin, another treatment option for CRE, has shown activity against organisms producing carbapenemases.[16] It is recommended in combination with other therapies, since resistance develops rapidly when fosfomycin is used as monotherapy.[17] Only 2 case reports showing that it has been clinically effective against infections caused by CRE have been published.[18] In addition, the utility of fosfomycin is limited to urinary tract infections (UTIs) in the United States, since it is available only as an oral formulation and has moderate absorption. A current study of intravenous fosfomycin for UTIs (NCT02753946) may lead to US Food and Administration (FDA) approval.

Aminoglycosides are also well-established agents that have variable activity against CRE isolates[19] and appear to be a treatment option for CRE-caused UTIs.[19-21] For other infections, however, evidence is lacking; study results have shown mortality rates >>

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ranging from 6.3% to 80% in patients who received aminoglycosides alone.[22] Yet they may have a place in therapy when given in combination with another antibiotic. A systematic review of the results of 20 clinical studies evaluating patients being treated for infections caused by CRE showed that the combination of aminoglycosides with a carbapenem was associated with the lowest mortality rates.[23] However, beta-lactamase inhibitor–based combinations were too new to be included in this review. Aminoglycosides also have an adjunctive role in as aerosolized agents in patients with pneumonia caused by CRE,[24] but when considering these agents, it is important to weigh the benefit against their well-known toxicities.

Tigecycline, a glycylcycline tetracycline, is frequently active in vitro against CRE.[25] However, clinicians should be cautious when using tigecycline since it has limitations. Resistance development during therapy has been seen in the setting of CRE bacteriuria.[26] Pharmacokinetic limitations, including bloodstream concentrations that average below the Clinical and Laboratory Standards Institute Enterobacteriaceae breakpoint of 2 mcg/mL and elimination via the biliary tract, indicate limited utility for UTIs.[27] Results of a clinical study indicating that tigecycline was statistically inferior to imipenem for the treatment of ventilator-associated pneumonia point to the possibility that higher doses might be needed.[28-31]

TABLE. Treatment Options in Late-Stage Development

DRUG	CLASS	INDICATION STUDIED AND/OR BEING STUDIED	NOTES
Cefiderocol (S-649266)	Siderophore cephalosporin	• cUTIs[1] with or without pyelonephritis • Severe infections caused by carbapenem-resistant Gram-negative pathogens (HCAP,[2] BSI,[3] HAP,[4] sepsis, or VAP[5]) • Treatment of nosocomial pneumonia caused by Gram-negative pathogens • Studies are ongoing for the treatment of severe infections caused by CRE[7]	• Novel mechanism of action relies on active iron transport • High stability against hydrolysis by ESBLs[6] and carbapenemase-producing organisms (including New Delhi metallo-beta-lactamase) • Showed superiority for the treatment of cUTIs and acute pyelonephritis compared with imipenem–cilastin
Plazomicin	Aminoglycoside	• cUTIs including acute pyelonephritis • Infections related to CRE (BSI, HAP, VAP, cUTI including acute pyelonephritis)	• Dosing strategies include using drug monitoring • Potential for once-daily dosing • Activity against aminoglycoside-modifying enzymes • Proved to significantly reduce 28-day all-cause mortality when compared with colistin for treatment of CRE BSIs • Superior to meropenem for cUTIs
Eravacycline	Tetracycline	• cIAIs[8] • cUTIs including acute pyelonephritis	• Largely unaffected by efflux pumps and ribosomal protected proteins • Shown to be noninferior for the treatment of cIAIs compared with ertapenem • Did not achieve the primary endpoint when compared with levofloxacin for the treatment of cUTIs
Imipenem–relebactam	Carbapenem/beta-lactamase inhibitor	• Imipenem- resistant infections (HAP, VAP, cIAI,[8] cUTI) • HAP and VAP	• Beta-lactamase inhibitor is a diazabicyclooctane inhibitor • Currently being studied in phase 3 studies

BSI indicates blood stream infection; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant Enterobacteriaceae; cUTI, complicated urinary tract infection; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; HCAP, health care–associated pneumonia; VAP, ventilator-acquired pneumonia.

Ceftazidime–avibactam is a newly approved combination agent with activity against most CRE. Avibactam has a diazabicyclooctane structure that is not based on the beta-lactam ring and does not function as a suicide substrate as beta-lactam–based inhibitors do. It is stable against *Klebsiella pneumoniae* carbapenemase and oxacillinase-48–like enzymes found in CRE, but not against New Delhi metallo-beta-lactamase (NDM) enzymes.[32]

Two small comparative studies have shown superiority of monotherapy ceftazidime–avibactam over other regimens in treating a variety of infections caused by CRE. The first study retrospectively evaluated CRE bloodstream infections and found that ceftazidime–avibactam treatment in these patients was associated with significantly higher clinical success (11/13; 85%) compared with those who received other treatment regimens, including a carbapenem plus aminoglycoside (12/25; 48%; P = .04), a carbapenem plus colistin (12/30; 40%; P = .009), and other regimens (15/41; 37%; P = .004).[33] The second study was a multicenter observational study comparing ceftazidime–avibactam with colistin for the treatment of multiple CRE infections. The results of a multivariate analysis among patients treated with ceftazidime–avibactam versus colistin indicated that all-cause in-hospital mortality after the start of treatment was 3/38 (8%) versus 33/99 (33%), respectively. It should be noted that resistance to ceftazidime–avibactam has been reported to arise during treatment, particularly in patients receiving prolonged therapy with uncontrolled sources.[34,35] It is imperative that clinicians are aware of the possibility of emergent resistance leading to ceftazidime–avibactam treatment failure, and that they retest susceptibilities if CRE are persistent in cultures.

An agent combining meropenem and vaborbactam received FDA approval in August 2017. Vaborbactam is a novel, boron-containing, serine-beta lactamase inhibitor that works by creating a covalent bond between its boron moiety and the serine side chain of beta-lactamases, preventing the beta-lactamases from destroying beta-lactams. The clinical data supporting meropenem–vaborbactam for infections caused by CRE are limited to those resulting from a single small trial, TANGO-2, but it was a prospective, randomized study. TANGO-2 investigated the efficacy of meropenem–vaborbactam compared with investigator-chosen best available therapy (BAT) in patients with serious infections caused by confirmed or suspected CRE. Randomization in the trial was stopped early after the results of an interim analysis showed statistically significant differences in favor of meropenem–vaborbactam over BAT for clinical cure at the test of cure visit (meropenem–vaborbactam 57.1% [16/28]) vs BAT 26.7% [4/15]; absolute difference 30.5% (95% CI, 1.5%-59.5%; P = .04).

As new agents emerge, resistance to them is inevitable. Neither ceftazidime–avibactam nor meropenem–vaborbactam are active against CRE-expressing metallo-beta-lactamases such as NDM enzymes, which are currently rare in the United States but common in parts of Asia. Several drugs in late-stage clinical development that are active against CRE include cefiderocol, plazomicin, eravacycline, and imipenem–relebactam (**Table**). The therapeutic indications of these pipeline agents for the treatment of infections caused by CRE, if they are approved, will take time to determine.

Infections caused by CRE are difficult to treat. Though limited in number, data have emerged that support the roles of ceftazidime–avibactam and meropenem–vaborbactam over polymyxin-based regiments for these infections. Clinicians must be vigilant not only for the detection of CRE infections, but for new literature that explores best treatment practices, as investigators begin to describe their experiences. New agents are in development, but none represent a magic bullet for the substantial problems that CRE infections present. ▲

References are available at ContagionLive.com

Staff nurses prove to be an asset to the goals of the interdisciplinary rounds and fitting advocates of antibiotic stewardship.

Actively Involving Nurses in Antibiotic Stewardship

Staff nurses are underused but potentially valuable contributors to antibiotic stewardship.

BY DAVID R. HA, PHARMD, AND MARY BETTE FORTE, MSN-ED, RN

As clinicians, we share within our codes of ethics the obligation to avoid causing harm to our patients: to "abstain from whatever is deleterious and mischievous".[1] This could not be more relevant to the use—and misuse—of antibiotics (see **Figure**). A substantial proportion of antibiotics prescribed in hospitals,[2,3] outpatient settings,[4,5] and nursing facilities[6] may be inappropriate or altogether unnecessary, leading to adverse drug reactions, *Clostridium difficile* (*C. difficile*) infection, and antibiotic resistance.[7] Antibiotic stewardship programs (ASPs) have been at the forefront of the effort to curtail inappropriate antibiotic use.[7]

Historically, guidelines for developing and implementing ASPs largely recognized the need for an interdisciplinary team, including physicians, pharmacists, infection preventionists, microbiologists, and others.[8-10] However, nurses have been frequently missing from mention in these publications.[11] Fortunately, in recent years, the dialogue surrounding antibiotic stewardship has evolved to include nurses. Evidence of this can be found in guidance documents from the US Centers for Disease Control and Prevention, National Quality Forum,[12] and American Nurses Association,[13] in which nurses are acknowledged as key contributors to these efforts. Although this recognition is a step in the right direction, studies to demonstrate specifically how nurses can actively participate in antibiotic stewardship and quantify impact are limited.[11,14]

In January 2016, the idea of involving bedside nurses was brought before the antibiotic stewardship committee of our institution, Pomona Valley Hospital Medical Center, a 437-bed community hospital in eastern Los Angeles County, California. The ensuing dialogue mirrored the literature at the time: support and enthusiasm to involve nurses but uncertainty as to how specifically to engage them. From the discussion, a task force composed of staff nurses, nurse administrators, infectious diseases pharmacists, and infection preventionists was formed to devise a potential solution.

Six months later, a pilot program was launched: interdisciplinary rounds held twice weekly on a 31-bed telemetry unit. Staff nurses led the rounds, which were attended by a clinical pharmacist, an infection preventionist, and a nurse practitioner. The hospital antibiotic stewardship committee and medical directors of infectious diseases and infection control provided oversight. Rounds focused on antibiotic use, acid suppressant use, urinary catheters, and central venous catheters. Staff nurses would present their patients and applicable issues to the interdisciplinary team and discuss potential intervention, such as discontinuing or modifying antibiotic or acid suppressant therapy and discontinuing urinary or central venous catheters. The nurses would then communicate the agreed-upon interventions to their patients' primary hospital provider. >>

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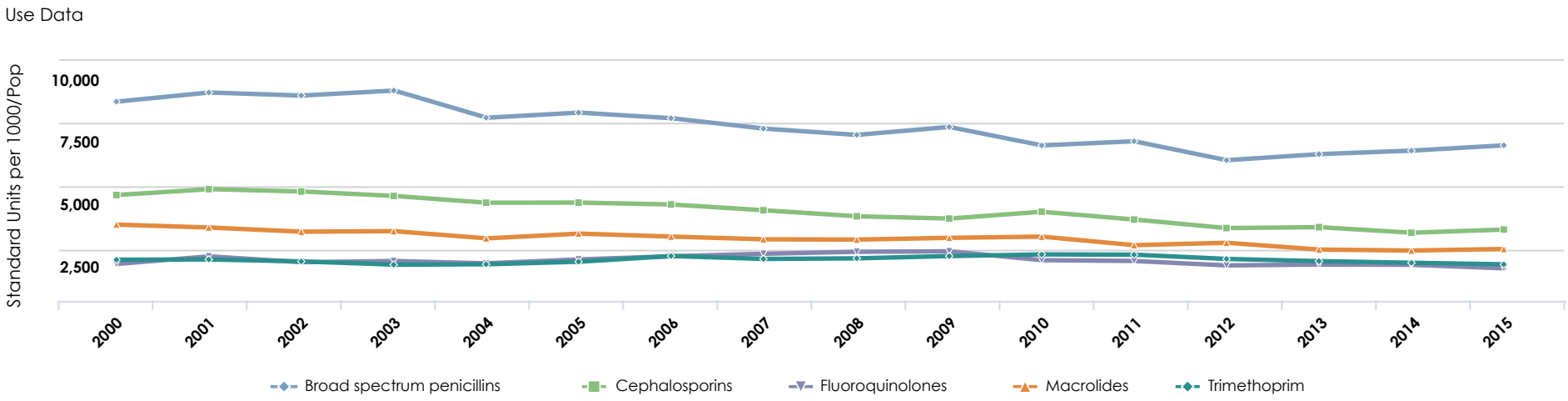
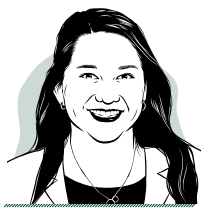
FIGURE: Antibiotic Use in the United States 2000 to 2015



Data includes aggregated resistance rates for isolates (includes intermediate resistance) from blood and cerebrospinal fluid (ie, invasive) from inpatients of all ages.

Source: Center for Disease Dynamics, Economics & Policy (cddep.org)



MARY BETTE FORTE, MSN-ED, RN

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The staff nurses proved to be an asset to the goals of the interdisciplinary rounds and fitting advocates of antibiotic stewardship. Their routine duties, including continuous monitoring of patient symptoms and responses to therapy, obtaining laboratory testing and receiving results, administering and reviewing medications, and assisting in the coordination of patient discharge, put them in an ideal position to perform timely intervention. Initially, the nurses' assessment and intervention occurred just on days when interdisciplinary rounds were performed; however, many nurses eventually incorporated these activities into their daily work. Over time, nurses increasingly reported having discussions with prescribers regarding the necessity of antibiotics, acid suppressants, and invasive catheters at the time of order receipt, occasionally ensuring they were appropriately modified or discontinued when such action was agreed upon between nurse and prescriber. Examples of such scenarios included antibiotics for asymptomatic bacteriuria, invasive urinary or central venous catheters for inappropriate indications, and *C. difficile* testing in patients with diarrhea secondary to osmotic or stimulant laxatives.

A NURSE'S ACCOUNT OF THE ROUNDS

Implementing an antibiotic stewardship program (or anything that involves change, for that matter) into our telemetry unit was no easy feat. The key aspects that proved crucial were education and active learning. Change is never easy, especially when the nurses are given an additional task with the countless other checklists that are already in their minds. What the nurses did not recognize was their true potential and the value that they brought to the interdisciplinary team.

In recent years, the dialogue surrounding antibiotic stewardship has evolved to include nurses.

Initially, there was pushback when we started rounds. Many nurses felt unsure if what they were reporting was necessary while figuring out the patient's plan of care concurrently. Speaking to a physician regarding changes recommended by the team was an initially daunting task that occasionally led to dissidence. What most nurses did agree on, however, was the interdisciplinary team's support and nonpunitive culture. Every encounter was a learning opportunity, which happened often if not always. Educating staff on what antibiotic stewardship meant and how this affected both them and their patients was crucial. As adult learners, the nurses needed to know how it was applicable to their practice. As they began to realize the difference they were making with their recommendations in their patients' plan of care, the more value it brought to their personal practice. Collaborative efforts of the charge nurse and nurse champions also proved helpful as additional support to the staff.

"Antibiotic stewardship" was no longer a foreign term to the 31-bed telemetry unit. It had become a part of the nurses' daily routine. Many nurses expressed their "new outlook" on their patient picture from a multidisciplinary perspective. Nurses proved to be more prepared during rounds, and feelings of nurse autonomy and confidence in their own practice was apparent. Over time, the medical staff became more receptive to the nurses' recommendations and developed a sincere appreciation for them.

The trend of institutions achieving Magnet recognition has also encouraged nurse-led initiatives and empowerment to make a difference. Such professional development reflects not only upon the nurse but also—primarily—on the impact that ASPs have on patient outcomes. (Editor's note: This is a first-hand account from co-author, Mary Beth Forte.)

Today, the pilot is no longer a pilot. Preliminary results have since been published.[15] The nurse-led antibiotic stewardship and infection prevention rounds have become a standard of practice at our institution and expanded to the 2 other telemetry units, with the continued attendance of clinical pharmacists and infection preventionists.

Patient safety and providing the best possible patient care are objectives that all clinicians share. Nurses are valuable contributors to antibiotic stewardship efforts but are widely underrecognized and thus underutilized for such roles. It is our hope that other institutions will actively involve their bedside nursing staff in antibiotic stewardship efforts, as well as share their approaches and outcomes, to shed more light on how best to partner with nurses to improve antibiotic use. ▲

References are available at ContagionLive.com

Patients with HIV should always be screened and evaluated for HCV treatment.

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Treating Hepatitis C Virus and HIV Coinfections in Intravenous Drug Users

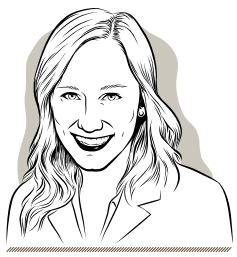
Unique considerations are called for when caring for intravenous drug users with newly diagnosed HIV/HCV coinfections.

BY RACHEL MURDOCK, PHARMD, AND MELISSA BADOWSKI, PHARMD, MPH, BCPS, AAHIVP

In 2016, an estimated 2.3 million people living with HIV were coinfected with chronic hepatitis C virus (HCV).[1] Of the coinfected population, more than half were intravenous drug users (IVDUs).[1] One meta-analysis of the HIV/HCV coinfection literature found that more than 80% of the coinfections were in IVDUs.[2] Yet, while it is established that persons who inject drugs make up a large part of this HIV/ HCV coinfected population, these patients are not clearly identified in the major HIV/HCV coinfection trials. Although this can be a difficult patient population to manage, they are a high priority from a population health standpoint. Eradication of HCV, in addition to complete viral suppression of HIV, would substantially decrease overall transmission of these viruses if these high-risk behaviors continue.

Initiation of antiretroviral therapy (ART) is recommended for all patients testing positive for HIV infection. In the coinfected population, this is even more important, as untreated HCV in HIV leads to more rapid liver disease progression and increases both morbidity and mortality.[1] In patients with HIV/ HCV coinfection, the choice of ART should take into consideration the potential need for concurrent HCV treatment. Other considerations include the ability to adhere to therapy, cost or insurance coverage of medications, hepatitis B virus status, and progression of liver disease or cirrhosis. Each of these factors can further dictate the medication regimen for both disease states.[3] **Table 1** outlines the recommended first-line and alternative direct-acting antiviral (DAA) medications for the treatment of HCV from the American Association for the Study of Liver Diseases (AASLD) and takes into consideration appropriate, as well as inappropriate, concomitant antiretroviral agents.[3]

Patients with HIV should always be screened and evaluated for HCV treatment. If they meet the criteria, therapy with a DAA should then be initiated based on HCV genotype and severity of disease.[3] The currently available DAA regimens result in high HCV cure rates, as measured by sustained virologic response (SVR). SVR is achieved in the HIV/HCV coinfected population at a similar rate as those with HCV monoinfection.[4-6] The trials investigating many of the DAA agents in the HIV/HCV coinfected population are outlined in **Table 2** (available at contagionlive.com). Some of the data on glecaprevir/pibrentasvir have been presented, but the full trial has not yet been published. No articles on the efficacy of the newest agent, sofosbuvir/velpatasvir/voxilaprevir, are available yet in this specific patient population. However, the phase 3 trials for this medication, published as the POLARIS series, have >>



RACHEL MURDOCK, PHARMD

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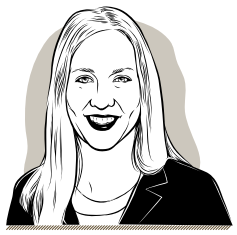
Table 1. HIV Medication Therapy Considerations for HCV Treatment Regimens[3*]

DIRECT-ACTING ANTIVIRAL REGIMEN COMPONENTS	HIV MEDICATIONS SAFE TO USE IN COMBINATION	HIV MEDICATIONS TO AVOID
Ledipasvir/sofosbuvir (LDV/SOF)	Safe with most ART	Ritonavir-boosted tipranavir
Sofosbuvir/velpatasvir (SOF/VEL)	Safe with most ART	Efavirenz, etravirine, nevirapine, and tipranavir
Elbasvir/grazoprevir (ELB/GRZ)	Abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir**	Cobicistat,efavirenz, etravirine, nevirapine, and any HIV protease inhibitor
Glecaprevir/pibrentasvir (GLE/PIB)	Abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir**	Atazanavir, efavirenz, etravirine, and ritonavir-containing ARVs
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)	Dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and rilpivirine	Ritonavir-boosted atazanavir, efavirenz, etravirine,and nevirapine
Paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD)	Atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir**	Cobicistat, darunavir, efavirenz, etravirine, ritonavir-boosted lopinavir, nevirapine, rilpivirine, and ritonavir-boosted tipranavir
Ribavirin	Safe with most ARVs	Didanosine, stavudine, and zidovudine
Simeprevir/sofosbuvir (SMV/SOF)	Abacavir, emtricitabine, enfuvirtide, dolutegravir, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir**	Cobicistat, efavirenz, etravirine, nevirapine, and any HIV protease inhibitor
Daclatasvir/sofosbuvir (DCV/SOF)	Safe with most ART	Ritonavir-boosted tipranavir

ART indicates antiretroviral therapy; HCV, hepatitis C virus.
*This table is adapted from the AASLD/IDSA HCV guidelines and is not all-inclusive.[3] The content addresses only the current preferred and alternative HIV/HCV medications seen in this patient population.

**Renal function should be monitored closely with both tenofovir alafenamide and tenofovir disoproxil fumarate. Tenofovir disoproxil fumarate cannot be used with some agents if creatinine clearance is less than 60 mL/min; therefore, generally, tenofovir alafenamide is preferred.



MELISSA BADOWSKI, PHARMD, MPH, BCPS, AAHIVP

Dr. Badowski is a clinical associate professor at the University of Illinois at Chicago (UIC), College of Pharmacy in Chicago, Illinois. She completed a PharmD at Midwestern University, Downers Grove, Illinois, an MPH at UIC, School of Public Health, and residencies at the University of Maryland Medical Center and College of Pharmacy in Baltimore. Her current practice setting is an interdisciplinary telemedicine clinic where she manages people living with HIV in the correctional setting for the state of Illinois.

shown SVR rates comparable with those of the agents listed below in HCV monoinfected patients. In treatment-naïve patients, 8 weeks of treatment with sofosbuvir/velpatasvir/voxilaprevir resulted in an SVR of 95%. In previously treated patients without cirrhosis, the SVR was as high as 99%.[7,8] Because of the high SVR in this population and the already well-established first-line agents, sofosbuvir/velpatasvir/voxilaprevir will be seen clinically primarily in patients who have failed prior therapy.

Although HIV/HCV coinfection is common in IVDUs, these patients are not commonly mentioned in clinical trials, despite making up a large portion of the real-world HIV/HCV coinfected population. In fact, IVDU is a common exclusion criterion for trials, especially those in which treatment adherence and follow-up are directly correlated to efficacy. For example, the C-EDGE and ION-4 trials list clinically relevant drug or alcohol abuse or a history of abuse within 12 months of screening as an exclusion criterion.[5,4] In the PHOTON-1 trial, persons who inject drugs were not explicitly excluded, however if any participant had a positive urine drug toxicology screening, he or she could not participate in the study.[9] The ledipasvir/sofosbuvir trial, the National Institute of Allergy and Infectious Disease's ERADICATE trial, inclusion criteria states that if patients were opioid dependent, they had to participate in supervised treatment while in the study.[10] Other studies give even less detail but state generally that anything that could affect adherence should be an exclusion criterion at the principal investigator's discretion.

When treating a person who injects drugs with newly diagnosed HIV/HCV co-infection, as with all patients, medication therapy for both infections should be initiated as soon as possible to prevent the progression of liver disease and decrease the transmission of the viruses. HIV viral load suppression should be obtained first, followed by the addition of HCV treatment. An ideal combination for a patient presenting with an HIV/HCV coinfection would be a regimen such as dolutegravir/abacavir/lamivudineand glecaprevir/pibrentasvir. If a patient is eligible for HIV treatment with dolutegravir/abacavir/lamivudine (namely HLA-B*5701 negative and without cardiovascular disease), glecaprevir/pibrentasvir can be safely added to this regimen with minimal risk of drug–drug interactions. Furthermore, as a pan-genotypic agent, glecaprevir/pibrentasvir has shown efficacy for all HCV infection genotypes. Perhaps most important for this patient population is that in individuals without cirrhosis, treatment is only 8 weeks, potentially increasing the likelihood of adherence.[3]

Starting at diagnosis and continuing with each health care encounter, it is important to address and evaluate the patient's illicit drug use. Studies have shown that in the HIV populations, ART is equally efficacious for IVDUs and non-IDVUs when patients are not actively using drugs.[11] Illicit drugs have been linked to depression and anxiety, which is a strong predictor of poor adherence and potentially poor treatment outcomes. Persons who inject drugs and have HIV have lower rates of ART if they also have additional risk factors such as recent incarceration or lack of access to rehabilitation programs. Therefore, management of substance use disorders is often necessary to successfully eradiate HCV and appropriately manage HIV.

It is important to build a relationship of trust with these patients and not only provide medical support for their HIV/HCV infections but also assist in getting them connected for their other comorbidities that affect patient adherence to medication therapies. This primarily includes a multidisciplinary approach to treating the patient's substance abuse disorders. In addition to medication therapy, it is prudent to stabilize these patients through treatment of psychiatric illnesses and substance abuse treatment. Further harm-reduction measures such as connecting patients with needle exchange programs and clinics to provide sexually transmitted infection screenings and free condoms are also important.

In a patient population that is commonly lost to follow-up, it is also pertinent to engage, link, and retain these patients from the community into care. This could be done through co-management of patient's infectious diseases in substance abuse programs or methadone clinics. As this is a high-risk population for transmission of HIV and HCV, population screening should also be provided to ensure adequate treatment for all individuals.

HIV/HCV treatments can be provided only if these patients are identified. With overlapping modes of transmission and affected populations, meeting these patients in the community is the first step for control of these conditions. With new medications being developed for both HIV and HCV, as clinicians we need to remain up-to-date on safety profiles, drug interactions, and clinical pearls for each medication. Armed with this knowledge, we can treat this unique population with the most targeted and multifaceted approach. ▲

References are available at ContagionLive.com

Orbactiv® (oritavancin) for injection

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

At presentation
Actual clinical trial wound infection image

Efficacy profile for single-dose ORBACTIV® (oritavancin) established in 978 patients[1,2]

Endpoints	ORB N=978 % (n)	VAN N=981 % (n)
Clinical response at 48–72 hours (primary endpoint)[§]	81.2% (794)	80.9% (794)
Clinical success at 14–24 days (secondary endpoint)[¶]	81.2% (794)	80.2% (787)

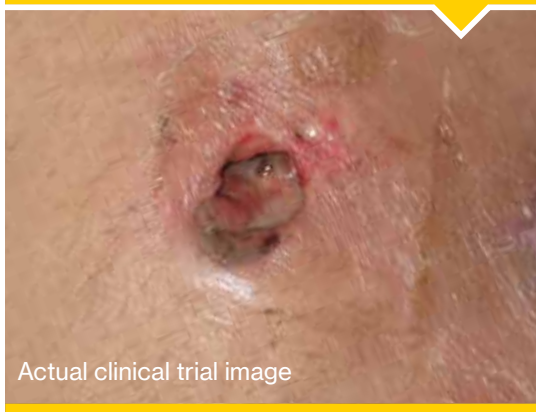
Pooled Clinical Data from SOLO I and SOLO II[3**]

[§] 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 evaluations were also performed at days 7–10 or the day the patient stopped study drug (EOT).
[¶] 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.
[**] 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.

Resolution following administration of single-dose ORBACTIV®

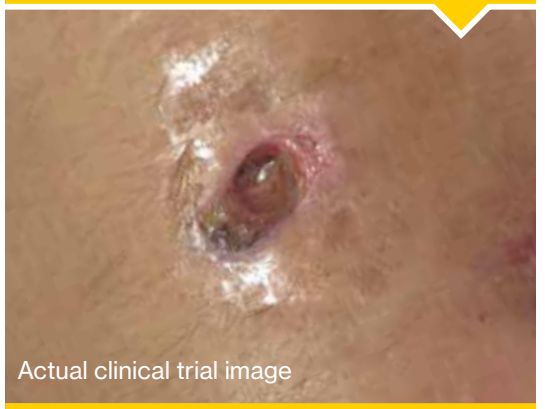
These photos show the response of an actual SOLO trial patient following ORBACTIV® administration. Individual results may vary and response may not be representative of all patient experiences.

48–72 hours[§]



Actual clinical trial image

7-10 days[‖]



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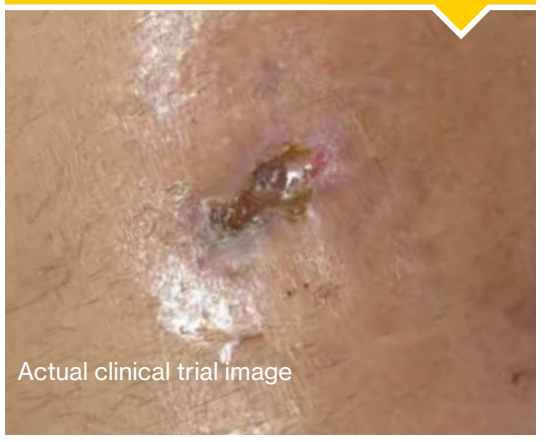
14 –24 days[¶]



Actual clinical trial image

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

*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 suspectedbacterial 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:
1. Corey GR, et al. *Clin Infect Dis*. 2015; 60: 254-262.
2. Corey GR, et al. *N Engl J Med*. 2014; 370: 2180-90.
3. Data on file.

Please see following page for Brief Summary of ORBACTIV® Prescribing Information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see package insert for full Prescribing Information

1. INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

ORBACTIV® (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 empiric selection of therapy.

4. CONTRAINDICATIONS

4.1 Intravenous Unfractionated Heparin Sodium

Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after ORBACTIV® administration because the activated partial thromboplastin time (aPTT) test results may remain falsely elevated for up to 120 hours (5 days) after ORBACTIV® administration [*see Warnings and Precautions (5.1) and Drug Interactions (7.2)*].

4.2 Hypersensitivity

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

5. WARNINGS AND PRECAUTIONS

5.1 Coagulation Test Interference

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

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

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

5.2 Hypersensitivity

Serious hypersensitivity reactions have been reported with the use of ORBACTIV®. If an acute hypersensitivity reaction occurs during ORBACTIV® infusion, discontinue ORBACTIV® immediately and institute appropriate supportive care. Before using ORBACTIV®, inquire carefully about previous hypersensitivity reactions to glycopeptides. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during ORBACTIV® infusion in patients with a history of glycopeptide allergy. In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in ORBACTIV®-treated patients was 1.2 days and the median duration of these reactions was 2.4 days [*see Adverse Reactions (6.1)*].

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 an ORBACTIV® dose [*see Warnings and Precautions (5.1)*].

Patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin [*see Drug Interactions (7.1)*].

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 a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [*see Patient Counseling Information (17)*].

6. ADVERSE REACTIONS

The following adverse reactions are also discussed in the Warnings and Precautions section of labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions (5.2)*]
- Infusion Related Reactions [*see Warnings and Precautions (5.3)*]
- Clostridium difficile-associated Diarrhea [*see Warnings and Precautions (5.4)*]
- Osteomyelitis [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

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

ORBACTIV® has been evaluated in two, double-blind, controlled ABSSSI clinical trials, which included 976 adult patients treated with a single 1200 mg intravenous dose of ORBACTIV® and 983 patients treated with intravenous vancomycin for 7 to 10 days. The median age of patients treated with ORBACTIV® was 45.6 years, ranging between 18 and 89 years of age with 8.8% ≥65 years of age. Patients treated with ORBACTIV® were predominantly male (65.4%), 64.4% were Caucasian, 5.8% were African American, and 28.1% 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 (5.8%) 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 dose of ORBACTIV® in the pooled ABSSSI clinical trials were: headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea.

In the pooled ABSSSI clinical trials, ORBACTIV® was discontinued due to adverse reactions in 36/976 (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 ≥1.5% 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 1: Incidence of Selected Adverse Reactions Occurring in ≥1.5% of Patients Receiving ORBACTIV® in the Pooled ABSSSI Clinical Trials

Adverse Reactions	ORBACTIV N=976 (%)	Vancomycin N=983 (%)
General disorders and administration		
Infusion site phlebitis	24 (2.5)	15 (1.5)
Infusion site reaction	19 (1.9)	34 (3.5)
Infections and infestations		
Abscess (limb and subcutaneous)	37 (3.8)	23 (2.3)
Investigations		
Alanine aminotransferase increased	27 (2.8)	15 (1.5)
Aspartate aminotransferase increased	18 (1.8)	15 (1.5)
Cardiac disorders		
Tachycardia	24 (2.5)	11 (1.1)

Reactions Occurring in ≥1.5% of Patients Receiving ORBACTIV® in the Pooled ABSSSI Clinical Trials

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*: hypoglycemia
- *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.

7. DRUG INTERACTIONS

7.1 Effect of ORBACTIV® on CYP Substrates

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

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

7.2 Drug-Laboratory Test Interactions

ORBACTIV® may artificially prolong certain laboratory coagulation tests (see Table 2) by binding to and preventing the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests [*see Contraindications (4.1) and Warnings and Precautions (5.1, 5.5)*]. For patients who require monitoring of anticoagulation effect within the indicated time after ORBACTIV® dosing, a non phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered.

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

Table 2: Coagulation Tests Affected and Unaffected by ORBACTIV®

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

8.3 Nursing Mothers

It is unknown whether oritavancin is excreted in human milk. Following a single intravenous infusion in lactating rats, radio-labeled [14C]-oritavancin was excreted in milk and absorbed by nursing pups. Caution should be exercised when ORBACTIV® is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate renal impairment [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3)*].

The pharmacokinetics of ORBACTIV® in severe renal impairment have not been evaluated. ORBACTIV® is not removed from blood by hemodialysis.

8.7 Hepatic Impairment

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

10. OVERDOSAGE

In the ORBACTIV® clinical program there was no incidence of accidental overdose of ORBACTIV®.

Based on an in vitro hemodialysis study, ORBACTIV® is unlikely to be removed from blood by hemodialysis. In the event of overdose, supportive measures should be taken.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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Panelists discuss the growing threat of antimicrobial resistance.

Pathogen and Treatment Paradigms for Multidrug-Resistant Infections

BY GINA BATTAGLIA, PHD

The increased prevalence of multidrug-resistant (MDR) infections over the past several years has become a major burden for patients, hospitals, and long-term care facilities. Optimizing antibiotic stewardship programs and improving the transition of care between hospitals and long-term care facilities will be important for improving management of MDR infections, according to panelists who participated in a *Contagion*® *Peer Exchange* panel.


Peter L. Salgo, MD

"We're facing a real crisis here," said moderator **Peter L. Salgo, MD**. "Our antibiotics are becoming less effective, and we've got diseases that we're having a lot of trouble treating."

OVERVIEW OF MULTIDRUG-RESISTANT INFECTIONS

The Centers for Disease Control and Prevention (CDC) estimates that MDR pathogens infect 2 million patients per year and are the cause of 23,000 mortalities,[1] and the panelists noted that the number has increased over the past several years. "Pick your favorite organism," said **Jason Pogue, PharmD**. "If you look at resistant versions of that bug, the numbers are going up over time, and that's why it's an urgent threat to us," he said.


Jason Pogue, PharmD

Additionally, infections that require multiple treatment attempts are burdensome to patients and hospitals, according to **Sandy J. Estrada Lopez, PharmD**. "Perhaps we had to try 2 things, 3 things, 4 things, and then they did eventually work," she said. "But the cases where there's extended length of stay, extended cost, or need to stay in the hospital, or that have repeat visits are becoming more common."


Sandy J. Estrada Lopez, PharmD

Andrew Shorr, MD, noted that crude mortality rates for infections with highly resistant gram-negative organisms are approaching rates seen in the pre-antibiotic era, and the prevalence of MDR infections will continue to increase with the aging population, changes in the epidemiology of pathogens, and increasingly aggressive use of immunosuppression for nearly every disease state.

"People are living longer, and they're not dying of their heart failure [or] renal disease," he said. "This is not going away, and I think we've all lamented it. I think the problem now is we've got to figure out how to solve it."

THE CAUSES AND IMPACT OF MULTIDRUG-RESISTANT INFECTIONS

Causes

Most experts agree that frequent use of antibiotics is a key contributor to the increase in MDR infections, but they disagree about whether antibiotics are overused. While Drs. Shorr and Salgo agreed that the increased prevalence of resistant infections is due in large part to overuse, Dr. Pogue stated that appropriate use of antibiotics would still lead to the development of resistance.

"Outsmarting Resistant Infections"

MODERATOR

Peter L. Salgo, MD

Professor of Medicine and Anesthesiology, Columbia University College of Physicians and Surgeons

Associate Director of Surgical Intensive Care at NewYork-Presbyterian Hospital, New York, New York

PANELISTS

Sandy J. Estrada Lopez, PharmD

Infectious Disease Clinical Pharmacist, Lee Memorial Health System, Fort Myers, Florida

Debra Goff, PharmD

Clinical Associate Professor and Infectious Disease Specialist, The Ohio State University Wexner Medical Center, Columbus, Ohio

Jason Pogue, PharmD

Infectious Diseases Clinical Pharmacist, Sinai-Grace Hospital of Detroit Medical Center

Clinical Assistant Professor of Medicine, Wayne State University School of Medicine, Detroit, Michigan

Andrew Shorr, MD

Section Head, Pulmonary and Critical Care Medicine, MedStar Washington Hospital Center

Professor of Medicine, Georgetown University, Washington, DC

ContagionLive.com/link/857

"Sure, we could mitigate it a little bit by more appropriate use [and] limiting unnecessary antibiotic use," he said. "But it's natural selection…we would expect this to occur."

Dr. Shorr argued that clinicians are the primary contributors to the problem and should be responsible for finding solutions moving forward. "This has been like watching a slow-motion car crash for a generation, and we're still playing catch-up. We've created the problem; we have to fix the problem," he stated.


Andrew Shorr, MD

Debra Goff, PharmD, added that antibiotic use in animals accounts for about 70% of antibiotic prescriptions in the United States and may contribute to the resistance seen in humans. "When you look at the animal-to-human transmission of resistance, there's a big component right now of who's to blame," she said. "Health care providers are part of it, but responsible use in the animal sector is another part."


Debra Goff, PharmD

Clinical and Community Impact

According to Dr. Pogue, the clinical impact is best illustrated by comparing patient outcomes between infections with MDR organisms and the drug-susceptible form. "What you're going to find…[is that] mortality rate doubles, and if the patient survives, length of stay is double, as is the need for extra care afterward," he said. "And from the hospital standpoint, there's a cost associated with every single one of those things."

Drs. Pogue and Goff also pointed out that the spread of resistant infections into the community can have devastating effects on otherwise healthy individuals. "We're seeing patients who have never had health care exposure acquire their first *Escherichia coli* [urinary tract infection that is] multidrug resistant," said Dr. Goff.

MULTIDRUG-RESISTANT INFECTIONS: CURRENT PATHOGEN AND TREATMENT PARADIGM

With the increased burden of MDR infections, much research has focused on the development of new antibiotics over the past 10 years, including a few new agents developed over the past 2 to 3 years that target gram-negative bacteria, such as multidrug-resistant *Pseudomonas* and carbapenem-resistant Enterobacteriaceae (CRE).

Dr. Shorr cautioned that none of the novel agents are a "cure-all" and that the agents targeted toward gram-negative pathogens have unique strengths and weaknesses. He explained that clinicians need to consider the role of a given antibiotic at a particular hospital and whether it fits in with the concept of antibiotic/microbial stewardship.

"They all have different spectrums of activity, and not 1 of them is going to be the right answer for every hospital," he said. "It's one of these issues where you actually have to do a lot of thinking and cognition to decide how you're going to utilize these on your formulary, if at all."

However, Dr. Goff pointed out that the selection of antibiotics is often managed by a stewardship program rather than the physician's belief of what will be most effective for treating the patient. "Most of the time, you're prescribing in the moment. You're not thinking about the impact on society."

She and the other panelists agreed that reconciling the responsibilities of treating the patient and considering society will be the next challenge moving forward and that stewardship programs will need to have input from multiple disciplines. "The different perspectives are a huge thing to appreciate," said Dr. Pogue. "That's why your stewardship program has to have all the key players on it. It can't just be [infectious disease] and pharmacy that [are] making these decisions."

The panel discusses how clinicians need to consider the role of a given antibiotic at their institution and determine whether or not it fits into their concept of antibiotic/microbial stewardship.

GRAM-NEGATIVE NOSOCOMIAL INFECTIONS: SYSTEMIC RISK

Although multiple factors, such as a suppressed immune system and hospital interventions that allow for growth of biofilms (such as insertion of tubes and lines), increase the risk for gram-negative MDR infections, prior antibiotic exposure is the main factor that selects out resistant pathogens, according to Dr. Shorr.

He said that clinicians need to consider the epidemiology of their hospital because the risk factors are not specific for a particular pathogen. "If you don't have CRE [at the hospital], the patient is not at risk for CRE. But it would also be helpful to know sometimes what the patient has been colonized or infected with in the process," he stated.

The panelists also discussed the high risk of resistant infections in nursing homes, long-term acute care hospitals (LTACHs), and skilled nursing facilities that are caused by the repeated transfers from the hospital to the long-term care facility. "Those places breed resistance because there's no focus necessarily on good infection prevention and very little focus on antibiotic prescribing," said Dr. Shorr.

Additionally, antibiotics are often continued in LTACHs even if an alternate diagnosis is found, said Dr. Shorr. "[In this situation], we stop these antibiotics in the hospital, but in those facilities, because you can't get the monitoring as closely, you're afraid that if you stop too soon, there might be a consequence."

The panelists also noted that poor communication between the LTACH and the hospital may contribute to continuation of antibiotics beyond the recommended time frame. "Patients going from the hospital to the LTACH [are] on antibiotics," said Dr. Lopez. "Maybe they've already been on antibiotics for 12 days [and] they need 3 more days. For whatever reason, that stop date gets lost in translation when they leave the hospital."

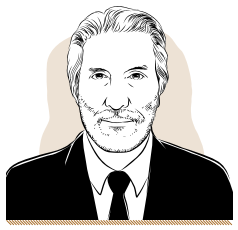
The panelists concluded that improving transition of care between the hospital and long-term care facilities will be a key area of advancement to reduce the burden of antibiotic resistance on patients and the health care system. "At some point, we have to marry each other because we're never going to solve the problem," said Dr. Goff. "There's a social responsibility to doing it right." ▲

References are available at ContagionLive.com

2018 BMT Tandem Meetings

Considerations for CMV in Allogeneic HSCT Recipients

BY BRIAN HOYLE, PHD



BRIAN HOYLE, PHD

Dr. Hoyle is a medical and science writer and editor from Halifax, Nova Scotia, Canada. He has been a full-time freelance writer/editor for over 15 years. Prior to that, he was a research microbiologist and lab manager of a provincial government water testing lab.

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that occur following transplantation. The normal post-HSCT strategy for over a decade has involved blood checks for the presence of CMV nucleic acid in patients who display no symptoms of infection. If the genetic material is detected, treatment swings to a reactive response involving intravenous (IV) ganciclovir or its oral prolog, valganciclovir, or the IV application of either foscarnet or cidofovir.

The reactive approach works, but its adverse effects (AEs), including myelosuppression and renal toxicity, mean that therapy is short-term. Enter letermovir and the idea of its preemptive use "from the get-go" in patients scheduled for allo-HSCT, explained Roy Chemaly, MD, MPH, from the University of Texas MD Anderson Cancer Center, Houston, Texas, during an interview with *Contagion*®. Dr. Chemaly was involved in the phase 3 letermovir prophylaxis study published in the *New England Journal of Medicine* (*NEJM*) and the poster described below.

As detailed in the poster, clinicians led by Dr. Chemaly retrospectively examined data from an 18-hospital database of HSCT patients to assess the clinical outcome and the economic burden of CMV reactivation. Between 2012 and 2015, 100 consecutive patients hospitalized at MD Anderson for allo-HSCT who experienced reactivation of CMV were enrolled. The scenario for these patients was the current status quo of care, which treats CMV preemptively.

Just over half the patients were male, and the majority (73%) had underlying leukemia. Fifty-nine patients underwent matched unrelated donor transplantation. At the time of their hospitalization, 62 patients had acute graft-versus-host disease. Steroid therapy was initiated within a month of CMV reactivation in 58 patients. Time until CMV reactivation varied widely from 2 to 174 days following allo-HSCT, with a median of 32 days.

Within the first year following HSCT, preemptive therapy was done 192 times. Medications included ganciclovir, foscarnet, or valganciclovir, with IV immunoglobulin used as an adjuvant therapy 20 times. Progression to CMV disease occurred in 4 of the 100 patients. The mean hospitalization time was similar for patients treated with ganciclovir and foscarnet.

To get a better handle on inpatient costs, the investigators analyzed the data from MD Anderson and 17 other hospitals using the Vizient database. The composite data revealed that the retroactive response added to the cost of treatment, particularly when there were serious adverse effects from the foscarnet therapy (the total direct cost per encounter in these patients was $284,006 versus $112,195 for patients without serious AEs).

The findings "underscore the significant impact of CMV reactivation and preemptive therapy in terms of economic and clinical burden in allo-HSCT patients," said Dr. Chemaly.

Whether the prophylactic letermovir strategy actually decreases the real-world burden of CMV beyond the recent clinical trial remains to be determined and is the subject of ongoing analyses. For now, though, the study makes clear the clinical and economic toll of CMV in the allo-HSCT setting.

The study presented in the other poster homed in on the use of letermovir, using a decision-analytic model to evaluate the cost-effectiveness of the letermovir prophylaxis compared with the status quo preemptive treatment. The total cost of patient treatment and the longer-term burden of CMV on the quality and length of life was measured by the parameters of life-years gained and quality-adjusted life-years. The model was deliberately designed to be simple and relied on data obtained from the phase 3 trial published in *NEJM*, boosting confidence in the real-life ramifications of the model predictions.

"The model is able to use clinical inputs and measures of health care resource utilization from a randomized, placebo-controlled clinical trial. These data are generally considered the gold standard for model inputs," explained Jonathan Schelfhout, PhD, Merck & Co Inc, Kenilworth, New Jersey, in an interview with *Contagion*®. Dr. Schelfhout was involved in both posters and in the phase 3 trial of letermovir prophylaxis.

The analysis involved 1000 patients who were followed until death. The actual patient data showed that the prophylactic use of letermovir reduced the number of CMV infections that required subsequent preemptive treatment (189 vs 443) 24 weeks after allo-HSCT. "Prophylaxis with letermovir resulted in fewer cases of mortality and an increase in life-years and quality-adjusted life-years," said Dr. Schelfhout.

The prophylaxis strategy did increase the cost of treatment; however, the longer-term benefits more than outweighed this expense. "The results of this model suggest that letermovir is an excellent value, with a cost per quality-adjusted life-year of $25,222. The number is well beneath the thresholds of $100,000 or $150,000 that are typically cited for evaluating whether an intervention is cost-effective in the United States. These results were robust to changes in the inputs of the model, as a probabilistic sensitivity analysis indicated that letermovir was cost-effective in 93.5% of iterations at $100,000 of quality-adjusted life-year gained and 95.2% of iterations at $150,000 per quality-adjusted life-year gained," said Dr. Schelfhout.

The relative lack of published cost data for CMV and the model's lack of inclusion of costs other than direct treatment costs are acknowledged limitations of the approach. Further research will flesh out these aspects and, it is anticipated, continue to strengthen the case for letermovir prophylaxis. ▲

DISCLOSURES

ROY F. CHEMALY, MD, MPH: Chimerix Inc, grants, and personal fees; Merk & Co Inc, grants, and personal fees; Novartis, grant; Astellas, personal fees; Oxford Immunotec, personal fees.

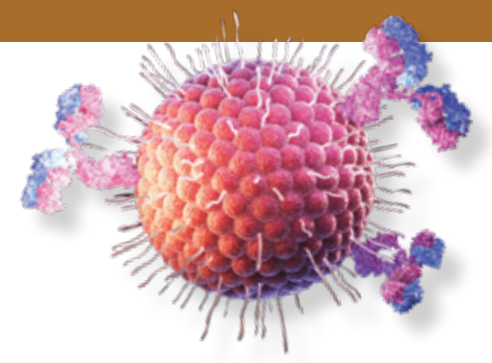
JONATHAN SCHELFHOUT, PHD: Merck & Co Inc, employee.

PRESENTATION

Poster Session: Infectious Diseases

ROY F. CHEMALY, MD, MPH
MD Anderson Cancer Center
Poster 542. Clinical & Economic Burden of Pre-Emptive Therapy (PET) of Cytomegalovirus (CMV) Infection in Hospitalized Allogeneic Hematopoietic Cell Transplant (allo-HCT) Recipients: The MD Anderson Cancer Center Experience

JONATHAN SCHELFHOUT, PHD
Merck & Co Inc
Poster 557. Cost Effectiveness of Letermovir as Cytomegalovirus Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients



2018 BMT Tandem Meetings

Shingrix Prevents Herpes Zoster Episodes Following HSCT

BY LISA ASTOR

(*continued from cover*)
autologous hematopoietic stem cell transplant, the herpes zoster subunit vaccine effectively prevented herpes zoster, independent of age, and postherpetic neuralgia," de la Serna et al wrote in their abstract. "The safety profile of the herpes zoster vaccine subunit in this population was clinically acceptable."

In the observer-blind, placebo- controlled phase 3 study, patients were randomized 1:1 to either the HZ subunit vaccine (n = 922) or placebo (n = 924). All patients had received autologous HSCT 50 to 70 days prior to the start of treatment and were followed for at least a year, as risk for HZ is highest in the first year after transplant.

The recombinant adjuvanted subunit vaccine, which contains recombinant varicella zoster virus (VZV) glycoprotein E and the $AS01_B$ adjuvant system, was administered intramuscularly in the deltoid region of the nondominant arm in 2 doses spaced 1 to 2 months apart.

Patients were also divided into 2 cohorts. The total population, which included those who received ≥1 dose of the vaccine and were analyzed for safety, was included in the total vaccinated cohort (TVC) and those who had not received dose 2 or who developed HZ less than 1 month after the second dose were included in the modified TVC (mTVC) cohort.

The modified cohort included 1721 patients: 870 treated with the vaccine and 851 treated with placebo. A majority of these patients (75.3%) were ≥50 years. Approximately half (54.4%) had multiple myeloma, and the remainder had other underlying diseases necessitating stem cell transplant.

In the overall population, baseline characteristics were well balanced between the 2 arms. The mean age at first dose was 54.8 years in the investigational arm and 55.1 years in the control arm. The majority of the patients (62.7%) were male.

The primary objective of the study was vaccine efficacy in the mTVC cohort as assessed by episodes of HZ, which were confirmed by polymerase chain reaction assay. At a median follow-up of approximately 21 months, 49 patients (5.6%) treated with the vaccine had an episode of HZ compared with 135 (15.9%) in the placebo arm.

Cases of postherpetic neuralgia were experienced by 1 patient treated with the vaccine compared with 9 in the placebo arm, amounting to a vaccine efficacy of 89.3% (95% CI, 22.5%-99.8%). Other HZ complications were experienced by 3 and 13 patients, respectively, in the treatment and placebo arms, for an efficacy of 77.8% (95% CI, 19.1%-95.9%). Hospitalizations due to HZ were experienced by 2 patients in the vaccine arm compared with 13 in the placebo arm, leading to an efficacy of 84.7% (95% CI, 32.2%-96.6%) for the vaccine.

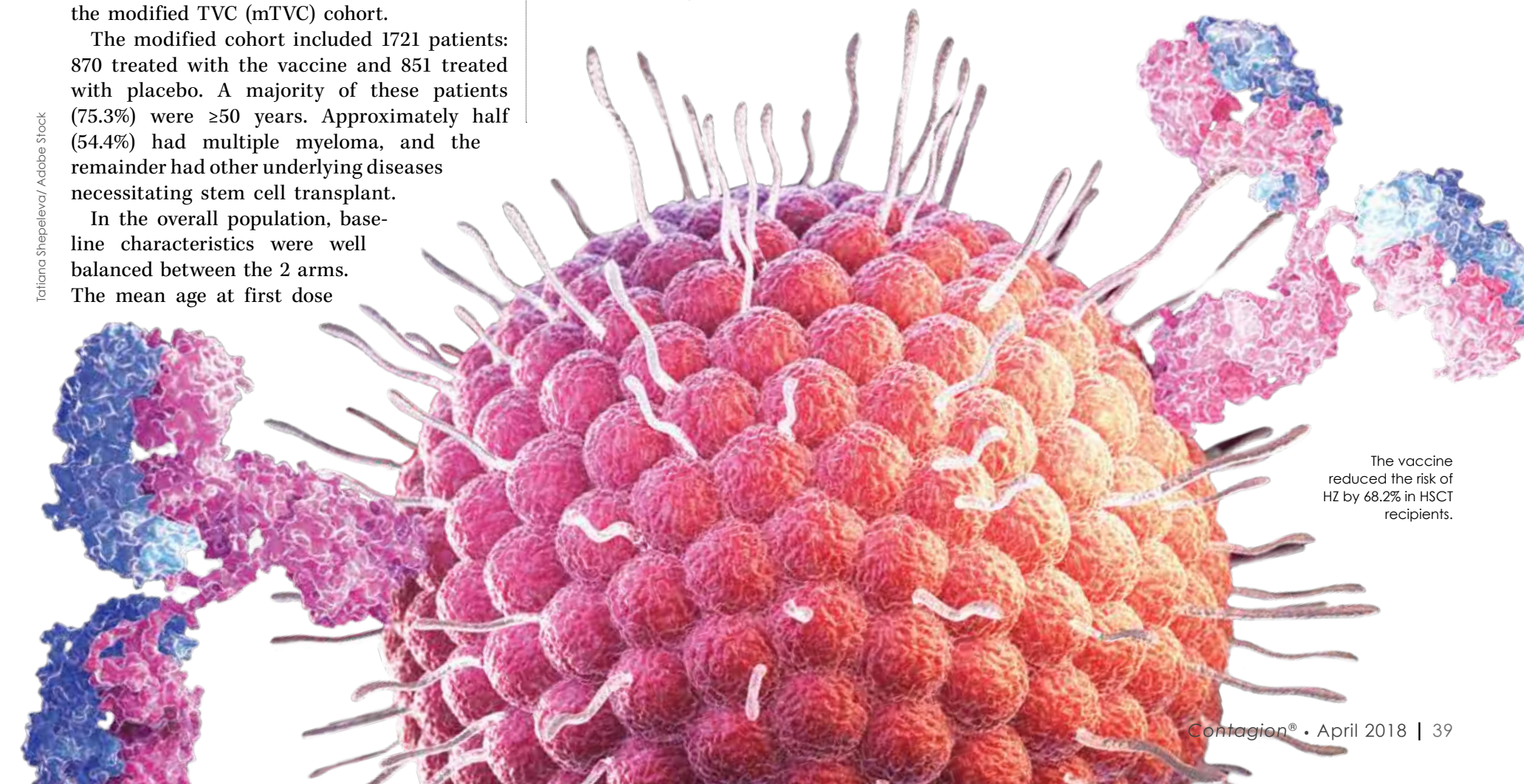
When looking at the patient population 50 years or older, HZ was experienced by 40 patients who were treated with the vaccine versus 106 who received placebo (vaccine efficacy, 67.3%; 95% CI, 52.6%-77.9%). In the younger patient population, there were 9 episodes of HZ with the vaccine and 29 with placebo (vaccine efficacy, 71.8%; 95% CI, 38.8%-88.3%).

In both age groups in the TVC cohort, incidence of local and general solicited adverse events (AEs) was more frequent in the investigational arm (85.8% local; 42.1% general) compared with placebo (10.4% local; 16.8% general), which Dr. de la Serna noted was expected. Grade 3 local events were experienced by 14.2% in the experimental arm compared with 0.3% in the control arm, and grade 3 general events were experienced by 7.8% and 1.0%, respectively.

The most common local solicited AEs, which occurred within 7 days after each dose, included injection-site pain (any-grade, 83.9% vs 9.3% with placebo), redness (33.4% vs 1.0%), and swelling (18.6% vs 1.0%). Common general AEs included fatigue (56.4% vs 38.0%), gastrointestinal AEs (26.4% vs 20.5%), headache (33.5% vs 18.6%), myalgia (53.7% vs 26.2%), shivering (26.3% vs 12.9%), and fever (20.3% vs 5.6%).

Serious AEs, which occurred up to 1 year after the second dose, were experienced by 28.5% of those treated with the HZ subunit vaccine compared with 26.1% treated with placebo. Of these serious AEs, 0.3% and 0.4%, respectively, were considered related to treatment, and 12.8% and 13.4% were fatal.

Relapses were experienced by 25.9% of patients who received the vaccine and 27.4% who received placebo. ▲



Tatiana Shepeleva/ Adobe Stock

The vaccine reduced the risk of HZ by 68.2% in HSCT recipients.

CROI 2018

D/C/F/TAF Performs Well in Treatment-Experienced Patients

BY DANIELLE MROZ, MA

(*continued from cover*)

For the phase 3, randomized (2:1), noninferiority trial, investigators examined the efficacy and safety of switching to darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg versus continuing use of the boosted protease inhibitor (PI) emtricitabine/tenofovir disoproxil fumarate (control) in 1141 treatment-experienced, virologically suppressed HIV-1–infected adults with a viral load (VL) of <50 copies (c)/mL for ≥2 months. One VL ≥50 and <200 c/mL was allowed in 12 months before screening, and previous non-darunavir virologic failure was also allowed.

According to the study authors, "the primary endpoint was the proportion of patients with virologic rebound (confirmed VL ≥50 c/mL or premature discontinuation with last VL ≥50 c/mL) cumulative through week 48. Virologic response was defined as VL <50 c/mL (FDA snapshot). Safety was assessed by adverse events (AEs) and changes in bone mineral density and estimated glomerular filtration rate (eGFR) from baseline to week 48. Results were evaluated in subgroups by age (≤50 vs >50 y), gender, and race (non-black/African American [AA] vs black/AA). A total of 382 (33.5%) [of the patients] were >50 years of age; 205 (18.0%) were women, and 237 (20.8%) were black/AA."

Contagion® sat down with the lead investigator, Gregory D. Huhn, MD, an infectious disease specialist in the Cook County Health system in Chicago, Illinois, who shared what made this trial unique. "EMERALD was a registrational trial," he explained. "It took treatment-experienced patients [who] were on a stable regimen [with a] boosted PI, along with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). It was a rather large trial, with over 1150 patients. [That] was unique. [In] normal switch trials where you take stable patients, virologically suppressed, usually in their background, they've always been virologically suppressed, they've always been taking their medication reliably. No virologic failures in some of these trials have been allowed. EMERALD actually took patients [who] perhaps had those prior failures [and who were] perhaps vulnerable to lapses in adherence. About 15% of these patients actually had prior antiretroviral (ARV) failures and about 7% had prior PI failures. The caveat was that they could not have had a prior darunavir failure.

"These patients were coming in with prior genotypes that showed no darunavir resistance; however, they could have had prior failures [and] other resistance and a multiplication of ARVs in their history," Dr. Huhn continued. "These patients were diagnosed a median of 9 years before entering the trial, [and] they had been started on antiretroviral therapy (ART) about 6 years prior to entering the trial, and so they were fairly heavily treatment-experienced patients. About 58% had multiple regimens before their stable regimen with FTC/TDF-boosted darunavir coming into the trial and about 25% had at least 7 or more ARVs in their background, and so [they were] a heavily treatment-experienced patient population that may have had prior resistance, which could speak to prior problems with adherence."

The results of the trial revealed that the virologic rebound rate in the D/C/F/TAF arm was 2.5% compared with 2.1% in the control arm. These results were consistent across gender, age, and race subgroups. Furthermore, "virologic response rates were similar for D/C/F/TAF (94.9%) and control (93.7%) in the total population and consistent across subgroups," according to Dr. Huhn. There was no resistance to the study drugs observed, and the overall rates of AEs—and subsequent discontinuations because of an AE—were not statistically significant across groups.

Dr. Huhn elaborated on these results, sharing that "the initial trial was presented at IDWeek in 2017, and it showed among this very large population very low levels of virologic failure: 2.5% in the patients [who] were switched to the single-tablet D/C/F/TAF versus 2.1% in those patients who remained on their stable, boosted-PI regimen. [We saw] very low rates of virologic failure and virologic rebounds during the 48 weeks for the primary outcome. [After doing a] post hoc analysis, looking at subsets of patients by age, gender, and race, [we found] very consistent results over 48 weeks, and very low levels of virologic rebounds as you slice and dice those subsets of patient populations.

"For example, about a third of those patients coming in were over 50, and again, they performed just as well as those younger than 50. [Similar results were seen across groups] by gender, as well as across black versus nonblack," Dr. Huhn said.

"There really wasn't anything surprising given the low failure rate of around 2.1% to 2.5% for both arms," he added. "In fact, even in the colorability profiles, looking at some urinary parameters, looking at small molecules that frequently filtered in the glomerulus, taken up in the proximal tubule, again, patients switched to TAF; those urinary markers, those biomarkers, actually decreased, showing preserved integrity of renal function. Bone mineral density increased a little bit in those patients [who] were switched to the D/C/F/TAF arm, given some of the properties in the TAF. Importantly, [there were] no virologic failures that would lead to resistance. There was 1 patient in the interventional arm D/C/F/TAF [who] was genotyped 'no ARV' resistance and 3 in the control arm [who] showed, again, no resistance."

Based on these results, the study investigators concluded that switching the treatment-experienced adults infected with HIV-1 to D/C/F/TAF "led to low rates of cumulative virologic rebound over 48 weeks that was overall non-inferior to the continuation of prior antiretroviral therapy." In addition, patients across all subgroups who received D/C/F/TAF experienced lower rebound rates and improved bone safety and renal function versus those patients in the control group.

When asked about the clinical significance of these results, Dr. Huhn shared, "Despite significant progress, there still remain clinical challenges in the patients with diverse backgrounds [who] may have had problems with adherence in the past or [who are] certainly at risk of drug resistance. I think the results here—the post hoc analysis, the data from EMERALD—speak to the real-life experiences that providers confront in treating different patient populations that have had different levels of experience. The drug is approved in Europe, but if it is approved here [in the United States], D/C/F/TAF offers a simplified, single-tablet regimen for providers to have at their disposal an option to either introduce this in treatment-naïve patients or switch patients [who] may be at risk for adherence factors that may lead toward drug resistance."

The drug, which is already in use in Europe, will be the first new boosted PI in a single-tablet regimen. As such, it offers another option for patients, both those who are treatment-naïve and those who are participating in the concept for rapid starts. As the World Health Organization advocates to start patients with newly diagnosed disease on ART within 1 week of diagnosis, Dr. Huhn shared that this drug, given the very high barrier of resistance of darunavir, would be an option for that patient, without having baseline genotype. Thus, practitioners would be able to start patients on a single-tablet regimen at the onset of diagnosis.

Janssen submitted its new drug application for D/C/F/TAF in September 2017 based on the results of the EMERALD and AMBER trials. Clinicians in the United States may potentially have access to this first-of-its-kind boosted PI single-tablet regimen by summer 2018. ▲

CROI 2018

Vaginal Microbiome May Influence Effectiveness of PrEP

BY KRISTI ROSA

(*continued from cover*)

Women face several challenges in the fight against HIV; however, the particular challenge that Dr. Klatt chose to address was a lack of understanding of how biological mechanisms influence transmission for the female reproductive tract.

Other factors typically associated with HIV transmission have already been studied, including the role of a damaged epithelial barrier (associated with inflammation), neutrophil infiltration, and, the focus of Dr. Klatt's presentation, an altered microbiome.

"The microbiome is the microorganisms in an environment. There are 10 trillion to 100 trillion microorganisms in each person, and a good anecdote that I like to give is that every adult has approximately 5 to 10 pounds of bacteria in the gastrointestinal tract," Dr. Klatt explained. "However, while we think of the microbiome as bacteria, it's not just bacteria, as it also includes things like viruses, fungi, protists, and archaea. Also, when we talk about the microbiome, it's not just the actual microorganisms; it's the genes that they have, the metabolites they make, and the other by-products that they may have made."

Although the most well-known microbiome is arguably the gut microbiome, Dr. Klatt zeroed in on the vaginal microbiome and how dysbiosis, which is highly associated with disease, could affect HIV transmission.

"A good microbiome, or a healthy microbiome, per se, would be *Lactobacillus* dominant. When we [look at] the single [bacterium] *Lactobacillus*, it's a very low pH, and it seems to be very protective," explained Dr. Klatt. "However, when we see this dysbiosis, we see a dominance of polymicrobial, mostly anaerobic bacteria; this is associated with increased pH, inflammation, and barrier damage, and it has been associated with transmission of several sexually transmitted infections." Essentially, the more diverse the microbiome is, the more anaerobes there are, and thus, the more dysbiotic it is.

The clinical diagnosis for microbiome dysbiosis is bacterial vaginosis (BV), which is detected by 1 of 2 tests: the Nugent score and Amsel criteria. Dr. Klatt stressed that "having a clinical diagnosis of BV does not necessarily mean that there is microbial dysbiosis, and having a microbial dysbiosis does not necessarily mean that that woman is clinically BV-positive."

The vaginal microbiome also varies across ethnicities. One study Dr. Klatt highlighted indicated that more *Lactobacillus* bacteria in the microbiome have been found in white women, whereas women of other ethnicities, such as black and Hispanic, have proved to have much more diverse dysbiotic communities. "This is why I hesitate, and I use quotes when I say 'healthy' or 'good' [microbiome] because we don't really know," she admitted. "Many women around the world have dysbiosis or these highly diverse communities, and so it may not necessarily be a bad thing; however, for HIV transmission it does seem to play a role."

Past research has shown that increased vaginal dysbiosis is highly prevalent in areas where rates of HIV infection in women are high. Dr. Klatt highlighted the differences seen in women's microbiomes between sub-Saharan Africa and North America to illustrate this point. In sub-Saharan Africa, where HIV prevalence is especially high, much fewer *Lactobacillus* bacteria are seen in the microbiome than with dysbiosis, whereas in North America it is the exact opposite.

"This becomes very important, as vaginal dysbiosis and BV status can increase HIV infection risk," Dr. Klatt stressed. She highlighted one study that found that in a group in which healthy *Lactobacillus* bacteria were present, there was no HIV infection risk, but as microbiome diversity increased, HIV risk also went up. Furthermore, the results of the study showed an increase in HIV infections in women with BV. "It's not just that women who have BV are at higher risk of HIV infection, but also, a man sleeping with a woman who has BV has a higher risk of HIV infection," she said. "There's also a higher risk of mother-to-child transmission with a woman who has BV."

Investigators are working to identify the mechanisms by which vaginal microbial dysbiosis increases HIV transmission. Some of these might include:

- **Inflammation,** which is known to be associated with HIV; vaginal microbial dysbiosis is also associated with inflammation.
- **Reduced epithelial barrier integrity** because of dysbiotic vaginal bacteria

Dr. Klatt encouraged investigators to take this understanding a step further to answer the question, Why might the vaginal microbiome affect the effectiveness of different clinical trials, such as those focusing on pre-exposure prophylaxis (PrEP)?

Although PrEP has proved to be about 80% to 90% effective in men, the range of effectiveness is much broader in women, anywhere from 50% to 75% effective. Although many of the variations noted in trials have been associated with adherence, Dr. Klatt suggested that biological factors may be influencing the effectiveness as well.

To study the influence of biological factors, Dr. Klatt and her team reviewed the results of the CAPRISA 004 trial, which studied the influence of a topical microbicide on tenofovir gel PrEP. The investigators found that the gel was 39% effective in reducing HIV infection in women. When looking at microbiome data, splitting the women into 2 groups (one dysbiotic with *Gardnerella* dominance and the other with *Lactobacillus* dominance), the effectiveness of the PrEP changed between the groups.

"What was really striking was that if you split these women up into *Lactobacillus* dominant versus non-*Lactobacillus* groups, suddenly the efficacy changed. Women with *Lactobacillus* in the vagina had an efficacy of 61% instead of 39%, and so the efficacy goes up," Dr. Klatt explained. "However, if you do not have *Lactobacillus* dominance of the vagina, your efficacy for tenofovir gel actually goes down to 18%, and so this was quite striking. We wanted to understand why the microbiome could be affecting the actual efficacy of the drug like this."

To study this, the team created an assay, which after some alterations found a direct correlation between infection rates in cells and the rate of degradation. "This indicates that the *Gardnerella* dysbiotic bacteria infection actually enhanced HIV infection, probably by metabolizing the tenofovir before it could actually affect the target cell," Dr. Klatt explained. Subsequent research looked at other PrEP drugs such as dapivirine and next-generation tenofovir alafenamide (TAF). For dapivirine, they found "a significant negative association between how much *Lactobacillus* is in each sample and the rate of degradation of dapivirine," which could "potentially explain some of the differences of efficacy in women [who] were in the dapivirine trials."

No differences in diversity were found with TAF, and there was no TAF degradation.

"Dysbiosis of vaginal bacteria is a key factor in vaginal inflammation, epithelial barrier integrity, and HIV acquisition. Dysbiotic bacteria can metabolize the PrEP drugs tenofovir and dapivirine and potentially contribute to decreased PrEP efficacy in vivo," Dr. Klatt concluded. "Importantly, TAF is not degraded by vaginal bacteria, and so this needs to be taken into consideration for more efficacious PrEP. We are also trying to assess other drugs and determine which drugs are the least metabolizable for the bacteria."

Her research underscores the need to better understand the role of the vaginal microbiome in HIV and highlights the need to find a way to increase *Lactobacillus* communities to prevent BV as well as dysbiosis recurrence; this is crucial for improving drug efficacy. ▲

47th Critical Care Congress

CDC Finds Decrease in Incidence of ICU Bacteremia

BY *CONTAGION*® EDITORIAL STAFF

The results of a new analysis have revealed that incidence of intensive care unit (ICU) bacteremia is decreasing over time. The study was presented at the 47th Critical Care Congress, which took place February 25-28, 2018, in San Antonio, Texas.

According to the US Centers for Disease Control and Prevention, between 2008 and 2014, there was a 50% decrease in central line–associated bloodstream infections (CLABSIs) in the United States. Furthermore, long-term acute care hospitals saw a 9% decrease in CLABSIs.

In 2008, the Centers for Medicare & Medicaid Services began to tie reimbursement with incidence of CLABSIs and other hospital-acquired conditions as incentive to reduce their rates. Trends can be seen between incidence of CLABSIs and blood culture ordering practices, so investigators from the National Institutes of Health, Harvard Medical School, and Commonwealth Informatics Inc set up a study to better understand these relationships.

Using Cerner Health Facts database data from 2009 through 2013, the investigators identified "ICU stays spanning ≥3 days in adult (≥20 years) patients admitted to US hospitals," according to the study. The investigators used *International Classification of Diseases, Ninth Revision* codes listed in the database to identify those patients who were given a central venous catheter (CVC). Microbiology data were used to identify those patients who had blood culture (BC) orders as well as whether a bloodstream infection (BSI) was present.

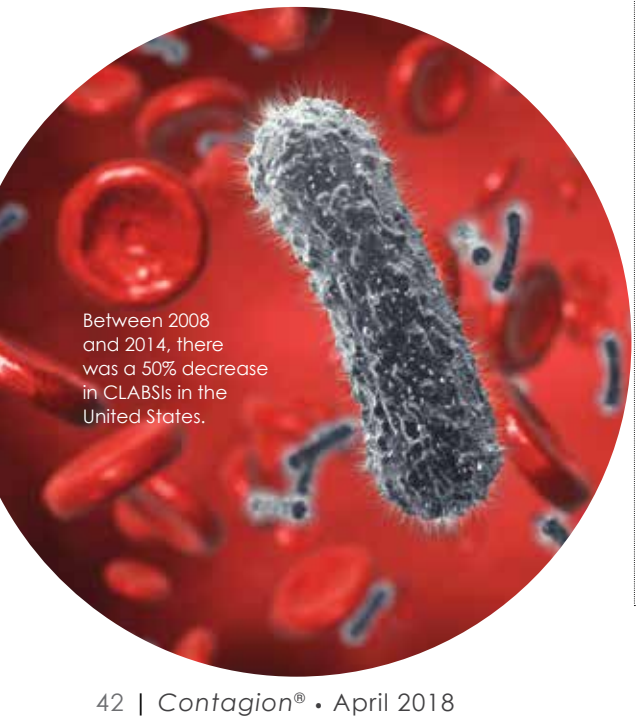
"CVC stays (CVC placed ± 1 day of ICU admission) were 1:1 matched to non-CVC stays (no CVC during hospitalization) on institution, age, admit year and ICU type, ICU admission Sequential Organ Failure Assessment (SOFA) score and ICU length of stay (LOS)," the study authors wrote.

A case of CLASBI was identified as a CVC case having 1 or more positive noncontaminant BCs between day 3 of the patient's ICU stay and discharge. Additionally, according to the authors, "adjusting for BC ordering trends over time, the adjusted Annual Percent Change (aAPC; 95% CI) in CLABSI versus non-CVC BSI cases over the 5-year period was calculated using Poisson regression separately for all hospitals and those reporting data for all 5 years."

A total of 9022 matched-encounter pairs were identified across 63 hospitals over 5 years from a total of 10,599 overall CVC cases and 35,790 non-CVC cases. The matched-encounter patients had a median age of 65 (range 54 to 76), a SOFA score of 4 (range 2 to 7), and LOS in the ICU of 6 days (range 4 to 9). Septicemia, acute respiratory failure, and pneumonia were the most frequent diagnoses among both matched-CVC and non-CVC patients.

The frequency of BC ordering "decreased comparably in CVC (APC = −4.1% [range −5.9% to −2.3%]) and non-CVC cases (APC = −4.4% [range −6.3% to −2.5%]); P = .81," according to the study authors. "After adjusting for the changing trend in BC ordering, CLABSI incidence decreased over time (aAPC = −5.8% [range −8.0% to −3.6%]), albeit at a rate that was comparable to non-CVC BSI (aAPC = −5.8% [range −8.1% to −3.4%]); P = .97. Similar trends in CLABSI (aAPC = −5.5% [range −8.0% to −3.0%]) and non-CVC BSI (aAPC = −4.7% [range −8.1% to −1.3%]; P = .77) were observed at 17 continuously reporting hospitals as well."

Although the reason why fewer cultures are being drawn in ICU patients is not known, the authors found a decrease across the board, in both CVC and non-CVC patients. Likewise, comparable decreases were seen in CLABSIs and non-CVC BSIs. ▲



Between 2008 and 2014, there was a 50% decrease in CLABSIs in the United States.

47th Critical Care Congress

Procalcitonin-Guided Antibiotic Cessation Reduces Mortality

BY *CONTAGION*® EDITORIAL STAFF

(*continued from cover*)

in patients with lower respiratory tract infections and ceasing treatment in patients with sepsis Most meta-analyses of this research have looked at the combined effects of PCT-guided therapy across all aspects of antibiotic management: initiation, cessation, and a combination of the 2. However, investigators from the Cleveland Clinic in Cleveland, Ohio, and Sunnybrook Hospital in Toronto, Ontario, took it a step further, performing a meta-analysis evaluating PCT-guided strategies during different phases of antibiotic management and focusing on the cessation of antibiotics stage. The results of the study were presented at the 47th Critical Care Congress, which took place February 25-28, 2018, in San Antonio, Texas.

For the analysis, the investigators first performed a systematic review that identified "randomized control trials evaluating PCT compared to usual care for the management of antibiotic therapy in critically ill patients," according to the abstract of the study. The primary outcome was short-term mortality (hospital mortality or mortality within 30 days). The investigators set the secondary outcomes as duration of antibiotic therapy, long-term mortality (60-100 days), hospital and intensive care unit length of stay, and the presence of recurrent infections.

A meta-analysis was performed for each outcome if the investigators found at least 3 studies in any of the PCT subgroups, thus providing sufficient data. "Random or fixed effects models were used as appropriate," the authors wrote.

A total of 1624 abstracts were identified, 15 of which were included: 3 on using PCT to guide initiation of antibiotic therapy, 9 on using it to guide cessation of the therapy, and 3 on using a combination of the 2 strategies.

The results revealed that the pooled odds ratio for short-term mortality for initiation PCT strategy was 0.99 (95% CI, 0.81-1.22; P = .96), 0.83 (95% CI, 0.70-0.97; P = .02) for cessation PCT strategy, and 1.02 (95% CI, 0.72-1.43; P = .93) for a mix of the 2 PCT strategies. Using PCT for cessation of antibiotic therapies and the combination of strategies resulted in a decrease in antibiotic duration at −1.26 days (P<.001) and −3.10 days (P = .04), respectively. Differences were not observed for the secondary outcomes.

Further research is needed to focus specifically on PCT-guided antibiotic cessation in critically ill patients; however, this analysis shows that the strategy resulted in reduced mortality in this population of patients. ▲

47th Critical Care Congress

SEP-1 Bundle Compliance Leads to Reduced Readmissions

BY DANIELLE MROZ, MA

(*continued from cover*)
Septic Shock (SEP-1) performance measure compliance and hospital readmission. The results of the study were presented at the 47th Critical Care Congress, which took place February 25 to 28, 2018, in San Antonio, Texas.

For the study, patients who were admitted to 1 of 12 hospitals in a single health system between October 2015 and May 2017 "with administrative coding for sepsis during their index hospital admission, were evaluated for SEP-1 eligibility," the study authors wrote. Those patients identified for the measure population were designated as either passing or failing SEP-1. The specific element of the bundle that led to the failure was also identified and recorded, with the most frequent element that lead to failure as initial lactate collection. Status of 30-day readmission was evaluated for those patients who survived the index hospitalization.

A total of 1986 patients were coded for sepsis during the study period, of which 87.1% (n = 1729) were eligible for the SEP-1 measure. Thirty-four percent (n = 596) of those patients passed SEP-1, and 90.3% (n = 1561) survived index hospitalization. The investigators found that survival was higher in those patients who passed SEP-1 than in those who failed SEP-1 (94.8% vs 87.9%; P<.01). Furthermore, according to the investigators, "readmission for index admission survivors was common (23.4% overall) and differed by facility (range 4.5% to 33.3%; P <.01)." Those patients who survived index hospitalization and passed SEP-1 bundle were readmitted less frequently than those who survived but failed SEP-1 (20.4% vs 25.1%, P = .03).

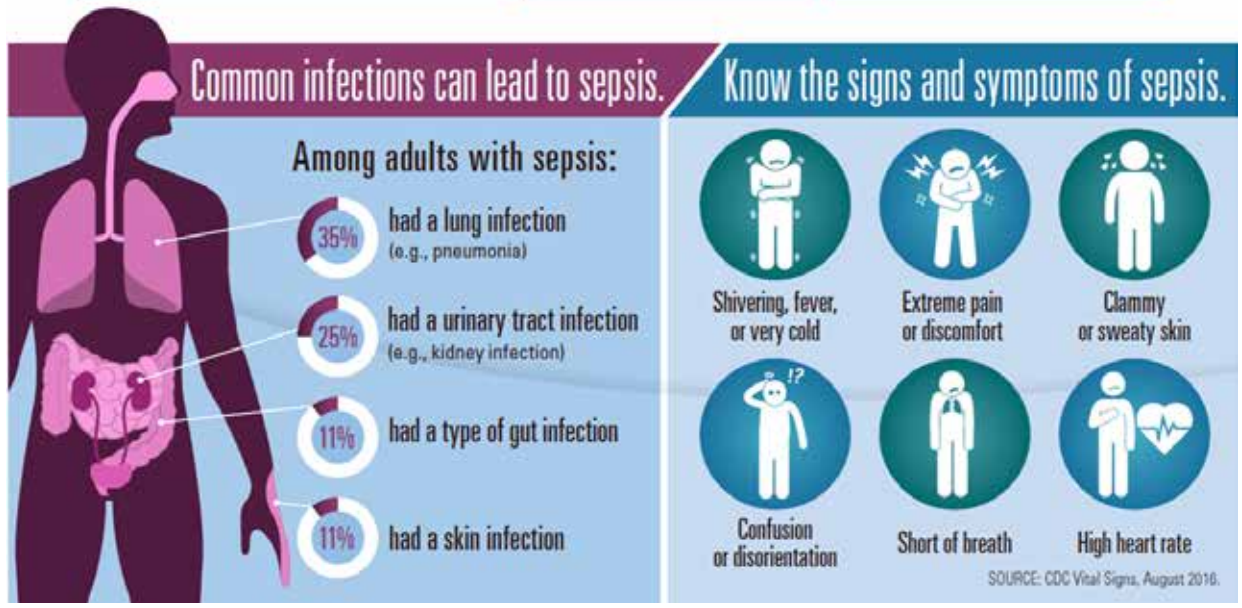
The investigators did not find an association between readmission and compliance with individual elements of the SEP-1 bundle (all P>.45); however, SEP-1 compliance was found to be independently associated with lower odds of readmission (odds ratio 0.73; 95% CI, 0.56-0.94; P = .02), after adjusting for facility with multivariable logistic regression.

The authors acknowledged that the main limitation of the study is that the data are from 1 health system. Although it is a large health-system with hospitals that represent several types seen across the United States, it is unclear if these data are similar at other health-systems. "Additionally, we were only able to account for hospital re-admissions within our health-system," commented co-author Seth R. Bauer, PharmD, FCCM, FCCP, BCPS, BCCCP, Critical Care Clinical Coordinator and Medical Intensive Care Clinical Pharmacist at Cleveland Clinic in Cleveland, Ohio, to *Contagion*®. "Most frequently patients return to our health-system, but not always. Thus, the number of re-admissions in each group may be under-represented."

Based on those results, the investigators concluded that SEP-1 bundle compliance was associated with lower odds of hospital readmission and, as such, may be an appropriate targeted intervention to reduce readmissions. According to Dr. Bauer, in the future, the team "plans to evaluate data in a larger sample in order to try to evaluate the contribution of individual SEP-1 bundle failure elements."

Interestingly, a systematic review published in the *Annals of Internal Medicine* this year reported that there is no high- or moderate-level evidence indicating that SEP-1 bundle compliance is associated with improved survival of adults with sepsis.[3]

SEPSIS FAST FACTS FROM THE CDC

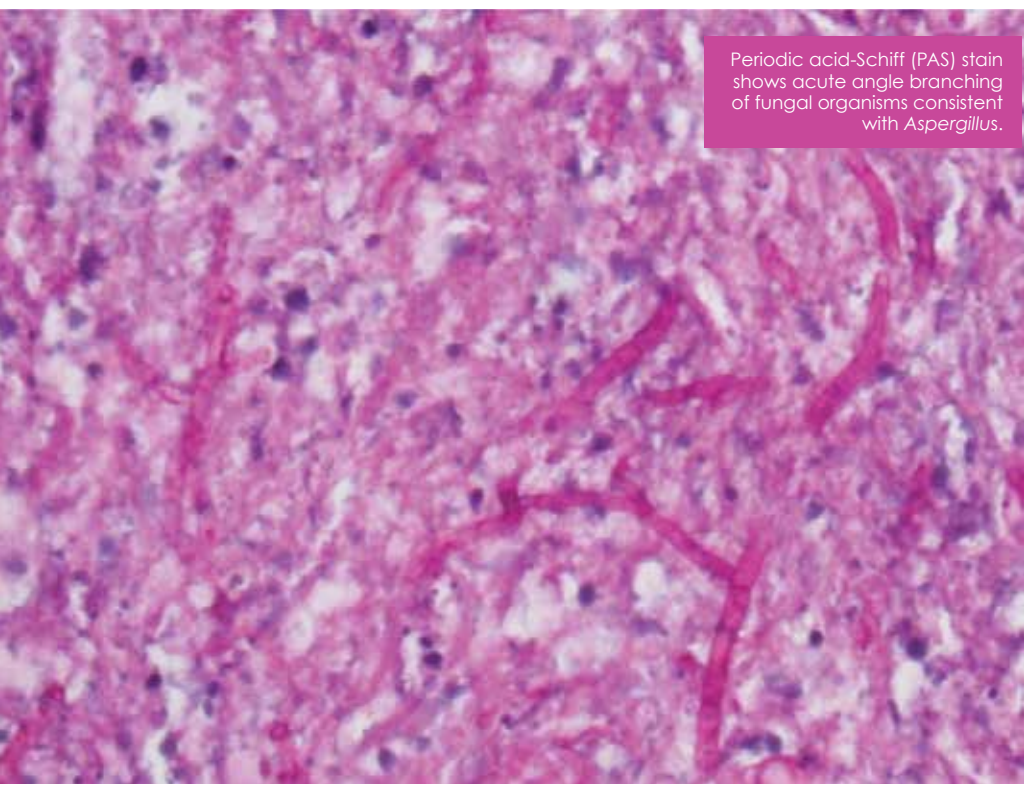


For the study, investigators searched bibliographic databases such as PubMed and clinicaltrials.gov for "randomized and observational studies of death among adults with sepsis who received versus those who did not receive either the entire SEP-1 bundle or 1 or more SEP-1 hemodynamic interventions, including serial lactate measurements; a fluid infusion of 30 mL/kg of body weight; and assessment of volume status and tissue perfusion with a focused examination, bedside cardiovascular ultrasonography, or fluid responsiveness testing [that were published] from inception to November 28, 2017," according to the study authors. "High- or moderate-level evidence required studies to have no confounders and low risk of bias."

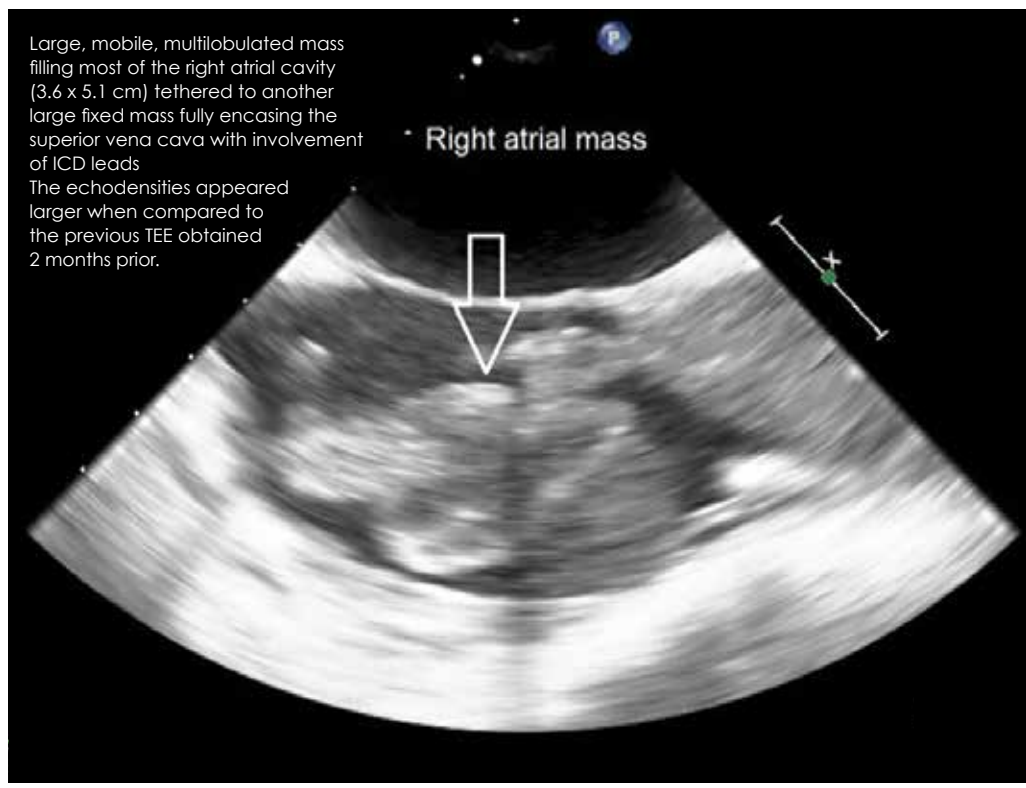
Of 56,563 references, only 20 studies met the inclusion criteria. Furthermore, only 1 single-center observational study found that lower in-hospital mortality was seen after implementing the SEP-1 bundle. A total of 16 studies (2 randomized, 14 observational) "reported increased survival with serial lactate measurements or 30-mL/kg fluid infusions," according to the study authors. "None of the 17 studies were free of confounders or at low risk of bias. In 3 randomized trials, fluid responsiveness testing did not alter survival."

The study is not without limitations, including the fact that the 2015 version of the SEP-1 was used in addition to the 2013 version of Centers for Medicare & Medicaid Services evidence criteria. Both of these were updated in 2017. ▲

Section Editor:
SARA SCHULTZ, MD



Periodic acid-Schiff (PAS) stain shows acute angle branching of fungal organisms consistent with *Aspergillus*.



Large, mobile, multilobulated mass filling most of the right atrial cavity (3.6 x 5.1 cm) tethered to another large fixed mass fully encasing the superior vena cava with involvement of ICD leads
The echodensities appeared larger when compared to the previous TEE obtained 2 months prior.

The Case of Late *Aspergillus Fumigatus* Infection of Implantable Cardioverter Defibrillator Leads

Quick action was needed against this very rare cause of fungal endocarditis.

BY ELIZABETH GANCHER, MD; JOHN CHAN, MD; GRACE MINAMOTO, MD; AND JACK JACOB, DO

HISTORY OF THE PRESENT ILLNESS

A 63-year-old male presented with persistent daily chills, lethargy, weakness, dyspnea on exertion, and weight loss for 2 months.

The patient had a recent admission, 2 months prior to presentation, for swelling over his implantable cardioverter defibrillator (ICD) site. At that time, purulent fluid from the ICD pocket was aspirated. Work-up of the specimen revealed <1 plus gram-variable bacilli and <1 plus yeast-like structures. The culture of the purulent fluid did not reveal any organisms, and multiple blood cultures were negative. A transesophageal echocardiogram (TEE) at the time showed a large clot in the superior vena cava and multiple mobile masses in the right ventricle, which were tethered to the ICD leads. These masses were thought to be thrombi, tumor, or vegetations. A biopsy of a superior vena cava mass was performed. Histological examination of the specimen showed acute inflammation and possible bacterial forms, but cultures did not reveal any pathogens. The patient was treated with a 7-day course of vancomycin, piperacillin/tazobactam, and micafungin, and he was discharged home. The patient returned to the cardiology clinic for a visit 2 months later and was found to have a low hemoglobin. He complained of persistent chills, lethargy, and dyspnea on exertion, and so was instructed to return to the hospital.

PAST MEDICAL HISTORY

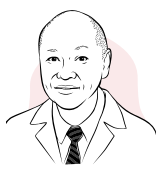
Severe pericardial effusion of unknown etiology treated with pericardial window, 5/2014; chronic systolic heart failure secondary to ischemic cardiomyopathy, with placement of dual-coil ICD for primary prevention of arrhythmia, November 20, 2007; myocardial infarction status post stent to left anterior descending coronary artery, July 26, 2007; hypertension, cardiac anterior wall aneurysm with apical clot status post a course of warfarin, 2003; left subclavian steal syndrome and superior vena cava narrowing, 2003; lung cancer in remote past with resection of right upper lobe.

ELIZABETH GANCHER, MD

Dr. Gancher is an assistant professor of medicine in the Division of Infectious Diseases & HIV Medicine at Drexel University College of Medicine where she is also the Director of Antimicrobial Stewardship. She completed a fellowship in infectious diseases at Albert Einstein College of Medicine & Montefiore Medical Center in Bronx, New York.

JOHN CHAN, MD

Dr. Chan is a professor in the Department of Medicine (Infectious Diseases) and Microbiology and Immunology at Albert Einstein College of Medicine in Bronx, New York.



GRACE MINAMOTO, MD

Dr. Minamoto is an associate professor in the Department of Medicine (Infectious Diseases) at Albert Einstein College of Medicine in Bronx, New York.

MEDICATIONS

Aspirin, carvedilol, warfarin, simvastatin.

ALLERGIES

No known drug allergies.

EPIDEMIOLOGICAL HISTORY

Patient was born in Korea, immigrated to the United States more 20 years ago, and has traveled back to Korea several times since then. He has not traveled to any other countries. Has worked

Images contributed by Jack Jacob, DO.

as owner of laundromat in Bronx, New York, for past 20 years. No history of intravenous drug use, no other illicit drug use. Social alcohol use. Ten pack a year history of smoking, quit 15 years ago. He has no pets and reports no animal exposure.

PHYSICAL EXAMINATION

The patient appeared chronically ill and fatigued. Blood pressure was 86/52 mm Hg, pulse 50 beats per minute, temperature 102.7°F, respirations 20 breaths per minute. Cardiac exam showed normal S1 and S2, regular rate and rhythm with a II/VI systolic murmur. Chest exam showed ICD in place at the left chest wall, without any warmth, edema, induration, or tenderness. Lungs were clear. Lower extremity exam showed trace edema.

STUDIES

Labs showed normal renal and liver function. Leukocyte count was 10.9 k/uL (normal range 4.8-10.8 k/uL) with 87% neutrophils; hemoglobin was 8.1 g/dL (normal range 14-17.4 g/dL); and hematocrit was 24.7% (normal range 41.5%-50.4%). The C-reactive protein was elevated at 8.4 mg/dL (normal range 0.0-0.8 mg/dL) and the erythrocyte sedimentation rate was 140 mm/hr (normal range 0-20 mm/hr). Multiple blood cultures were obtained off antibiotics and antifungals and showed no growth.

Repeat TEE showed a large, mobile, multilobulated mass filling most of the right atrial cavity (3.6 x 5.1 cm) tethered to another large fixed mass fully encasing the superior vena cava with encasement of ICD leads. The echodensities appeared larger when compared with the previous TEE obtained 2 months prior.

DIAGNOSTIC PROCEDURES AND RESULTS

The patient underwent removal of the superior vena cava mass. In addition, the superior vena cava was debrided and reconstructed, and the ICD and leads were removed.

Pathology of the superior vena cava wall showed foci of necrosis with acute and chronic inflammation. Grocott-Gomori methenamine silver staining of the specimen revealed, within the foci of necrosis, fungal organisms which were morphologically consistent with *Aspergillus*, displaying septate hyphae with branching at an acute angle. This histopathological appearance was consistent with the diagnosis of angioinvasive aspergillosis. Cultures of the surgical specimens were unrevealing.

A sample was sent to the University of Washington, where a polymerase chain reaction targeting *Aspergillus fumigatus* came back positive. At the time of diagnosis and before the initiation of antifungal therapy, a serum sample for (1,3)-beta-D-glucan assay was found to be 418 pg/ml (Viracor-IBT Laboratories, Lee's Summitt, MO; negative <60 pg/ml), while a serum *Aspergillus galactomannan* enzyme immunoassay was .149 optical density index (ODI) (Platelia Aspergillus ELISA, Bio-Rad, Hercules, CA) (normal cut-off <.5 ODI).

TREATMENT/FOLLOW-UP

The patient did well postoperatively and was discharged home on oral voriconazole. His ICD was re-implanted after 5 months of voriconazole therapy. The patient's symptoms completely resolved and he was continued on voriconazole for 1 year, with (1,3)-beta-D-glucan assay after 1 year of therapy found to be negative at 56 pg/ml. Voriconazole was stopped after 1 year of therapy with plans for quarterly assessment of (1,3)-beta-D-glucan and clinical monitoring.

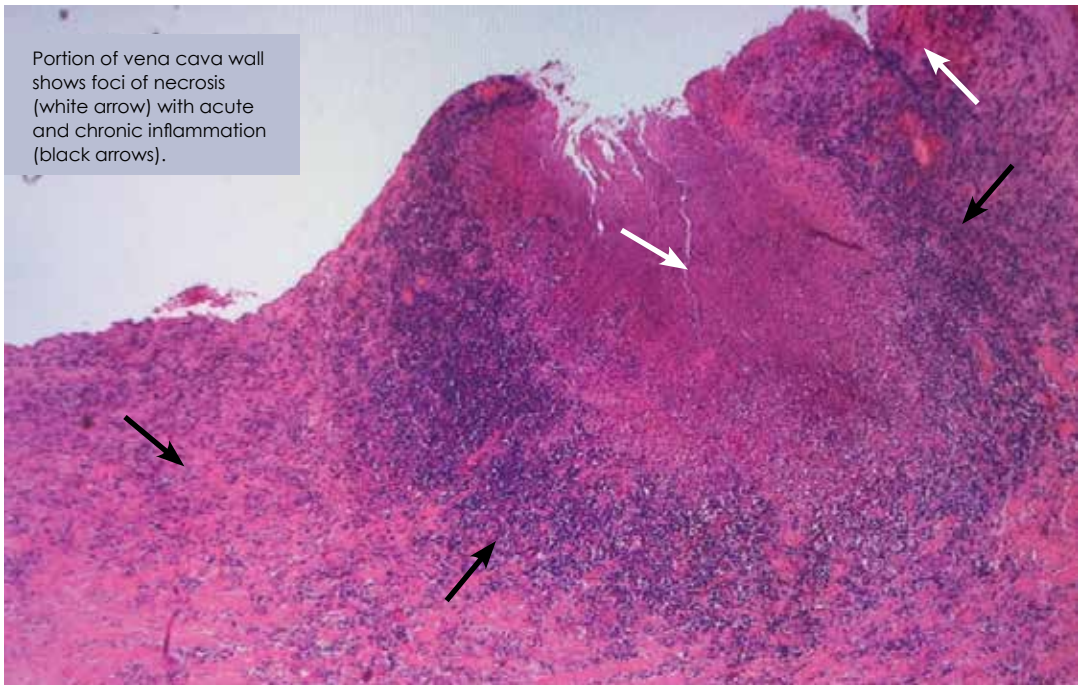
DISCUSSION

Fungal endocarditis is associated with a high mortality rate, and survival depends on early diagnosis and treatment. *Aspergillus* is a very rare cause of fungal endocarditis. A recent review of all case report between 1950 and 2010 identified 53 cases of *Aspergillus* endocarditis. A total of 57% of cases had fever at presentation, and 53% had evidence of embolic disease. Blood cultures were almost always negative.[1] To help establish diagnosis, (1,3)-beta-D-glucan may be a useful adjunctive test, but it has not been studied in *Aspergillus* endocarditis.

Infections account for <2% of the complications associated with cardiovascular implantable electronic devices, and only about 2% of these are secondary to a fungal pathogen.[2] The first case of *Aspergillus* infection of a transvenous pacing lead was reported in the 1980s, and a limited number of cases have been documented in the literature since then.[3] A review of the published cases showed that common risk factors include immunosuppression, long-term antibiotic or corticosteroid use, diabetes mellitus, heart failure, chronic kidney disease, prolonged hospitalization, and cardiothoracic surgery.[4] TEE is the most accurate diagnostic test and is superior to transthoracic echocardiography for detecting vegetations on transvenous pacemakers or ICDs.[5]

The recommended antifungal for most invasive *Aspergillus* infections, including endocarditis, is voriconazole.[6] There is no consensus on duration of treatment of ICD *Aspergillus* infection, but there is agreement that treatment is rarely successful unless the entire device is removed. Lifelong antifungal prophylaxis has been advocated in many series based on prior experience with *Aspergillus* native valve endocarditis, where late recurrent fungal endocarditis is common.[7] ▲

References available at ContagionLive.com.



Portion of vena cava wall shows foci of necrosis (white arrow) with acute and chronic inflammation (black arrows).

Grocott's Methenamine Silver stain demonstrating widespread aspergillosis infiltration.

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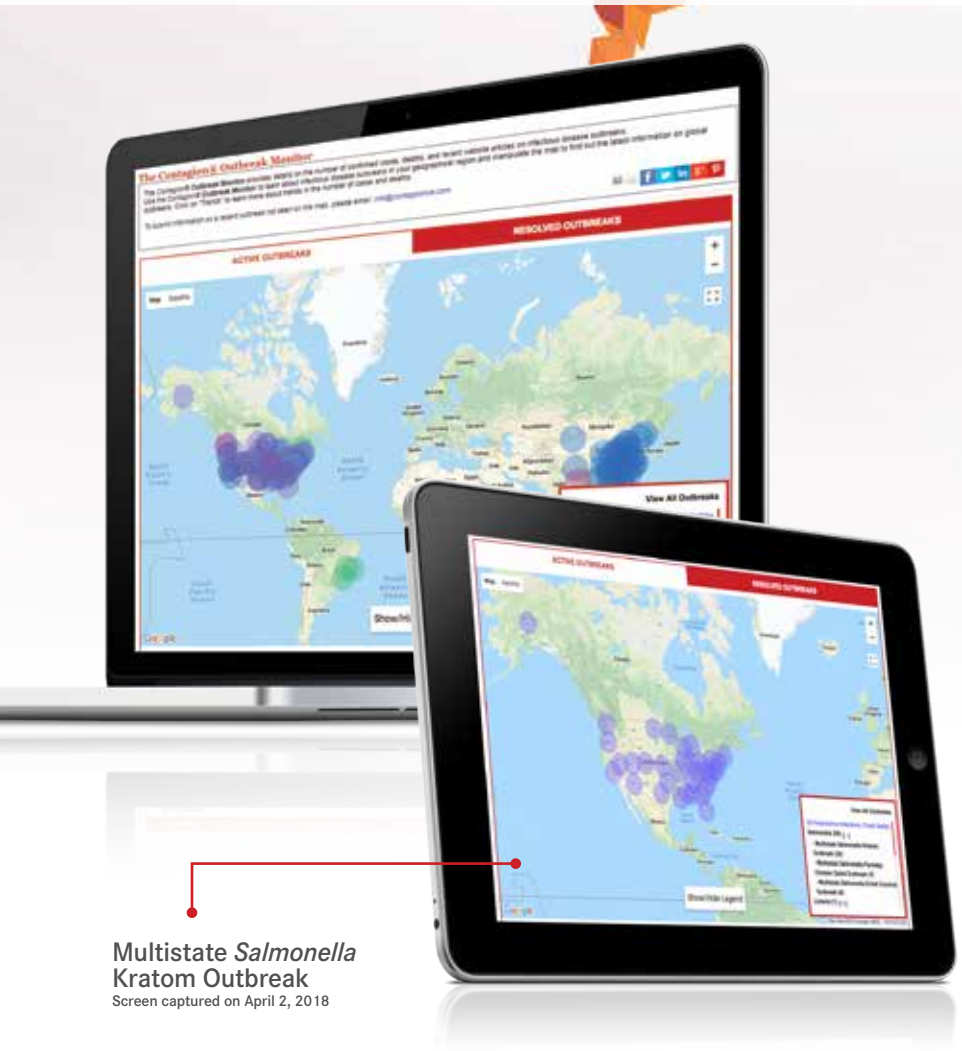

Multistate *Salmonella* Kratom Outbreak
Screen captured on April 2, 2018

This global **Outbreak Monitor** allows users to visualize occurrences of infectious diseases, such as **Zika** and **Hepatitis A** on a local, regional, national, and international level. The monitor also tracks trends and details on confirmed cases and deaths, matched with recent coverage related to each outbreak. Use the ***Contagion*® Outbreak Monitor** to learn about infectious disease outbreaks in your geographical region, and manipulate the map to find out the latest information on global outbreaks.

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