IAS 2017
As HIV Drug Resistance Grows, WHO Calls for Global Action

In a statement released on July 20, 2017, the World Health Organization (WHO) alerted countries around the world to the growing threat of resistance to HIV drugs. WHO learned of this alarming trend through national surveys, and the results were presented in the organization’s HIV Drug Resistance Report 2017.

“Six of the 11 countries surveyed in Africa, Asia, and Latin America showed that over 10% of people starting antiretroviral therapy had a strain of HIV that was resistant to some of the most widely used HIV medicines,” according to the report. Once these countries reach a threshold of 10%, WHO advises that they should “urgently review their HIV treatment programs.”

Tedros Adhanom Ghebreyesus, MD

HIV-Infected Child Maintains Remission Without ART Since 2008

Although progress has been made in reducing the number of new HIV infections among children aged 0 to 14 years, the number infected annually on a global scale (see Table) is still “unacceptably high,” according to investigators presenting at the 9th International AIDS Society (IAS) Conference on HIV Science in Paris, France in June 2017. Investigators are hopeful that these children may be spared the lifelong burden of therapy and the associated immune health consequences.

This hope comes in the form of a 9-year-old South African child who received a diagnosis of the virus at just 1 month of age. The child received early antiretroviral therapy (ART) during infancy, achieved viral suppression, and has maintained remission.

HEALTH CARE-ASSOCIATED INFECTIONS
Is Greater BSA Use for Sepsis, Bacteremia Affecting HO-CDIs?

By Alyssa B. Christensen, PharmD, and Viktorija O. Barr, PharmD, BCPS-AQ ID

Clostridium difficile infections (CDIs), which were responsible for over 500,000 infections and 44,000 deaths in 2014, represent a substantial burden to patients and our health care systems. The rate of CDI is higher among hospitalized patients in part because of the higher rate of extrinsic risk factors in this population, such as broad-spectrum antibiotic (BSA) use. BSAs are commonly used in the health care setting for empiric treatment of suspected infections.

(continued on page 27)

ASM Microbe 2017
Beta-Lactams: Do They Deserve a Second Look?

Is it time to reassess prescribing practices on beta-lactams for patients with penicillin allergies? The answer is an unquestionable “Yes!” according to Meghan Jeffres, PharmD, assistant professor in the Department of Clinical Pharmacy at the University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, in Aurora, Colorado.

Dr. Jeffres spoke about the issues that penicillin allergies present to healthcare investigators from all over the world who came together to share recent research that could help the field get a leg-up on infectious diseases. Unfortunately, it is also the home to a severe ongoing hepatitis A outbreak that has infected a staggering 481 individuals thus far, leaving health officials scrambling.

In light of the outbreak, Monique Foster, MD, MPH, from the Division of Viral Hepatitis at the Centers for Disease Control and Prevention (CDC), and Eric McDonald, MD, MPH, from the Epidemiology and Immunization Services Branch of the San Diego County Health and Human Services Agency, discussed the “surprising return” of the virus as part of the “Late Breakers I” symposium at the conference.

(continued on page 28)

About 10% of US Patients With Candidemia Have CDI Coinfection

Of Americans hospitalized for treatment of candidemia, Clostridium difficile (C. difficile) coinfection was present in almost 10% of the cases. Infections caused by C. difficile and Candida species are important health care-associated infections. A multi-state survey carried out in 2014 by the Centers for Disease Control and Prevention (CDC) reported C. difficile and Candida in 61 of 504 (12.1%) and 32 of 504 (6.3%) infections, respectively, with C. difficile responsible for 70% of all recorded gastrointestinal infections and Candida responsible for 22% of all bloodstream infections. Both infections carry a high mortality rate. The root of Candida-C. difficile coinfection was discussed.

(continued on page 30)
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Reassessing Practices Is Critical During an Infectious Disease Outbreak

As global public health officials focus on the growing pneumonic plague outbreak in Madagascar,\(^1\) the ongoing hepatitis A virus (HAV) outbreak in San Diego, California, is a glaring reminder that infectious disease outbreaks can occur even in the United States. As of October 19, 2017, more than 600 individuals have been infected with HAV and 19 have died. California Governor Jerry Brown underscored the severity of the outbreak when he declared a state of emergency on October 13, 2017, to free up funding to respond to the outbreak and stop it from spreading. The outbreak has become so critical that it warranted a late-breaker presentation by experts from the Centers for Disease Control and Prevention and the California Department of Health at this year’s ID Week conference. Vaccinations are essential to the prevention effort as is the reassessment of practices that may not be working, such as infection control and sanitation measures, which have since been reworked to be more effective. A summary of the findings and efforts that are underway to combat the epidemic can be found on page 31.

As an entrepreneur, the constant reassessment of business practices is necessary to ensure that practitioners are not wasting valuable time, resources, and effort on activities that are not producing the desired results. Such can be seen in the health care field, too, and our feature article on page 18 focuses on a reassessment of the empiric use of broad spectrum antibiotics in patients with bacteremia and sepsis to decrease the risk of *Clostridium difficile* (*C. difficile*) infection. The increased use of broad-spectrum antibiotics has resulted in higher rates of hospital-onset *C. difficile* infections. These infections and the growing incidence of infections in the community setting have contributed to more severe infections and the emergence of hypervirulent strains of the bacterium with fatal complications. These reasons led Alyssa B. Christensen, PharmD, and Viktorija O. Barr, PharmD, BCPS-AQ ID, to urge practitioners to focus on the use of broad-spectrum antibiotics in these patient populations.

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Stay informed, and thanks for reading!

Mike Hennessy, Sr
Chairman and CEO

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**Additional Resources**

- **New-Generation Cephalosporins**
  pharmacytimes.com/link/172

- **What Do Pharmaceuticals Really Cost in the Long Run?**
  ajmc.com/link/2787

- **DAAs Proves Capable for HCV-Infected Heart Transplant Patients**
  mdmag.com/link/1742
HEALTH CARE-ASSOCIATED INFECTIONS

FEATURE

Is Greater BSA Use for Sepsis, Bacteremia Affecting HO-CDIs?

An examination of broad-spectrum antibiotic use in this patient population is essential for developing strategies to mitigate the risk of these infections.

BY ALYSSA B. CHRISTENSEN, PHARMD, AND VIKTORIJA O. BARR, PHARMD, BCPS-AQ_ID

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Probiotic Proves Deadly Against *Clostridium Difficile*

By Einav Keet

In the fight against bacterial pathogens, investigators are finding new weapons in “good” bacteria, as results from a new study suggest that probiotics may be used to kill dangerous *Clostridium difficile* (*C. difficile*) bacteria.

According to the Centers for Disease Control and Prevention (CDC), the United States sees nearly 500,000 *C. difficile* infections each year. The superbug is 1 of the biggest drug-resistant threats plaguing the country’s health care system, killing an estimated 14,000 individuals each year and costing about $1 billion annually in medical expenses. *C. difficile* infections typically occur in individuals who have recently taken antibiotics to fight another infection, as the antibiotics kill the beneficial bacteria in the gut and thus make patients more susceptible to infection if they come into contact with contaminated surfaces. *C. difficile* spores can also be spread by health care workers’ hands. The pathogen leads to inflammation in the colon, and symptoms of an infection include watery diarrhea, fever, nausea, and loss of appetite; such infections are becoming increasingly drug resistant and recurrent.

In addition, more than 80% of deaths caused by *C. difficile* infections occur in adults who are 65 or older.

In a new study published in the journal *Infection and Immunity*, investigators from Baylor College of Medicine examined how next-generation probiotics can be used along with antibiotics to fight *C. difficile*. The study team identified the probiotic *Lactobacillus reuteri* as a candidate for adjunct therapy to be used with antibiotics such as vancomycin, metronidazole, and fidaxomicin against *C. difficile*.

“We wanted to find an alternative treatment, a prophylactic strategy based on probiotics that could help prevent *C. difficile* from thriving in the first place,” said the study’s lead author, Jennifer Spinler, PhD, in a recent news release.

The investigators studied the effects of *L. reuteri* on *C. difficile* grown in a laboratory and found that when the probiotic was supplemented with glycerol, it converted it into the broad-spectrum antimicrobial compound reuterin. The reuterin acted as an antimicrobial agent and worked as well as vancomycin to inhibit *C. difficile* growth. In addition, the investigators found that glycerol or *L. reuteri* alone were not effective against *C. difficile* and that the reuterin did not harm the good bacteria in the complex gut community.

“Probiotics are commonly used to treat a range of human diseases, yet clinical studies are generally fraught by variable clinical outcomes, and protective mechanisms are poorly understood in patients,” explained senior author Tor Savidge, PhD. “This study provides important clues [to] why clinical efficacy may be seen in some patients treated with 1 probiotic bacterium but not with others.”

While the results are preliminary, the authors noted that their findings suggest that the combination of *L. reuteri* and glycerol could be used as a novel treatment against *C. difficile* infections as well as preventively in patients before they receive antibiotics. The new study is part of a growing body of research supporting the use of beneficial bacteria against antibiotic-resistant pathogens as an alternative to antibiotic drugs.

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**Zika Virus May Persist in Semen Less Than 6 Months**

By Contagion® Editorial Staff

Zika may not survive in semen as long as investigators have previously thought. Although earlier reports indicated that the virus may persist in semen for up to 188 days, a new study, recently published in the *New England Journal of Medicine*, is disputing that finding, instead providing evidence that the Zika virus lasts in semen for only about a month.

In the new study, investigators from the Military Center for Epidemiology and Public Health in Marseille, France, looked at semen and blood samples from 12 men in French Guiana who were infected with the Zika virus. The results of the study indicated that 1 man excreted Zika virus in his semen for at least 3 days, and 7 men had Zika-laced semen for at least a month. The maximum duration of detectable semen was 45 days, according to a press release. In addition, the investigators discovered that the virus is able to replicate in the testicles and semen-producing glands. This was determined because the viral load detected in the men’s blood was significantly different from that in their semen.

“These data suggest that not all men who are symptomatically infected with Zika virus will have Zika virus RNA detectable in semen,” study author Franck de Laval, MD, and colleagues wrote. “[However,] more data are needed to better inform public health recommendations.” The current Centers for Disease Control and Prevention (CDC) recommendations state that men with pregnant partners should use condoms or abstain from sex for the duration of the pregnancy. Men with partners who are not pregnant but are planning to become pregnant should wait at least 6 months post exposure to the Zika virus or visiting Zika-endemic areas before trying to conceive. In the press release, Daniel Caplivski, MD, director of the Travel Medicine Program and associate professor in the Division of Infectious Diseases at the Icahn School of Medicine at Mount Sinai in New York, New York, stated that the CDC guidelines are unlikely to change after this report. “Unfortunately, the fundamental recommendations of public health experts regarding delaying pregnancy after Zika virus infection or exposure are unlikely to change, given the degree of uncertainty that remains from other studies in which the genetic material of the virus was detectable for longer periods of time,” he said.

Even for men who have partners who are not planning to become pregnant, it is important to practice safe sex or abstain completely for 6 months postexposure. “Because it is unclear which men will have longer persistence, it is important for Zika-infected/exposed men to practice safe sexual practices for 6 months post infection to avoid transmission of the virus,” Amesh Adalja, MD, senior associate with the Johns Hopkins Center for Health Security, in Baltimore, Maryland, stated.

Jill Rabin, MD, a women’s health specialist, highlighted in the press release that although it is good news that the virus may not persist in semen as long as previously thought, “...we need to have a larger sample size and follow people for a longer period of time. Because we don’t have enough data and we don’t have enough people, we can’t really say what is the time period needed to be free of infection.”
Cases of Rare Mosquito-Borne Virus Spring Up in 2 US States
By Kristi Rosa

A relatively rare mosquito-borne virus hit several US states this summer, and it has health officials urging individuals to take the proper precautions against mosquito bites. The disease in question? Jamestown Canyon virus (JCV).

Spread to individuals through the bite of an infected mosquito, JCV is an orthobunyavirus in the California serogroup known to be capable of causing "acute febrile illness, meningitis, or meningoencephalitis," according to the Centers for Disease Control and Prevention. A recent analysis confirmed 31 cases of JCV in the United States from 2000-2013, spanning 13 states. The geographic range of JCV remains unclear; cases occurred in western, midwestern, northeastern, and southern states from 2000-2013. JCV infections tend to occur from spring to early fall, with about half of reported cases resulting in hospitalization. The good news is that no associated deaths have been reported to date.

On July 13, 2017, the Maine Center for Disease Control & Prevention, an office of the Maine Department of Health and Human Services, confirmed a case of the virus in an adult from Kennebec County. The infected individual reportedly had symptom onset in early June 2017. Although the case required hospitalization, the individual has since returned home to recover.

Health officials in Maine worked on promoting awareness of the relatively rare disease, as well as other arboviruses, such as West Nile virus (WNV), that tend to be prevalent during the summer. “This case reminds us all that mosquitoes are more than a nuisance—they also carry disease,” epidemiologist Siiri Bennett, MD, commented in the official press release. "Prevention is key if Mainers are going to protect themselves from mosquito-borne diseases.”

A local news hub, Bangor Daily News, reported 2 more confirmed cases of the virus in the state. Dr. Bennett was reported to have said that the significance of the 2 additional cases is "hard to pin down." Since the illness is not incorporated into routine testing, she suspects that there are even more cases of the virus in Maine that have yet to be identified.

"There’s so much we don’t know about this virus,” she admitted. "It’s alarming to know that it’s out there, that there’s a virus you need to be aware of.”

Meanwhile, in New Hampshire, the Department of Health and Human Services identified its first case of the virus in a Hanover resident, in late August 2017. “Jamestown Canyon virus is 1 of several viral infections that can be transmitted through the bite of an infected mosquito in New Hampshire,” state epidemiologist Benjamin Chan, MD, reported in the official press release. “It is an uncommon infection to be found, but similar to WNV and Eastern equine encephalitis, it also has the potential to cause serious health complications, including central nervous system infection. Because of the risk for various infections from mosquitoes, we want to remind people to take steps to avoid mosquito bites and remove areas of standing water around their homes where mosquitoes might breed and reproduce.”

Preventing this illness depends on 2 factors: avoiding mosquito bites and removing standing water around the home. Avoiding outdoor activities at peak feeding times for mosquitoes, wearing long sleeves and long pants, and using insect repellent are all good ways to avoid bites. Removing or emptying any containers that are outside that can collect water, changing bird baths once a week, checking gutters and frequently removing leaves that collect there, and filling tree holes with dirt or sand can all work to prevent mosquito breeding.

To stay up-to-date on JCV infections in the United States, be sure to visit the Contagion® Outbreak Monitor. ▲

ACIP Releases Immunization Recommendations for 2017-2018 Flu Season
By Jennifer Barrett

The Centers for Disease Control and Prevention (CDC) has shared Advisory Committee Immunization Practices (ACIP) recommendations regarding the prevention and control of seasonal influenza with vaccines for the 2017-2018 season.

Based on discussions during ACIP meetings held over the past year, just as the vaccine has been updated, the new report provides updates to the 2016-2017 recommendations, as well. For the 2017-2018 season, the committee states that quadrivalent and trivalent influenza vaccines will be available.

- Inactivated influenza vaccines and recombinant influenza vaccines will be available in trivalent and quadrivalent formulation.
- Live-attenuated influenza vaccines are not recommended for use during this season.

The updated recommendations include the following: The trivalent influenza vaccines will contain A/Michigan/45/2015 [H1N1] pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brussels/60/2008-like virus. Quadrivalent influenza vaccines will contain these 3 viruses and an additional influenza B vaccine virus, a B/Phuket/3073/2013-like virus.
- Afluria Quadrivalent and Flublok Quadrivalent vaccines now have an expanded age indication.
- Pregnant women may receive any licensed, recommended, age-appropriate influenza vaccine.
- Afluria may be used for individuals 5 years and older, consistent with US Food and Drug Administration-approved labeling.
- FluTixt Quadrivalent should not be used during the 2017-2018 influenza season because of concerns about its effectiveness against influenza A(H1N1)pdm09 viruses in the United States during the 2013-2014 and 2015-2016 influenza seasons.

Routine annual influenza vaccination is recommended for all individuals 6 months of age and older who do not have contraindications. The committee recommended that individuals should be vaccinated before the onset of flu activity in the community and that vaccinations should be offered before the end of October and continue to be offered as long as influenza viruses are circulating and unexpired vaccine is available. ▲
Individuals With HIV Face Risk of Cancer Death
By Laurie Saloman, MS

The good news about HIV is that over the past several decades, antiretroviral therapy (ART) has made it possible for infected individuals to avoid developing full-blown AIDS and enjoy a much longer life span. The bad news is that they may be at higher risk of dying of cancer, compared with uninfected individuals. Although it’s true, naturally, that not dying of AIDS means they’ll die of something else, it’s also true that ongoing inflammation, even among patients who take ART, may hasten the development of cancer cells.

To find out just how many patients with HIV are dying of cancer and from what kinds of cancer, a team from the National Cancer Institute in Rockville, Maryland, examined data from a variety of studies on nearly 47,000 individuals with HIV, mostly male, who were receiving ART. The data spanned the years 1995-2009, and participants were followed for an average of 5.7 years, for a total of more than 267,000 person-years studied. The team separated AIDS-defining cancers such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer from non-AIDS-defining cancers such as lung, liver, colorectal, and prostate cancers.

The scientists found that 2.6% of deaths that occurred among the participants during the years of the study were due to AIDS-defining cancers, and 7.1% were due to non-AIDS-defining cancers—a total of almost 10% of deaths due to some type of cancer. The proportion of deaths due to non-AIDS-defining cancers grew during the study period. Older participants and men had a higher risk of death from cancer, compared with younger participants and women. Participants whose CD4 blood counts were low, indicative of an immune system hampered by HIV, had the highest mortality rates from both AIDS-defining and non-AIDS-defining cancers.

“Immunosuppression increases the risk for some cancers, such as Kaposi sarcoma and non-Hodgkin lymphoma,” Eric Engels, MD, MPH, chief of the Infectious Diseases and Immunology Branch of the Division of Cancer Epidemiology and Genetics at the National Cancer Institute, and the lead author of the study, told Contagion®. “Also, HIV-infected people with cancer have a higher risk of dying from their cancer than HIV-uninfected cancer patients, which might be due to immunosuppression or differences in cancer treatment.”

Lifestyle differences can come into play, too, according to Dr. Engels. “HIV-infected people in the United States frequently have infections with other viruses that cause cancer—for example, human papillomavirus [or] hepatitis C virus—and many HIV-infected people smoke cigarettes,” he said. “These factors contribute to the high risk of cancer.”

Health care providers who treat individuals with HIV can play a valuable role in helping them reduce their risk of cancer, either by helping them make lifestyle changes or by helping them be more proactive about disease treatments.

“Clinicians should focus on reducing cancer incidence by facilitating adherence to HIV treatment, enabling smoking cessation, and treating hepatitis B and C virus infections,” Dr. Engels told Contagion®. “In addition, HIV-infected cancer patients must be provided access to timely and effective cancer treatment, coordinated by experienced HIV and cancer specialists.”

Herpes Study Yields Surprising Discovery: A Potential Broad-Spectrum Antiviral
By Kristi Rosa

A large proportion of the world’s population is infected with herpes simplex virus (HSV), and because most individuals do not present with symptoms, often they are not aware of their status. Primary infection and reactivation of the virus can have negative health implications, ranging from cold sores and mild genital lesions to severe ocular manifestations that can result in loss of vision entirely. Therefore, treatment for the virus is imperative.

Investigators from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Rockville, Maryland, may have found a solution in a new target for treatments against the virus. They conducted a study that offers insight into how a particular cellular enzyme complex regulates HSV. Their findings were surprising—by inhibiting the cellular enzyme complex in question, EZH2/1, they were able to suppress the infection. Furthermore, the investigators showed that the EZH2/1 inhibitors “also enhanced the cellular antiviral response in cultured cells in mice,” according to the official press release.

The study authors wrote that once an individual is infected with HSV, the virus “establishes lifelong latency in sensory neurons.” However, latent genomes can be reactivated and cause recurrent disease. Many of the pharmaceuticals on the market designed to fight HSV “target the viral DNA polymerase” to stop “late-stage viral replication,” they said.

However, some strains of the virus have developed resistance to these pharmaceuticals, particularly in infected individuals with weakened immune systems. The authors also noted that “these [pharmaceuticals] do not adequately control subclinical infectious viral shedding, which is the most prevalent means of transmission.” Because of these limitations, the health care community needs new therapeutic approaches to fight HSV.

In the study, the investigators turned to epigenetic therapeutics. Epigenetic regulation “is based on a network of complexes that modulate the chromatin character and structure of the genome to impact gene expression, cell fate, and development,” the authors noted. Epigenetic modulators, “which are responsive to changes in the cellular environment and often linked to the nuclear architecture,” according to Nature Reviews: Genetics, are used in the treatment of several harmful diseases. Epigenetic machinery also regulates herpesviruses, and therefore, epigenetic therapeutics are a novel approach to controlling not only infection but also persistence of the virus to prevent recurrence.

Past research has found a link between EZH2/1 and the control of lytic and latency stages of several herpesviruses, HSV among them. The authors noted that “specific epigenetic inhibitors can modulate HSV lytic infection, latency, and reactivation.” “Inhibitors of the histone H3K9 demethylases (LSD1, JMJD2) block initiation of HSV infection, while inhibitors of the histone H3K9 and H3K7 demethylases (UTX/JMJD3) block reactivation from latency,” the authors wrote. “Most strikingly, inhibition of LSD1 in vivo enhances epigenetic repression of the latent HSV genomes, which correlates with a reduction of reactivation and viral shedding.” By treating the primary cells with EZH2/1 inhibitors, the investigators managed to suppress HSV gene expression and decrease infection spread to adjacent cells. Furthermore, the EZH2/1 inhibitors also blocked spread of reactivation in a mouse model.

Further investigation into the “antiviral activities” of the EZH2/1 inhibitors showed that “treatment [with the inhibitors] induces multiple components of antipathogen pathways that result in an enhanced cellular antiviral state.”

The authors stressed that the antiviral effects of these inhibitors are not limited to HSV; the inhibitors were also capable of suppressing human cytomegalovirus, adenovirus, and even Zika virus infections, albeit in cell culture “using human primary fibroblast cell lines.” The authors speculated that the EZH2/1 inhibitors “have considerable potential as broad-spectrum antivirals.”

Cancer cell image by AKS and Herpes virus by nobeastsofierce/ Fotolia
Efficacy profile for single-dose ORBACTIV® (oritavancin) established in 978 patients

Endpoints

<table>
<thead>
<tr>
<th>ORB N=978 % (n)</th>
<th>VAN N=981 % (n)</th>
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<tr>
<td>Clinical response at 48–72 hours (primary endpoint)*</td>
<td>81.2% (794)</td>
</tr>
<tr>
<td>Clinical success at 14–24 days (secondary endpoint)**</td>
<td>81.2% (794)</td>
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Pooled Clinical Data from SOLO I and SOLO II

**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, and Enterococcus faecalis (vancomycin-resistant isolates only).

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

Clostridium difficile-associated colitis: Evaluate patients if diarrhea occurs.

Concomitant warfarin use: Patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin.

Osteomyelitis: Institute appropriate alternate antibacterial therapy in patients with confirmed or suspected osteomyelitis.

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

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

References:

Please see following page for Brief Summary of ORBACTIV® Prescribing Information.
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 anticoagulant activity of unfractionated heparin sodium may be increased for up to 120 hours (5 days) after ORBACTIV® administration [see Warnings and Precautions (5.3) and Drug Interactions (7.2)].

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

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

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

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

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

In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in ORBACTIV®-treated patients was 1.2 days and the median duration of these reactions was 2.4 days [see Adverse Reactions (6.1)].

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 antibiotic 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 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, antibiotic 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 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 95 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: 10/976 (1.1%) in ORBACTIV® and 12/983 (1.2%) in vancomycin.

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 ≥15% of patients receiving ORBACTIV® in the pooled ABSSSI clinical trials. There were 540 (55.3%) patients in the ORBACTIV® arm and 559 (56.9%) patients in the vancomycin arm, who reported ≥1 adverse reaction.
Clinical Trials

Table 1: Incidence of Selected Adverse Reactions Occurring in ≥1.5% of Patients Receiving ORBACTIV® in the Pooled ABSSSI Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ORBACTIV Vancomycin</th>
<th>N=976 (%)</th>
<th>N=983 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration</td>
<td>Infusion site phlebitis</td>
<td>24 (2.5)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Infusion site reaction</td>
<td>19 (1.9)</td>
<td>34 (3.5)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Abscess (limb and subcutaneous)</td>
<td>37 (3.8)</td>
<td>23 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>24 (2.5)</td>
<td>11 (1.1)</td>
</tr>
</tbody>
</table>

Table 2: Coagulation Tests Affected and Unaffected by ORBACTIV®

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

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).

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 500 mg, or 25% of the single clinical dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicity 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.

8.2 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 have not been studied [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

10. OVERDOSAGE

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

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

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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Infectious diseases pose a threat from multiple avenues—naturally occurring events such as outbreaks, accidental incidents like lab errors, and intentional acts of bioterrorism. Globalization, growing populations, and increasing encroachment of humans onto animal habitats have increased the risk for spillover and natural outbreaks. From the laboratory side, the threat is a mixture of biosecurity and biosafety. Biosecurity measures are those that seek to protect the organisms from nefarious actors, while biosafety practices look to protect investigators (or the public) from accidental exposures. The Ebola outbreak in 2014 and 2015, the Zika virus epidemic of 2015 and 2016, findings of smallpox vials in National Institutes of Health laboratory freezers in 2014, and continual lab errors involving mishandling and shipping of live select agents all highlight the threat of natural and accidental events. Although these recent occurrences have reinforced the need for preventive and responsive measures, the threat of bioterrorism can seem a bit distant; however, with advances in biotechnology and global travel, we must remain vigilant.

The 2001 Amerithrax attacks easily come to mind when discussing the threat of bioterrorism. Following the September 11, 2001, attacks, letters laced with anthrax added a new horror to the United States, a country that was already vulnerable. The Amerithrax attacks killed 5 individuals and sickened 17 and are considered the worst biological attacks in US history. The decontamination costs alone were estimated to be $320 million, and challenges with postexposure prophylaxis recommendations and compliance only added to the chaos. Perhaps one of the most unexpected aspects of this attack was the conclusion that US Army Medical Research Institute of Infectious Diseases biologist and anthrax expert Bruce Ivins, PhD, was considered the most likely culprit (he later took his own life prior to charges being filed).

Typically, bioterrorism is thought of in terms of attacks like the ricin release by Aum Shinrikyo in the Tokyo subway and the poisoning of salad bars with *Salmonella* by the Rajneesh cult in Oregon. All these attacks involved fanatical groups and revealed deep-rooted challenges with the science of acquiring, growing, weaponizing, and disseminating complex biological weapons. The Amerithrax attacks were different because the anthrax was delivered in a fine powder that ensured easy inhalation exposure. Many were surprised that the threat came from not only a scientist but also an American researcher working at an infectious disease institute aimed at protecting the United States. Moreover, Dr. Ivins had the means and capacity to make the attack exponentially worse but simply had chosen not to.

It was during this time that significant gaps were found within the United States’ response to such an attack. Whether it was who was responsible for decontamination, physician capacity to diagnose agents likely to be used for bioterrorism, or the...
sensationalized news, numerous factors left the United States truly struggling to handle such an event. The Amerithrax attacks gave insight into not only the poor American preparedness and response for bioterrorism but also a new source for weapons: skilled scientists.

Although there is always the potential for nonstate actors—ISIS, for example—to develop crude biological weapons, a more recent focus regarding bioterrorism has aimed at emerging technology. The scientific capabilities and tacit knowledge of bioterrorism will ultimately affect the biowarfare, whether it be the selection of organism, the crude design or complex dissemination method, etc. The Amerithrax attacks gave us a small window into the capabilities of a nefarious individual with significant skills and knowledge in bacteria. Recent biotech advances have added a new spin to biothreats.

For example, the biotech industry is rapidly growing, bringing new technologies like synthetic biology, digital-to-biological converters, and gene-editing tools like CRISPR-Cas9 to the masses. CRISPR can effortlessly be purchased online for $150, making the process significantly easier. A tool that can easily edit DNA like a pair of scissors with a copy and paste has the potential to prevent mosquitoes from transmitting malaria and to remove chronic conditions from humans. Gene editing also has the capacity for gene drive, which allows genetic traits to be quickly passed down through generations. The potential for CRISPR is endless, and yet it has many scientists worried. The ease of use and access, not to mention very limited federal oversight, could have unintended effects due to a garage-biohacker’s tinkering around with DNA. Jennifer Doudna, PhD, one of the inventors of CRISPR, expressed her worry about this very act, noting, "I think there’s sort of the potential for unintended consequences of gene editing in people for clinical use. How would you ever do the kinds of experiments that you might want to do to ensure safety?"

Although CRISPR has made gene editing easier and more accessible, there also exists the hazard of dual-use research of concern (DURC), like that of gain-of-function research (GoF). DURC is life sciences research that, despite its good intentions, has the capacity to be directly misapplied to pose a threat to humans, animals, the environment, agriculture, etc. The recent news that a Canadian research team reconstituted horsepox with little specialized knowledge, mail-ordered DNA fragments, and $100,000 highlights the DURC debate. Although the research has yet to be published, the concern is not only that this process could be applied to reconstitute smallpox but also that the research was not flagged in the review process for risks related to dual-use research. The horsepox experiment points out the possibility that such work can be done and that even at the most structured level, proper risk review is not being done. Moreover, such an experiment raises concerns for lowering the barriers to experiments using smallpox and normalizing DURC in a manner that could be dangerous.

GoF is one of the most common examples of DURC. Experiments with GoF involve increasing the virulence, transmissibility, or host range of pathogens. Although this research is performed to better understand current diseases and what it would take for them to evolve to have more pandemic potential, this research inherently worries many in the research community because of the risk of accidental release or intentional misuse by a nefarious actor. This became an issue in 2012 when 2 research teams genetically modified H5N1 viruses to transmit efficiently between mammalian hosts to show the genetic mutation needed for the virus to sustain human-to-human transmission. The concern over this research led to a federal moratorium’s halt—despite the fact that this incident is not an accident; rather, it has occurred because of a person with bioterrorist ambitions who acquired access to these labs or even a lab failure, which history proves can happen, that results in the release of a strain of H7N9 that has been modified to be easily transmitted among people or a strain of Neisseria meningitis that is highly resistant to antibiotics. This becomes even more relevant as the dramatic increase in biodefense activities and in the number of biosafety level 4 labs continues. Moreover, imagine that this incident is not an accident; rather, it has occurred because of a person with bioterrorist ambitions who acquired access to these labs or even an insider threat like Bruce Ivins. The truth is that the threat of bioterrorism is no longer beholden to the state program or cultish group with a makeshift lab in their garage but may also include a DIY biohacker or laboratory worker with nefarious intent.

How can we, as infectious disease practitioners, prepare or respond? First, knowledge is key. It is crucial to understand the threats, whether they are a natural outbreak, a lab breach you read about, or even just a review of the signs and symptoms of organisms we tend to worry about but may not see in the United States (such as severe acute respiratory syndrome, Middle East respiratory syndrome, anthrax, etc). Researchers should also consider the implications of their work and take the necessary review processes to ensure the proper biosecurity measures are taken.

Second, as simple as it sounds, practice vigilant infection control. That’s right—hand hygiene, personal protective equipment use, rapid isolation of potentially infectious patients, and working with your infection prevention and control (IPC) resources. Fundamentally, these practices will provide the first and most vital line of defense against the exposure and spread of a disease. Third, keep an open communication channel with those IPC resources and your local public health department. If something seems off, say something. You are without a doubt the most vital part of identifying patients with unusual or concerning disease presentations. Every outbreak begins with someone asking questions and knowing when to bring in additional resources. Consider a surge of patients with the same symptoms during an off time of year or with symptoms of a rare disease. Although the surge could be a flu epidemic, or the result of a crowd from a major sporting event being exposed to a food-borne pathogen, it could also be something more sinister. By touching base with public health officials, you allow them to start investigating.

Last, don’t stop what you’re doing. Infectious disease threats present from all angles—natural, accidental, or as acts of bioterrorism—but they all require identification, isolation, and treatment from practitioners. The field of infectious disease and public health isn’t for the weary, and every person is vital to global health security.
Although incredible advances in the development and dissemination of antiretroviral therapy (ART) have enabled many individuals with HIV to avoid progressing to AIDS, the efficacy of this therapy means the population may now live long enough to succumb to diseases that often plague the non-HIV–infected population. Chief among these is liver disease, specifically nonalcoholic fatty liver disease (NAFLD), which is characterized by fatty deposits in the liver and can lead to liver fibrosis (stiffness), cirrhosis, or death.

In patients who do not have HIV, the primary driver of NAFLD is metabolic syndrome. According to the National Heart, Lung, and Blood Institute, metabolic syndrome pertains to a cluster of risk factors that predispose a person to heart disease, diabetes, and stroke, and its incidence is rising worldwide. Prominent among these risk factors is obesity concentrated in the abdominal area. Additional risk factors include hypertension, a high fasting blood glucose level, and high triglyceride and low high-density lipoprotein (HDL) cholesterol levels. Now, NAFLD driven by metabolic syndrome is becoming more common in individuals with HIV as well—approximately one-third have NAFLD, according to the authors of a new study on the link between liver fibrosis and metabolic syndrome in individuals living with HIV.

The study was conducted by a European team that analyzed 405 HIV-monoinfected adults, mostly male, who appeared in a database of patients being followed for treatment at a Paris hospital. The subjects all had been diagnosed with HIV at least 5 years prior to the study, and none had a history of excessive alcohol consumption. Their average age was 53, and 203 had metabolic syndrome. Upon enrollment, each participant had the stiffness of his or her liver measured using transient elastography, a noninvasive method similar to an ultrasound. Blood samples also were taken after a 12-hour fast.

The team found that liver stiffness, along with cirrhosis, was measurably higher in patients who had markers of metabolic syndrome, including low HDL cholesterol and high triglycerides. Practitioners who treat individuals living with HIV must help patients lose weight and get more active.
The higher the patient’s body mass index (BMI), the higher the risk of fibrosis and cirrhosis. Patients with a BMI of at least 30 kg/m² were especially likely to have fibrosis, as were patients whose blood work suggested insulin resistance. Overall, 25.1% of HIV-monoinfected patients who had metabolic syndrome had significant fibrosis, with 8.4% found to have cirrhosis. Among HIV-monoinfected patients without metabolic syndrome, fewer than 8% had fibrosis. Because fibrosis is a known marker of the severity of chronic liver disease, and because it has a proven association with deaths due to liver disease in individuals with NAFLD who don’t have HIV, these findings have important implications for the HIV community.

Liver disease has long been a concern in individuals living with HIV, especially as they’ve seen their lives extended thanks to ART. “Most of the time, patients with HIV develop liver fibrosis/cirrhosis in a background of viral hepatitis (hepatitis B virus [HBV] or hepatitis C virus [HCV]) coinfection,” Maud Lemoine, a senior clinical lecturer at Imperial College London and the lead author of the study, told Contagion. “But in patients without HBV or HCV coinfection, metabolic syndrome [arises] mainly due to obesity inducing fat into the liver, which can progress to inflammation and fibrosis.”

Exactly how and why NAFLD and metabolic syndrome contribute to liver fibrosis in individuals living with HIV is not well understood. Researchers are unsure of the causative biological processes, but they have confirmed that HIV-monoinfected patients with metabolic syndrome experience changes in the levels of proteins emitted by fat tissue as well as higher levels of cells that induce an immune response. “The HIV infection itself is connected to a chronic inflammatory state,” Dr. Lemoine said, but added that scientists do not know whether HIV has a direct impact on the liver. “We analyze patients that are very well suppressed, with no detectable viral load.”

What she and her team do know is that adipose tissue from obesity is the main driver of this condition. “So far, it has been a neglected problem in HIV patients,” she said, noting that there have been many studies examining the role of obesity and metabolic disease in individuals without HIV.

HELPING PATIENTS WHO HAVE HIV AND METABOLIC SYNDROME

As it is now recognized that individuals living with HIV are becoming more likely to fall prey to non-AIDS-related maladies as their lifespans increase, the health care community needs to respond accordingly. The causes of obesity in individuals living with HIV, said Dr. Lemoine, include poor diet and lack of exercise—much as they do in the general population. Practitioners who treat individuals living with HIV must be aware of the impact of these factors and help patients create and adhere to strategies to lose weight, get more active, and control their diabetes and hypertension, if those conditions are present.

Alcohol, too, may play a role in the development of liver fibrosis, which physicians and other providers should address. “Excess alcohol consumption is definitely a risk factor for fibrosis, and any discussion about fibrosis must make note of this reversible cause,” Benjamin Young, MD, PhD, senior vice president and chief medical officer of the International Association of Providers of AIDS Care (although not an author of this study), told Contagion. “Alcohol consumption and dependency should be assessed and addressed, and for those with chronic hepatitis or liver fibrosis, a harm reduction approach should be used to support reduction and cessation.”

According to the National Institute on Drug Abuse, alcohol and drugs are significant problems for individuals living with HIV: one of 3 used drugs or binged on alcohol between 2005 and 2009, and 24% have a problem serious enough that they should be in a substance-abuse treatment program.7

Patients with HIV also need to be screened for hepatitis, traditionally a major driver of liver disease in this population. “Diagnosis, treatment, and—in the case of hepatitis C—cure, of viral hepatitis should be done, and for uninfected individuals, vaccinations to prevent hepatitis A and B should be administered,” Dr. Young said.

What role, if any, does ART play in the development of liver fibrosis? “This has not been clearly demonstrated,” Dr. Lemoine told Contagion, “Probably [there is] an indirect role…but in our study, the role of ART was not significant.”

A more accurate question might be which drugs used in ART pose the most risk rather than whether ART itself is problematic, as the medical community recognizes that the risks of forgoing ART are greater than the potential risks of administration. “It’s generally appreciated that treating HIV with antiretrovirals reduces the risk of liver fibrosis,” said Dr. Young. “Yet there remains controversy as to whether any particular antiretroviral drug might increase the risk over others.” Older drugs, such as d4T ( stavudine) and azidothymidine (AZT), Dr. Lemoine said, seem to be more toxic than newer therapies and might best be avoided. Other studies have shown, for example, that when HIV-infected patients with NAFLD switch from efavirenz to raltegravir, liver steatosis is significantly improved.3

Treatment for NAFLD remains a work in progress. A recent study out of Case Western Reserve University in Cleveland, Ohio, examined whether statins are an appropriate therapy for people living with HIV who have NAFLD, as they have been suggested as a viable NAFLD treatment option for people without HIV.5 Interestingly, the HIV-positive subjects treated with statins experienced an increase in their liver fat scores after 96 weeks compared with the liver fat scores of the HIV-positive placebo takers. Therefore, it would seem that although statins are effective at reducing cardiovascular risks, they cannot be relied upon to treat fatty liver disease—and in fact may be counterproductive.

This study had a few limitations, including its use of a non-invasive method to scan for liver fibrosis and the absence of histological confirmation of this diagnosis with liver biopsies. A small percentage of participants (13%) had invalid transient elastography results that could not be used. The participants were overwhelmingly male, which could have skewed the findings as a previous study found that women living with HIV have significantly lower levels of liver steatosis, or fatty liver, than women without HIV. Also, as this was a cross-sectional study, follow-up is necessary to examine rates of morbidity and mortality in this population. The authors hope the medical community engages in further research to learn more about the exact mechanisms that lead patients with HIV to experience liver fibrosis and how this can be prevented. ▲

References are available at ContagionLive.com.
Treating HCV in HIV-Coinfection: Still a Therapeutic Dilemma?

Despite the availability of highly active agents against HCV, HIV-infected patients require special considerations for drug interactions when considering treatment options.

BY JENNIFER ANDRES, PHARM.D, BCPS, AND AMY CHENG, PHARM.D, AAHIVP

Chronic hepatitis C virus (HCV) infection affects an estimated 2.7 million to 3.9 million people in the United States. HCV can lead to cirrhosis, hepatocellular carcinoma, and end-stage liver disease if left untreated. In patients with HIV, the progression to cirrhosis is more rapid than in mono-infected patients. In the United States, about one-quarter of HIV infected patients are also coinfected with HCV. Across the world, patients with HIV are 6 times more likely to be infected with HCV than the general population. People who inject drugs are most likely to have coinfection, and in the United States, 50% to 90% of HIV-infected injection drug users are also coinfected with HCV. All patients with HIV infection should be screened at least once for HCV. In patients with continued risk factors, such as intravenous (IV) drug use or men who have sex with men, HCV screening should be repeated. Consequently, there are several treatment sensitivities that need to be taken into account when treating coinfected individuals.

TREATMENT CONSIDERATIONS

The overall treatment response to interferon and ribavirin has been found to be low in HCV-mono-infected patients, and HCV coinfected patients have been shown to have an even lower response. Well-tolerated and efficacious oral drug regimens now exist for the treatment of the general patient population with HCV, which now includes patients coinfected with HIV. With one exception, there is no difference in the efficacy of direct-acting antivirals (DAAs) in an HIV-coinfected or mono-infected patient, and the current guidelines recommend that HIV-infected patients be treated the same as noninfected patients.

When the decision is made to treat HCV, consideration must be given to drug interactions with HIV therapy. None of the currently available DAAs are free from drug interactions with HIV antiviral agents. Although some clinicians may choose to defer antiretroviral therapy (ART) until HCV therapy is completed, the US Department of Health and Human Services HIV guidelines recommend ART should be initiated in all HIV/HCV coinfected patients regardless of their CD4 cell count. HIV therapy should not be withheld to facilitate easier treatment with DAAs; rather, the patient should be referred to an HIV specialist who can select an HIV regimen to accommodate HCV therapy by avoiding drug–drug interactions and toxicities. In general, most pharmacy benefit managers require patients to be on a stable HIV regimen prior to beginning HCV therapy.

NEW THERAPIES

Prior to August 2017, shortened regimens were not recommended for HCV treatment in coinfected patients. Ledipasvir/sofosbuvir was not recommended to be shortened to 8 weeks,
even if the patient was treatment-naive and noncirrhotic and had a low-baseline HCV viral load. Now, the recommendations include glecaprevir/pibrentasvir (GLE/PIB), a newly approved pangenotypic combination of an NS3/4A protease inhibitor and an NS5A inhibitor. It is administered as 3 tablets of GLE 100 mg/PIB 40 mg once daily with food, and can be used for 8 weeks in select populations. In addition to having pangenotypic properties, GLE/PIB does not undergo renal excretion, allowing it to be used without dose adjustment in patients with chronic kidney disease and on dialysis.9

In the EXPEDITION-2 trial to study GLE/PIB, a total of 137 coinfected patients without cirrhosis received 8 weeks of GLE/PIB, while 16 patients with cirrhosis received 12 weeks of GLE/PIB. All of the patients were treatment-naive or previously treated with pegylated interferon/ribavirin with or without sofosbuvir. The treatment duration in the study is identical to current US Food and Drug Administration (FDA)–approved treatment durations and is the same for mono-infected patients.

The study results showed 99.3% sustained viral response for 12 or more weeks in patients receiving GLE/PIB for 8 weeks. This includes 1 patient who withdrew from the study due to an unrelated adverse effect. In patients with cirrhosis, all but 1 patient attained SVR12, although this was a small group of patients. None of the patients had HIV breakthrough. The combination of GLE/PIB was well tolerated, with none of the patients reporting an adverse effect related to the study drug. Efficacy was similar to other clinical trials that did not include the HIV-infected population. All ART agents used in the trial were free of drug interactions with GLE/PIB. None of the patients were on protease inhibitor–boosted antivirals, in whom coadministration with GLE/PIB is not recommended.8,10 Efavirenz should also be avoided with GLE/PIB due to the risk of decreased GLE/PIB levels. Of note, when using GLE/PIB with elvitegravir/cobicistat-based regimens, a dose adjustment is not required.8 The current guidelines do not yet address the use of GLE/PIB; however, it is likely that this agent will be recommended for use in the HIV population.8

Additional research has shown that currently available nonstructural protein 5A (NS5A) inhibitors for HCV infection—ledipasvir and velpatasvir—interacted with the HIV therapy drug tenofovir disoproxil fumarate (TDF).9 Because 4 out of 5 of the first-line–recommended HIV regimens contain tenofovir, this interaction could affect a number of coinfected patients.9 Through P-glycoprotein inhibition, levels of TDF could increase, potentially causing increased (stronger or more) adverse effects. This is more concerning in patients with preexisting renal impairment, even with a glomerular filtration rate of 60 ml/min.5 No dose adjustment is required; however, it is necessary to monitor for TDF toxicity. In April 2016, the FDA approved the new formulation of tenofovir, tenofovir alafenamide (TAF), as part of the combination drug Descovy (emtricitabine/tenofovir alafenamide). TAF is a new oral prodrug of TDF, a nucleotide analogue that inhibits HIV-1 transcription. Unlike TDF, TAF is a more stable prodrug of tenofovir (TFV) in the plasma, which allows for high concentrations of TFV inside target cells. This reduces the plasma TFV exposures at approximately one-tenth the clinically approved dose of TDF.11 Intracellular activation of TAF allows for higher concentrations inside target cells and a lower concentration of TFV in the plasma, reducing off-target toxicities such as renal and bone complications. TAF is much safer to use in patients with renal impairment as part of their nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone. This makes tenofovir one of the safest NRTIs, with minimal hepatic toxicity and few to no drug interactions with HCV drug regimens.

CONCLUSION
Highly active agents against HCV are available for HIV-infected individuals coinfected with HCV, including a new option allowing for an 8-week treatment duration in treatment-naive patients without cirrhosis. Although there is no difference in efficacy in coinfected patients, the HIV-infected patient will still need special considerations with regard to drug interactions when considering treatment for HCV infection. Consultation with HIV and HCV specialists is crucial when drug interactions exist. Fortunately, most of the commonly used HIV therapies do not have many drug interactions with HCV therapy. Five out of the 6 recommended first-line antiretroviral therapies are integrase strand transfer inhibitor–based regimens, which do not have any drug interactions with HCV therapy, with the exception of elvitegravir boosted cobicistat (See Table). Because HIV-infected patients remain a less studied population in the treatment of HCV, despite the high risk for coinfection, more research should be done on medications with less potential for cross-reactivity.▲

References are available at ContagionLive.com.
Exploring the Threat of MDR-TB in the United States

The virulent pathogen has significant individual and public health implications.


T uberculosis (TB) has been labeled as one of the deadliest infectious diseases to humankind. Advances in *Mycobacterium tuberculosis* (MTB) research, coupled with the discovery of the antituberculous medications isoniazid and the rifamycins, propelled multiple international efforts to control TB that drastically changed the disease landscape. Yet, per the World Health Organization (WHO), 10.4 million TB cases occurred in 2015, ranking the infection among the top 10 causes of death worldwide.2

A major threat to global TB control is drug-resistant disease. Treatment for drug-sensitive TB involves prolonged combination therapy—usually at least 6 months of multidrug treatment—because of MTB’s inherent ability to evade host defense mechanisms.3 Inadequate treatment (eg, from inappropriate drug administration or nonadherence) may lead to resistance. Additionally, resistant TB strains may infect and cause disease in individuals not previously exposed to antituberculous therapy. Accordingly, the WHO, with support from the International Union Against Tuberculosis and Lung Disease, established the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, the oldest and largest initiative of antimicrobial resistance surveillance in the world.4 The most serious forms of drug-resistant TB include rifampin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB). MDR-TB is defined as TB with resistance to at least isoniazid and rifampin, the most effective anti-TB drugs.5 XDR-TB is defined as MDR-TB also resistant to any fluoroquinolone and at least 1 injectable agent.6 MDR- and RR-TB account for about 3.9% of new TB cases, representing about 1% of persons with TB disease.7,8 Eighty-five percent were foreign-born persons, and nearly 82% were individuals without a history of TB disease.9 These statistics emphasize how global control will undoubtedly affect progress toward national TB elimination.

DISEASE BURDEN IN THE UNITED STATES

In the United States, 9287 cases of TB were reported in 2016, contributing to an incidence rate of 2.9 cases per 100,000 persons.7 Seemingly reassuring, the small magnitude of incidence decline from the prior year predicts that national elimination of TB will not occur during this century.7

Demographically, roughly two-thirds of TB cases occurred in foreign-born individuals, with the highest incidence in Asians (26.9 cases per 100,000).2 California, Florida, New York, and Texas accounted for over 50% of cases.2 A source case study of national TB cases between 2011 and 2014 indicated that the vast majority were presumably due to reactivation of latent TB infection.4

Fortunately, MDR-TB remains relatively rare in the United States. The most recent MDR-TB data, from 2015, include 88 cases, representing about 1% of persons with TB disease.9,10 Eighty-five percent were foreign-born persons, and nearly 82% were individuals without a history of TB disease.7,9 These statistics emphasize how global control will undoubtedly affect progress toward national TB elimination.

MDR-TB requires extended courses of medications that are more expensive, less effective, and often more toxic than first-line treatment.

FINANCIAL IMPLICATIONS AND RESOURCE UTILIZATION

MDR-TB requires extended courses of medications that are more expensive, less effective, and often more toxic than first-line treatment for drug-sensitive TB, thereby imposing a significant financial burden on patients and health care systems. Marks and colleagues analyzed costs of treatment for MDR- and XDR-TB in high-risk areas of the United States from 2005 to 2007.11 Treatment duration ranged from 20 to 32.3 months, depending on resistance profiles, and 73% of patients were hospitalized at least once during their treatment. Average direct costs were $134,000 per MDR-TB patient and $430,000 per XDR-TB patient; direct-plus-productivity-loss costs averaged $260,000 to $554,000. The extrapolated total direct-plus-productivity-loss costs to the US health care system were approximately $100 million. A follow-up study indicated that 98 of 135 MDR-TB patients were hospitalized during treatment, averaging 1.5 hospitalization episodes per patient and an average duration of 94 days.12 The most common reasons for hospitalization were severe worsening of TB and the need to initiate or change treatment regimens. Risk factors for more frequent
hospitalization included being age 65 years or older, having AIDS, and having private insurance. The average cost per hospitalization was $54,883 for MDR-TB and $191,374 for XDR-TB—among the highest for any disease in the United States.

**DIAGNOSIS**

Drug-resistant TB is diagnosed by identifying MTB and then performing drug-susceptibility testing (DST). DST is often limited to state or other specialized laboratories, and final test results may be delayed by up to several weeks. Recent data suggest that despite improvements, incomplete and/or delayed DST results persist in the United States.11

Also concerning is reduced disease suspicion due to unfamiliarity of US health care providers with TB, leading to delayed or missed diagnoses and health care worker exposure. A study of pulmonary TB in New York, New York, from 2010 to 2014 sought to capture and quantify this risk.10 The average time between admission and placement on airborne isolation was 3.3 days, and the average time between admission and diagnosis was 5.1 days. This led to an average of 41 staff members requiring exposure-related follow-up per patient and nearly 40 hours of infection control workload.

**TREATMENT OUTCOMES**

The WHO estimates a global treatment success rate (defined as the sum of cure and treatment completion) of 52% in MDR- and RR-TB patients, compared with 85% for drug-susceptible disease.12 Outcomes from an aforementioned study in the United States reported an MDR-TB treatment completion rate of 78% (n = 134), with no failures or recurrences within 1 year.11 Twelve (9%) deaths occurred during treatment, of which 75% were attributable to TB. Death was associated with an age range of 65 years and above, smoking, and HIV infection.

Medication accessibility and drug toxicity are other key safety outcomes. A 2010 survey indicated 81% of health departments reported difficulty obtaining second-line agents for MDR-TB.16 In a report from 5 international WHO sites, 30% of patients required cessation of a suspected drug(s) because of toxicity, and 2.1% stopped treatment entirely because of adverse effects.17 The Centers for Disease Control and Prevention reports that 19% of patients treated for drug-resistant TB in the United States experience depression or psychosis, 13% develop hearing impairment or hepatitis, and 11% experience kidney injury.18 Recently, shorter-course regimens have been introduced, with improved treatment success rates and associated safety profiles.19,20 Though a complete review of treatment exceeds the scope of this review, the WHO MDR-TB guidelines and common medication toxicities are summarized in Tables 1 and 2.

**PREVENTION STRATEGIES**

Prevention strategies are key to minimizing and eliminating the transmission of both drug-sensitive and drug-resistant TB. US public health departments are tasked with TB control, particularly to ensure prompt diagnosis and completion of appropriate treatment. Programs also provide transportation and childcare assistance, food and housing incentives, directly observed therapy, and alternative treatment delivery sites to optimize treatment success.21 In December 2015, the National Action Plan for Combating Multidrug-Resistant Tuberculosis was released to identify targeted interventions and address domestic and global challenges associated with resistant TB.22 The plan outlines 3 broad goals to combat MDR-TB, including (1) strengthening domestic capacity, (2) improving international capacity and collaboration, and (3) accelerating basic and applied research and development.23 This intervention solidified the investment and coordination of government resources for this important cause.

Although seemingly uncommon in the United States, drug-resistant TB has significant individual and public health implications. Limitations in disease surveillance, DST, medication access, and patient management remain. Government programming, scientific research, and health care professionals must collaborate in optimizing MDR-TB diagnosis, treatment, and monitoring. A significant joint effort will be required for global eradication of tuberculosis. ▲

*References and Table 2 are available at ContagionLive.com.*

**Table 1. Highlighted Summary of the WHO Treatment Guidelines for Drug-Resistant Tuberculosis 2016 Update**

| Regimen of at least 5 effective TB medications during the intensive phase—preferable pyrazinamide plus 4 core second-line TB medications (1 from group A, 1 from group B, and at least 2 from group C) |
| An agent from group D2 or other agents from group D3 may be added to bring the total to 5. |
| Regimens may be further strengthened with high-dose isoniazid and/or ethambutol. See below: |
| A. Fluoroquinolones |
| Levofloxacin |
| Moxifloxacin |
| Gatifloxacin |
| B. Second-line injectable agents |
| Amikacin |
| Capreomycin |
| Kanamycin |
| Streptomycin* |
| C. Other core second-line agents |
| Ethionamide/prothionamide |
| Cycloserine/terizidone |
| Linezolid |
| Clofazetine |
| D. Add-on agents |
| D1 Pyrazinamide |
| Ethambutol |
| High-dose isoniazid |
| D2 Bedaquiline |
| Delamanid |
| D3 Para-aminosalicylic acid |
| Imipenem/cilastatin |
| Meropenem |
| Amoxicillin/clavulanate |
| Thiocetazone* |

**Duration of conventional MDR-TB courses (valid from 2011)**

| Intensive phase of 8 months is suggested for most patients; may be modified according to treatment response. |
| In patients with newly diagnosed MDR-TB, a total treatment duration of 20 months is suggested for most patients; may be modified according to treatment response. |
bacteremia and sepsis. Guidelines for the treatment of sepsis have led to increased use of BSAs and, therefore, higher rates of hospital-onset CDI (HO-CDI).\textsuperscript{4}

Increasing rates and severity of CDIs in the community and hospital settings have also been attributed to the emergence of a hypervirulent strain, B1/NAP1/027.\textsuperscript{5,6} The NAP1 strain demonstrates a higher rate of toxin production that has led to outbreaks and epidemics exhibiting a high incidence of severe and fatal complications.\textsuperscript{2,7,8} In the face of epidemiologic changes in CDIs, increased incidence of NAP1 strains, and overwhelming use of BSAs for sepsis, an examination of BSA use in this patient population is essential in developing strategies to mitigate these risks.

**CDI AND BROAD-SPECTRUM ANTIBIOTIC USE**

Risk of CDI remains highest after the use of fluoroquinolones, clindamycin, and the broader spectrum beta-lactams.\textsuperscript{9} A cohort study by Brown and colleagues analyzed the charts of 34,000 patients admitted to an acute care hospital for more than 2 days, and the results revealed that antibiotic use was the strongest predictor of CDI incidence.\textsuperscript{10} Every 10% increase in antibiotic use was associated with an increase in CDI incidence of 2.1 per 10,000 patient days. To assess the risk of CDIs in patients admitted for sepsis, it is important to distinguish between overall antibiotic use and those commonly used to treat sepsis. In patients without antibiotic allergies, common regimens include vancomycin, beta-lactam/beta-lactamase combinations, third- and fourth-generation cephalosporins, and fluoroquinolones.

In many scenarios, vancomycin is the preferred empiric agent for the treatment of sepsis due to its broad activity against gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*. Vancomycin is not often associated with development of CDI; however, a retrospective cohort study of 382 patients with HO-CDIs revealed that use of intravenous (IV) vancomycin for more than 7 days was independently associated with the development of HO-CDI (odds ratio [OR] 1.9).\textsuperscript{11} This was in contrast to metronidazole, which was shown to decrease the risk of HO-CDI (OR, 0.5). Several other studies’ results demonstrate similar associations between vancomycin and CDI.\textsuperscript{12,13} Hecht and colleagues describe a case of CDI after 29 days of IV vancomycin for the treatment of osteomyelitis.\textsuperscript{12} These findings may be due to the fact that IV vancomycin disrupts the gastrointestinal (GI)
Fluoroquinolones are highly active against bacteria found in the GI tract and have recently risen to the top as one of the major causative agents of CDIs.

Fluoroquinolones are highly active against bacteria found in the GI tract and have recently risen to the top as one of the major causative agents of CDIs.

remained the strongest risk factor for CDI. These data are concerning given that ceftiraxone is a common antibiotic for empiric treatment of pneumonia and urinary tract infections, which are 2 common causes of sepsis in patients presenting to the emergency department.16

Piperacillin/tazobactam is a beta-lactam/beta-lactamase inhibitor combination often used for empiric treatment of sepsis. Although all antibiotics have been associated with an increased risk of CDI, piperacillin/tazobactam is not often categorized as a high-risk antibiotic. Piperacillin/tazobactam has in vitro activity against *Clostridium difficile* (*C. difficile*) and achieves adequate concentrations in the GI tract to inhibit these organisms; however, there is contradicting data on whether or not this agent provides any protective effects against CDI. During a 2014 piperacillin/tazobactam shortage, Gross and colleagues analyzed the impact of alternative agents on the incidence of CDI.14 This analysis revealed a shift toward alternative high-risk antibiotics and an increase in CDI incidence. In contrast, a retrospective chart review on the impact of a 2002 piperacillin/tazobactam shortage revealed a 47% decrease in rate of CDI.14 It is unclear whether this decrease was due to the removal of piperacillin/tazobactam or a decrease in other high-risk antibiotics observed during the same time period.

Fluoroquinolones are highly active against bacteria found in the GI tract and have recently risen to the top as one of the major causative agents of CDIs.

incidence of HO-CDIs.23 Tapaert and colleagues performed a retrospective quasi-experimental study using an interrupted time series and showed a significant reduction in the incidence of CDI (incidence rate ratio [IRR], 0.34; 95% CI 0.20-0.58; P < .0001) all while substantially decreasing the use of fluoroquinolones by 105.33 defined daily doses per month.22 Restriction of high-risk antibiotics, particularly the fluoroquinolones, has shown that a reduction in use often leads to a reduction in the incidence of CDI.

**CDIS IN PATIENTS WITH SEPSIS**

BSA use is a well-known risk factor for the development of CDIs, and patients suffering from sepsis uniformly receive these agents. A retrospective cohort study that evaluated the risk of HO-CDIs in patients initially presenting with sepsis found that approximately 1 in 100 patients with sepsis developed CDI.23 These patients were 1.6 more times likely to die in the hospital. The Surviving Sepsis Campaign (SCC) recommends strategies for early identification of sepsis and prompt treatment, within 1 hour, with BSAs.24 However, a recent time-series analysis by Hiensch at colleagues demonstrated that adoption of sepsis screening and treatment protocols can have unintended consequences, such as an increase in BSA use and rates of HO-CDIs.4 They observed a substantial increase of 10.8 HO-CDI cases per 10,000 patient days in the post-implementation period.

The 2016 SCC update recommends 1 or more antimicrobials to cover all likely pathogens and de-escalation once a causative organism is identified. Up to one-third of patients with sepsis do not have a causative pathogen identified,25 making it difficult to predict which patients can be safely de-escalated. Even though de-escalation has been shown to have a positive effect on morbidity,26 it is infrequently done.27 Further studies are needed to define de-escalation strategies for patients with sepsis.

**CONCLUSION**

Studying the impact of antibiotics for sepsis is difficult due to the multiple confounding factors, such as severity of illness, time to diagnosis, length of stay, and availability of adequate control groups. Current evidence suggests that antibiotic selection for sepsis can have a severe impact on the rate of CDIs. Vancomycin and piperacillin/tazobactam appear to be low-risk antibiotics for the development of CDIs, whereas cephalosporins and fluoroquinolones carry a much greater risk. Use of BSAs for sepsis requires a delicate balance between appropriate empiric therapy and prevention of CDIs. Further studies are needed to quantify the risks associated with antibiotic use in sepsis, identify patients at greatest risk of CDIs, and establish effective de-escalation practices. ▲

References are available at ContagionLive.com.
Keeping Up With Adult Vaccinations
BY CHRISTOPHER MCCOY, PHARMD, BCPS AQ-ID

Adult vaccination updates have always been an annual occurrence, with many anxiously awaiting updates from the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP). More frequently, however, as new vaccines become available, an increase in emerging data and more complex recommendations lead to provider confusion. Registration and follow-up studies of these new products or formulations have provided important insight into vaccine effectiveness and decision making based on high-risk populations. Additionally, local and national outbreaks have driven more awareness in health care professionals and the lay public about the importance of protection. Ultimately, many still depend on the specific guidance from the ACIP and/or the CDC for vaccine recommendations. In the interest of brevity, the focus here will be on updated adult immunization recommendations for meningococcal disease, influenza, and pneumococcal disease, including some details of the data as support.

The general adult vaccination schedule with a special population supplement is published each year in February (Table 1). The special population and notable comorbidities are detailed in Table 2. This past February, notable changes included the removal of live activated influenza vaccine as an influenza vaccine option for any population and removal of egg allergy as a contraindication for influenza vaccination. Meningococcal polysaccharide diphtheria toxoid conjugate vaccine subtype ACWY vaccination is now recommended for patients with HIV infection. One of the newer meningococcal subtype B vaccines is now recommended for either anatomical or functional asplenia or persistent complement component deficiencies, including those receiving eculizumab.

To update the annual table, meetings are convened in June and October of each year. A notable session was held this past June, focusing on meningococcal vaccination and highlighting more reportable disease in recent years, newer product availability, the withdrawal of a product, and new published data.

The CDC reported in 2015 that the rate of reported meningococcal disease in the United States was 370 (0.11/100,000), with 60 deaths (0.02/100,000). One concerning trend since that time has been the increase in meningococcal subtype B infections and associated mortality. Two new subtype B vaccines have become available in recent years, one a combination of Neisserial adhesin A (NadA), Neisserial heparin binding antigen, and factor H binding protein (fHBP) MenB-4C (Bexsero) and the other a combination of two lipidated fHBP variants, one subfamily A and one from subfamily B named MenB-FHbp (Trumenba) (Table 3). The quadrivalent serotype A, C, Y, W vaccines were available as conjugate or polysaccharide vaccines similar to pneumococcal formulations; however, the polysaccharide vaccine MPSV4 (Menomune) has been withdrawn from the market, given shorter immunogenicity and lesser vaccine effectiveness versus one of the conjugated meningococcal vaccines (groups A, C, Y and W-135), eg, Menactra.

Many providers remain confused because the label for Menomune states that it is the only vaccine with proven efficacy for prevention of disease in patients over 55. This issue was discussed at the June 2017 ACIP Advisory Board meeting, and thus the MenACWY conjugate vaccine is now recommended by the ACIP for all adult age groups. Additionally, the ACIP recommended booster doses of MenACWY every 5 years throughout life for high-risk persons. For the MenB vaccine, the ACIP noted the same recommendations for boosters every 5 years.

Quadrivalent meningococcal B vaccines are recommended for higher-risk individuals who work in microbiology labs, those with asplenia (functional or otherwise), those with complement deficiencies, and those undergoing therapy with Soliris, given its effect on the complement system. Newer data have emerged that suggest that the protection of the vaccine for both MenACWY...
and MenB currently in this population is not fully effective. This was based on reports to the US Food and Drug Administration (FDA) of 16 cases of meningococcal infection after vaccination from 2007-2014, including 1 fatal instance. The recent death was of a 16-year-old girl who had received both vaccines prior to therapy but developed nongroupable infection 6 months after the last vaccine and a week after her first dose of eculizumab. A discussion of possible antibiotic prophylaxis with penicillin has been ongoing at the CDC.

For pneumococcal disease, the 2015 rate of reported invasive disease was 29,500 cases (9.2/100,000), with 3350 fatalities (1.04/100,000). Recommendations for the use of the pneumococcal conjugate 13-valent vaccine (PCV13) and the polysaccharide 23-valent vaccine (PPSV23) were last updated in 2015. The complex decision-making algorithm for vaccine administration and timing is noted in Table 4. A recent study examined longer-term immunogenicity in immunocompetent patients 65 and older by measuring serial PCV13 serotype-specific opsonophagocytic activity titers and immunoglobulin G concentrations at 1 month, 12 months, and 24 months post immunization. A placebo comparison was able to be designed because the study was conducted in the Netherlands, where there is no mandate for PCV13 vaccination. Geometric mean titers were sustainably higher in the treatment group. A post hoc subgroup analysis demonstrated that in patients over 80, the titer response waned, bringing into question the relative influenza vaccine effectiveness (VE) with advanced age. Until that is determined, only a single dose is recommended for those over 65 currently.

For influenza, the rate of reported positive influenza swabs for the 2016-2017 season was 130,500, with the number of visits for influenza-like illness at 278,706 and reported mortality at 9788 cases. The majority of 2016 isolates were classified as H3N2. The recommendations for the 2017-2018 influenza season were just released at the end of this past August. The recommendations for vaccination of the entire population over 6 months unless contraindicated remain in place. Regarding the choice of vaccine, the live attenuated vaccine is again not recommended because of concerns regarding effectiveness. This was supported by follow-up studies identifying lowered hemagglutinin activity of the attenuated strain from 2013-2014, leading to a lower replicative capacity and a subsequently lower immunogenic response to produce antibodies. Investigators are actively studying newer formulation strains so that the live product may become a viable alternative again. Trivalent and quadrivalent vaccines remain in equipoise, while standard dose (SD) versus high dose (HD) in select elderly patients is still a matter of ongoing debate. The prevailing public health goal is to improve vaccination rates, particularly in younger adults at higher risk.

According to the annual review by the ACIP regarding these vaccines, the overall VE across all strains of influenza vaccine for all ages was 48%. This was largely driven by lower effectiveness of the egg-based vaccine for H3N2. Administration of the higher-dose recombinant vaccine (RIV4), however, was found to result in an improved relative efficacy (compared with active comparator vaccine) against influenza A of 36% (95% CI, 14%-53%) (hazard ratio [HR], 0.64; 95% CI, 0.48-0.86; P = .003) but no difference with respect to influenza B. Recombinant vaccine also contains no egg by-products, reducing the likelihood of a reaction in patients with a history of a truly severe egg allergy.

Relative to specific effectiveness in the population over 65 years, there continues to be potential evidence that a higher dose can overcome immunologic senescence. The results of the most recent study of nursing home residents—a comparative-effectiveness, cluster-randomized trial from 823 centers given either the HD or SD vaccine during the 2013-2014 predominantly A/H1N1 influenza season—showed a reduction of respiratory-related hospital admissions of 0.5%, with an adjusted relative risk of 0.87, (95% CI, 0.78-0.98, P = .023). There were no laboratory data to confirm influenza, however. As a result, patient and provider preferences are the only deciding factors between low and high dose in elderly individuals.

As stated previously, the adult vaccine landscape remains ever changing, with an annual schedule recommendation in February plus interim recommendations for influenza in August of each year in addition to individual product updates as needed. To remain the most updated, review the ACIP’s excellent website and listserv resources, as well as releases from Morbidity and Mortality Weekly Report and other major publications on vaccine effectiveness, as study results evolve.

References and Tables 3 and 4 are available at ContagionLive.com.

Table 1: ACIP Adult Immunization Recommendations for Select Vaccines Classified by Age Group

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19-21 Years</th>
<th>22-26 Years</th>
<th>27-59 Years</th>
<th>60-64 Years</th>
<th>≥65 Years</th>
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<tr>
<td>Influenza**</td>
<td>Annual</td>
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<td>Pneumococcal conjugate vaccine (PCV13)</td>
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<tr>
<td>Pneumococcal polysaccharide vaccine (PPSV23)</td>
<td>Indication based**</td>
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<td>Meningococcal B vaccines subtype ACWY</td>
<td>Indication based**</td>
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<td>Meningococcal B vaccines subtype B</td>
<td>Indication based**</td>
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*Those with a severe egg-allergy history can now receive the recombinant product.

**Table 2: ACIP Adult Immunization Recommendations for Select Vaccines Clarified by Comorbidities or Special Populations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Pregnancy</th>
<th>Immuno-compromised*</th>
<th>HIV Infection</th>
<th>Asplenia/ Complement Deficiencies</th>
<th>Kidney failure, End-Stage Renal disease, or Hemodialysis</th>
<th>Heart or Chronic Lung Disease or Alcoholism</th>
<th>Chronic Liver Disease</th>
<th>Diabetes</th>
<th>Health Care Personnel</th>
<th>Men Who Have Sex with Men</th>
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<tbody>
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<td>Influenza</td>
<td>Annual</td>
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<td>Meningococcal B vaccines subtype ACWY</td>
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*—Including primary immunodeficiency, HIV Infection: chronic renal failure and nephrotic syndrome; leukemia, lymphoma, Hodgkin disease, generalized malignancy, and multiple myeloma; solid organ transplant; and iatrogenic immunosuppression including long-term systemic corticosteroid and radiation therapy.

**—Annualized timeline for influenza vaccination unless contraindicated remains in place.
Invasive fungal infections are a significant cause of mortality and morbidity, particularly in immunocompromised patients with hematologic malignancies and hematopoietic stem cell recipients, as well as solid organ transplant recipients. In the United States, Candida accounts for the majority of cases of health care–associated bloodstream infections. Even in light of newly available antifungal agents, the costs of antifungals are substantial, while the mortality for invasive aspergillosis and invasive candidiasis remains high. Retrospective studies report that 30% to 50% of overall antifungal prescriptions were not optimized or inappropriate. The rate of inappropriate antifungal prescribing is similar to that for antibiotics, demonstrating the alarming need for antifungal stewardship. The role of stewardship may offer value to optimizing clinical outcomes while minimizing antifungal overuse and costs, therefore also controlling resistance developed from selection pressure. Other challenges of treating invasive fungal infections include rising drug resistance and delayed initiation of therapy due to the lack of rapid and accurate diagnostic tools.

The extent of knowledge and understanding about antymycotic resistance and drug-resistant fungal infections is still unclear. Particularly, infections caused by Candida auris are of recent serious concern because of the inherent multidrug resistance of the fungi pathogen, limiting therapeutic options. According to the Centers for Disease Control and Prevention (CDC) surveillance data, approximately 7% of all Candida bloodstream isolates were fluconazole resistant and mostly identified as Candida glabrata. Additionally, echinocandin resistance in C. glabrata isolates has doubled from 4% in 2008 to 8% in 2014. Not only is antifungal resistance emerging with Candida species but it is also, more recently, increasing with Aspergillus species. Reported widespread azole resistance is also increasing in Aspergillus fumigatus, which was first documented in the Netherlands and is now seen in various regions of the world. Recent surveillance studies have identified azole resistance as a result of widespread environmental fungicide use.

Compared with antibiotic stewardship, published experience focusing on antifungal stewardship, as well as drug-resistant fungal pathogens, is sparse and limited but emerging. Nevertheless, rising bacterial and fungal resistance is an internationally recognized and public threat, leading to the increasing need for the implementation of antimicrobial stewardship as addressed by the newly effective Joint Commission standard for hospitals. Additionally, the CDC offers support that complements other existing guidelines pertaining to antimicrobial stewardship, such as the recent 2016 guidelines by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America. The IDSA guideline recommendations regarding interventions for optimal antifungal use focus on immunocompromised patients, including those with hematologic malignancy or solid organ transplant.

The Time for Antifungal Stewardship Programs Is Now

The growing threat of resistance and substantial costs for treating these infections accentuates the need for programs focused on appropriate treatment.
IMPLEMENTATION AND IMPACT OF ANTIFUNGAL STEWARDSHIP PROGRAMS

In parallel with the CDC core elements of antimicrobial stewardship, Muñoz and colleagues described 7 essential elements for antifungal stewardship.18,20 Although limited studies exist, there are some that highlight an overall positive impact of antifungal stewardship and interventions. A 12-month prospective study in a British tertiary referral hospital either discontinued or changed nearly half of amphotericin B and echinocandin treatments after implementation of an antifungal stewardship on high-cost antifungals, leading to significant health care cost savings.21 Alternatively, a different stewardship approach may include interventions made on positive fungal cultures, which have shown various results on the impact on clinical outcomes, which may improve time to effective therapy,22 increase proportion of patients who receive an ophthalmologic examination,23 or reduce 30-day mortality.24

CHALLENGES AND BARRIERS TO ANTIFUNGAL STEWARDSHIP PROGRAMS

There are numerous challenges in early diagnosis and treatment of invasive fungal infections, requiring the expertise of a collaborative group of trained infectious diseases specialists, clinical microbiologists, and other specialists in main prescribing departments such as hematology and oncology.19 Microbiology labs at institutions may not be able to readily test and determine susceptibilities for fungal isolates. Therefore, clinicians are limited in distinguishing drug-resistant infections based only on clinical suspicion.20

Within the IDSA guidelines, recommendations related to antifungal stewardship include interventions that incorporate nonculture-based fungal markers, candidemia-care bundles, and prospective audit and feedback, similar to antibiotic stewardship.19 Utilization of galactomannan, (1-3)-β-D-glucan, or fungal polymerase chain reaction has demonstrated effective and safe reductions in antifungal treatment in high-risk patients with hematological malignancies. In addition, β-D-glucan is currently being studied to assist stewardships in de-escalation of broad-spectrum antifungals in patients with severe sepsis or septic shock receiving treatment in a multicenter, prospective, open-label, randomized trial.25 An example of other stewardship interventions includes implementation of candidemia-care bundles, which was associated with improved care such as increasing use of appropriate antifungal therapy and rates of ophthalmologic examinations.26

Specifically, with antifungal stewardship, there are certain areas for interventions that may differ from antibiotic stewardship to reduce antifungal resistance and selection pressure. For example, appropriate indications for antifungal prophylaxis and treatment should be evidence-based and selected in clinical situations that are efficacious, while avoiding use where fungal or mold colonization may occur.26 Only 55% of physicians were able to correctly differentiate between infection and colonization in a survey of 200 providers, including those from medicine, pediatrics, and surgery, implying that there is a need for education on appropriate antifungal use.27 Both antimicrobial and antifungal stewardships prioritize education as a core element.18,20 Pharmacists have an expertise in pharmacotherapy that is pertinent for effective therapeutic drug monitoring, especially in optimizing antifungals with pharmacokinetic variability.28 However, there are also limitations in availability of laboratory assays and validated efficacy and safety data on drug monitoring.

Overall, there is a great need for establishing antifungal stewardships in institutions with significant antifungal use due to the growing resistance, substantial costs, and potential to optimize outcomes. This is a collaborative effort that requires the teamwork of specialists in dynamic areas among physicians, pharmacists, and microbiologists, at minimum. The success of antifungal stewardship is defined on institution-specific needs and the epidemiology of the hospital. Documented inappropriate use of antifungals warrants opportunities for improvement and education, as part of the core elements of stewardship. Opportunities include interventions requiring infectious diseases consultation for fungemia, candidemia-care bundles, appropriate use of diagnostic biomarkers, therapeutic drug monitoring, and retrospective audit and feedback.29

References are available at ContagionLive.com.

Clinicians are limited in distinguishing drug-resistant infections based only on clinical suspicion.
Improving Diagnosis of Lyme Disease: Laboratory and Clinical Approaches

BY GINA BATTAGLIA

Diagnostic testing for Lyme disease is challenging because of the low sensitivity of currently approved laboratory tests, the broad spectrum of clinical presentations, and differences in how clinicians interpret findings. Therefore, diagnosis may be optimized with a careful assessment of risk factors for exposure and the patient’s pattern of symptoms, according to experts who participated in a Contagion® Peer Exchange panel.

The panelists also discussed novel technologies that could improve the sensitivity and specificity of laboratory-based diagnostic testing for Lyme disease, particularly in early-stage infections, but stated that mainstream adoption of these tests may be slow due to the reluctance of the Centers for Disease Control and Prevention (CDC) and other governing organizations to adopt new methods.

LABORATORY-BASED DIAGNOSTIC TESTING: THE 2-TIERED APPROACH

The current guidelines for diagnostic testing of Lyme disease from the CDC and the Infectious Diseases Society of America recommend 2-tiered serologic testing with an enzyme-linked immunosorbent assay (ELISA) followed by a confirmatory Western blot test if the ELISA is positive. However, the sensitivity for this 2-tiered approach is only about 50%, according to Samuel Shor, MD, FACP, and has been shown to be less sensitive in the early stages of the disease because of the lag time between infection and development of detectable levels of antibodies.

Dr. Shor also pointed out that similar to results from tests for other infectious diseases, an antibody immune response is likely to be demonstrated in patients with greater immune suppression. “The sicker you are, paradoxically, the more likely you’ll be overlooked,” he said.

Cultures of the Borrelia burgdorferi (B. burgdorferi) pathogen are considered by most experts to be the gold standard for confirming Lyme disease. However, culturing the pathogen is not routinely available in clinical practice because of the relatively low sensitivity, long incubation time (cultures are kept for 8 to 12 weeks before being considered negative), and need for complex growth media. Furthermore, a single dose of antibiotics may interfere with the ability to culture the B. burgdorferi pathogen.

However, Leonard Sigal, MD, noted that the sensitivity and specificity of the 2-tiered
testing approach depends on what the clinician perceives as the gold standard and how he or she defines Lyme disease. Furthermore, Robert C. Bransfield, MD, DLAPA, stated that using solely an antibody-based test for detection of the Borrelia burgdorferi organism is problematic given that the microbe suppresses and evades the immune system.

However, he and the panelists agreed that the immunosuppressive nature of B. burgdorferi is not the sole contributor to the inaccuracy of testing, as ELISAs and Western blotting are highly sensitive for HIV. Nevertheless, the panelists stated that the 2-tiered serologic testing has insufficient sensitivity to diagnose Lyme disease.

CLINICAL DIAGNOSIS: GEOGRAPHIC CONSIDERATIONS AND MULTISYSTEMIC MANIFESTATIONS

In the absence of a highly sensitive laboratory test, the panelists discussed the importance of considering a patient’s risk factors for exposure and clinical presentation when assessing the likelihood of Lyme disease. According to data from the CDC, 95% of confirmed cases of Lyme disease were reported from 14 states in the northern and northeastern parts of the United States.5

However, Patricia V. Smith also noted that many investigators believe that Lyme disease is more widespread than traditionally thought, and Shor emphasized the importance of using clinical judgment when obtaining a patient history. He cited risk factors for exposure, including travel or location within a high-risk environment, but also stated that patients can still contract the disease in low-risk areas of the country, particularly in grassy areas and low brush, which are habitats for ticks and the mice that transfer them.

When assessing the patient’s clinical presentation, Drs. Bransfield and Shor emphasized the importance of recognizing characteristic symptom patterns. According to Dr. Shor, arthralgia and arthritis often migrate from one joint to another with or without inflammation, and the autonomic nervous system is often affected, with symptoms such as postural orthostatic tachycardia syndrome and fractioned and nonrestorative sleep. “I ask over 300 questions whenever I see a patient with Lyme disease,” said Dr. Bransfield.

“You see a certain pattern that evolves; it’s a multisystemic illness that can evolve over time.”

However, Dr. Sigal pointed out that the broad spectrum of clinical presentations can drastically influence the clinician’s index of suspicion. Although the characteristic erythema migrans, facial palsy, lymphocytic meningitis, rapidly progressive heart block from Lyme carditis, and arthritis with large effusions would raise the clinician’s index of suspicion (particularly in endemic areas), patients who have less well-defined symptoms with causes that are difficult to identify require a more careful assessment, stated Dr. Sigal. “The index of suspicion has to be high enough for you to actually say, ‘Well, I don’t know that this is Lyme disease, but if it is, I want to make sure that this person is treated.’” The question is, “What’s the reasonably high level of likelihood?”

For patients in whom he has a moderate level of suspicion, Dr. Shor administers a therapeutic trial of minocycline, because of its high central nervous system penetration, for 1 month and assesses whether symptoms improve to determine if the symptoms were caused by Lyme disease. However, he warned that patients with Lyme disease may exhibit a Jarisch-Herxheimer response, an inflammatory response related to the introduction of or change in antibiotics in spirochetal infections, which may make their symptoms appear worse at first.

IMPROVING SENSITIVITY OF LABORATORY-BASED DIAGNOSTIC TESTING

The low sensitivity of the current 2-tiered testing and the broad spectrum of clinical presentations make diagnosis of Lyme disease a complex clinical process, according to Dr. Bransfield. He and the panelists discussed novel technologies that could improve laboratory-based testing and diagnosis, particularly in the early stages of disease.

Dr. Shor discussed a recent study6 that he and his colleagues published in which they used a novel analyte harvesting nanotechnology (Nanotrap particles) to super-concentrate urinary Borrelia outer surface protein A (OspA), a highly specific protein across multiple strains, and probed the urine samples with a highly specific anti-OspA monoclonal antibody. Prior to treatment, all 24 patients who received a new erythema migrans rash diagnosis tested positive for urinary OspA and 8 of 8 patients went from detectable to undetectable levels after symptom resolution post treatment.

Dr. Shor also noted that this test could be particularly useful for patients in the early stages of disease, who often test negative on ELISA tests because they have not had an immunologic response. Dr. Sigal also added that Nanotrap particle–based testing may introduce a sensitive and specific option that is more convenient than polymerase chain reaction testing, which may be useful for diagnosing an active infection in patients but is difficult to perform regularly.

However, Smith noted that the biggest obstacle for this and other novel technologies may be persuading the CDC to adopt new testing methods. “The CDC is very reluctant to move on to new technology,” she said. “They want to stick with a 2-tier, antiquated test that, again, is probably missing at least 50% of our patients.”

References are available at ContagionLive.com.
HIV-Infected Child Maintains Remission Without ART Since 2008

By Kristi Rosa

This is not the first time that a child who received treatment early on in their life achieved prolonged control of the virus after stopping treatment.

(continued from cover)

The child had been enrolled in a clinical trial, called Children With HIV Early Antiretroviral Therapy, or CHER, which was funded by the National Institute of Allergy and Infectious Diseases (NIAID). In the trial, investigators looked at HIV-infected infants who were randomly assigned to 1 of 2 groups. One group of children received deferred ART, while the other received early, limited ART for either 40 or 96 weeks. The South African child was 1 of 143 infants who received early ART for 40 weeks.

Before receiving ART, the infant presented with a high viral load, but after treatment, by the time the child was about 9 weeks, viral suppression was achieved, according to the press release. After the child reached 40 weeks, the investigators stopped the treatment and kept a close eye on the infant’s immune health. During follow-up examinations over the course of several years, the child was reported to have remained in "good health," according to the press release. The release also stated that although it is "not standard practice in South Africa to monitor viral load in people who are not on ART, recent analyses of stored blood samples taken during follow-up showed that the child has maintained an undetectable level of HIV."

When the child was 9 and a half years old, the investigators performed laboratory and clinical studies dedicated to looking at the child’s immune health and HIV presence. Their findings, according to the press release, were as follows:

- Other than a reservoir of virus that was integrated into a tiny proportion of immune cells, they did not detect evidence of infection. The child had a healthy level of immune cells and an undetectable viral load and presented with no associated symptoms. A trace of immune system response to the virus was detected, but they found no evidence that the virus was capable of replication.

Furthermore, the child did not exhibit any genetic characteristics associated with spontaneous control of the virus, which suggests that the “40 weeks of ART provided during infancy may have been key to achieving HIV remission.”

“To our knowledge, this is the first reported case of sustained control of HIV in a child enrolled in a randomized trial of ART interruption following treatment early in infancy,” said Amy Violari, FCPaed, coleader of the reported case and CHER trial, in the press release. Caroline Tiemessen, PhD, whose laboratory is analyzing the child’s immune system, added that they believe there may be other factors at play in addition to the early ART suggesting that the “40 weeks of ART provided during infancy may have resulted in HIV remission. They hope to find out more by further studying the child.

This is not the first time that a child who received treatment early on in their life achieved prolonged control of the virus after stopping treatment. The "Mississippi baby," who was born with the virus in 2010, received treatment just 30 hours after birth and stopped the treatment at about 18 months. The child did not need drugs to control the virus for 27 months before it was detected in her blood. Investigators reported another similar case in 2015, when a French child born with the virus in 1996 started treatment at 3 months and stopped treatment between 5.5 and 7 years of age. That child achieved prolonged control of the virus without drug assistance “more than 11 years later,” according to the press release.

“Further study is needed to learn how to induce long-term HIV remission in infected babies,” Anthony Fauci, MD, director of NIAID, of the National Institutes of Health, said in the press release. “However, this new case strengthens our hope that by treating HIV-infected children for a brief period beginning in infancy, we may be able to spare them the burden of lifelong therapy and the health consequences of long-term immune activation typically associated with HIV disease.”

<table>
<thead>
<tr>
<th>SUMMARY OF THE GLOBAL HIV EPIDEMIC (2016)</th>
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<tbody>
<tr>
<td>Number of people living with HIV in 2016:</td>
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<tr>
<td>Total 36.7 million [30.8 million - 42.9 million]</td>
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<tr>
<td>Adults 34.5 million [28.8 million - 40.2 million]</td>
</tr>
<tr>
<td>Women 17.8 million [15.4 million - 20.3 million]</td>
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<tr>
<td>Men 16.7 million [14.0 million - 19.5 million]</td>
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<tr>
<td>Children (&lt;15 years) 2.1 million [1.7 million - 2.6 million]</td>
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<tr>
<td>People newly infected with HIV in 2016:</td>
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<tr>
<td>Total 1.8 million [1.6 million - 2.1 million]</td>
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<tr>
<td>Adults 1.7 million [1.4 million - 1.9 million]</td>
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<tr>
<td>Children (&lt;15 years) 160,000 [100,000 - 200,000]</td>
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<tr>
<td>AIDS deaths in 2016:</td>
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<tr>
<td>Total 1.0 million [830,000 - 1.2 million]</td>
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<tr>
<td>Adults 890,000 [740,000 - 1.1 million]</td>
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<tr>
<td>Children (&lt;15 years) 120,000 [79,000 - 160,000]</td>
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Source: UNAIDS/WHO estimates.
As HIV Drug Resistance Grows, WHO Calls for Global Action

BY DANIELLE MROZ, MA

(continued from cover)

WHO director-general, commented on this growing threat in the alert, stating, “Antimicrobial drug resistance is a growing challenge to global health and sustainable development. We need to proactively address the rising levels of resistance to HIV drugs if we are to achieve the global target of ending AIDS by 2030.”

WHO stressed in its alert statement that “mathematical modelling shows [that] an additional 135,000 deaths and 105,000 new infections could follow in the next 5 years if no action is taken, and HIV treatment costs could increase by an additional US $650 million during this time.”

HIV can develop resistance to drugs when individuals do not adhere to their prescribed treatment plan, according to the statement. This lack of adherence is often the result of not having consistent access to quality HIV treatment and care. According to the report, those individuals who do have resistance to the HIV drugs will often “start to fail therapy and may also transmit drug-resistant viruses to others. The level of HIV in their blood will increase, unless they change to a different treatment regimen,” something that may require more-expensive drugs that individuals in low- and midincome countries may have a hard time obtaining.

A total of 36.7 million individuals are living with HIV worldwide, and, according to available data from the WHO report, 19.5 million of these individuals “were accessing antiretroviral therapy in 2016.” Although the majority of these individuals are reported to be responding well to treatment, additional instances of drug resistance continue to occur. To this end, WHO will be issuing new guidelines “to help countries address HIV drug resistance,” according to the alert. Those countries where resistance has been detected are urged to reassess their HIV treatment programs and take immediate action if treatment failure is detected.

“When levels of HIV drug resistance become high, we recommend that countries shift to an alternative first-line therapy for those who are starting treatment,” said Gottfried Hirnischall, MD, director of WHO’s Department of HIV/AIDS and Global Hepatitis Programme, in the alert. Collaboration with major partners from all corners of the world will be required to tackle the threat of HIV drug resistance. Therefore, according to the alert, WHO is releasing a new 5-year Global Action Plan that will “call on all countries and partners to join efforts to prevent, monitor, and respond to HIV drug resistance and to protect the ongoing progress [toward] the Sustainable Development Goal of ending the AIDS epidemic by 2030.”

WHO also announced that it is developing “new tools to help countries monitor HIV drug resistance, improve the quality of treatment programs, and transition to new HIV treatments, if needed.” The new guidelines and reports were presented at the International AIDS Society Conference in Paris: 9th IAS Conference on HIV Science.

Box: WHO Key Guidelines and Normative Tools include:

- A new information note on point-of-care early infant diagnosis assays to support the timely detection of children with HIV
- The results of the Self-Testing Africa initiative, an implementation research effort, together with a new landscape report on rapid diagnostic tests for HIV self-testing
- A prioritized research agenda for children and adolescents to address low treatment scale-up and quality care for this group
- New guidelines on advanced HIV disease and rapid initiation of antiretroviral therapy (ART) recommending screening, treatment, and prophylaxis for major opportunistic infections (such as tuberculosis and cryptococcal disease) and rapid initiation of ART and adherence support for people with advanced HIV
- A new report outlining how countries can provide differentiated-care tailored services for different needs of patient groups
- A new technical update advising countries on what to consider when transitioning to a new treatment regimen, including dolutegravir
(continued from cover)

clinicians, at the Society of Infectious Disease Pharmacists Society Day at the American Society for Microbiology Microbe 2017 conference, particularly considering the recent introduction of the PRE-PEN, a test for penicillin allergy now used at many hospitals across the country.

According to Dr. Jeffres, the majority of penicillin allergy labels indicated for patients are inaccurate, and it is this inaccuracy that leads to an increase in the use of secondary antibiotics (such as vancomycin and fluoroquinolones). Increased use of these antibiotics may lead to an upsurge in resistant infections. In addition, further data have shown that the mislabeling of penicillin allergies has led to more treatment failures and an overall cost increase to the patient.  

As any clinician will admit, though, once a patient is labeled as having a penicillin allergy, it is hard to declassify them. When a clinician attempts to prescribe a preferred antibiotic to that patient, red flags abound in the electronic medical record indicating potential cross-reactivity for that antibiotic class for the patient. Dr. Jeffres argues, however, that clinicians should not be looking at cross-reactivity among drug classes but rather between specific antibiotics, even within class.

For example, results from new research have shown that patients with a true-penicillin allergy tend to have similar reactions to those antibiotics that share a common side chain with penicillin. To illustrate, Dr. Jeffres shared a chart (available online at contagionlive.com/link/218) showing the side chain similarities between cephalosporins and penicillin. She highlighted that cefotaxin and penicillin share a similar side chain, but cefazolin, for example, does not share a side chain with any beta-lactam.

Clinical data to support these findings include a study out of Italy that looked at patients with delayed onset reactions to penicillin. The investigators performed skin and patch testing on 214 patients and found that none had reactions to beta-lactams with similar side chains (data on the penicillin to penicillin class cross-reactivity notwithstanding).

Additional research included a “robust” study of 24 individuals who were indicated to have immediate allergic reactions to cephalosporins. The investigators performed skin tests of different cephalosporins on the individuals and found that 9 of the 24 individuals had more than 1 cephalosporin allergy. Eight of the 9 individuals all had cross-reactivity between cefotaxime, ceftriaxone, and/or cefuroxime. All these antibiotics share a similar R1 chain (which amounts to a double bond off a nitrogen, next to the beta-lactam base structure).

According to Dr. Jeffres, there are adequate data to support that skin, oral, and intravenous challenges show a lack of allergic reaction in patients with a penicillin allergy to antibiotics with dissimilar side chains (data on the penicillin to penicillin class cross-reactivity notwithstanding).

Based on these findings, what should clinicians do when they have a patient with a history of penicillin allergy who needs a penicillin to treat an infection? As with most medical conundrums, the answer is not simple. Certainly, clinicians can give every patient with a penicillin allergy a skin test. Research has shown that these tests are simple and quick and work to increase appropriate beta-lactam use. However, Dr. Jeffres said that the test has low clinical utility. The penicillin skin test identifies only immunoglobulin E (IgE) reactions, and the results of the test would not de-label a patient as no longer having an allergy to penicillin, unless they have a history of IgE reaction. Clinicians should know that they can safely use cephalosporins and carbapenems in these patients without administering a skin test.

Once a patient is labeled as having a penicillin allergy, it is hard to declassify them.

Because of the importance of side chains, Dr. Jeffres advised the audience to not blindly accept a penicillin, cephalosporin, or carbapenem allergy listed on a patient chart. Clinicians should push further to find out the specific medication to which the patient showed an allergic reaction. Dissimilar cephalosporins and carbapenems should be used, and clinicians should update the patient’s allergy label if a beta-lactam is tolerated, even if the tolerance is unrelated. The more data made available to all clinicians interacting with the patient, the easier it will be to make informed and appropriate decisions about that patient’s care.

Although these actions may amount to some small extra steps for the clinician, they could amount to greater positive outcomes for the patient and more-appropriate antibiotic use, which would ultimately positively affect the entire population.  

References available on ContagionLive.com.
ASM Microbe 2017

David Relman, MD, on the Potential of the Microbiome in Medicine

BY W. TODD PENBERTHY, PHD

(continued from cover)

Contagion®: How do you think the future of medicine will incorporate microbiome-based therapies?

Dr. Relman: That is hard to predict given so many uncertainties. One area of the future may be microbiome research, which may help with diagnostics and prognostics to find patients at greater risk for developing infections like Clostridium difficile (C. difficile). A second area may be in treatment, but I’m cautiously optimistic as it is still not so simple. A few examples of therapeutically beneficial small molecules made by bacteria have been identified.

The third area of future focus is in prevention. It will be possible at some point to sort out what confers stability or resilience in a person who is about to enter hospitalization, or take a drug, or experience a surgical procedure, or is at risk of some disease condition. An intervention may involve provision of groups of organisms thought to be beneficial, into the gut, followed by feeding of those organisms to keep them there. It is important to remember that data indicate that it is hard to instill an organism and get it to stay. Therefore, we must know how to feed and promote said therapeutic groups of organisms.

Can we get these organisms through an orally ingested pill, instead of insertion of a pill rectally (as in the case of fecal microbiota transplant)?

Fecal transfer is being done in a pill, but it turns out you need more organisms to have an effect if you administer it orally than if you administer it rectally. We are talking about needing lots of pills, like 20 to 30 big pills a day, to get past the stomach. Someday we should be able to do this, for sure. There are many companies and researchers trying to sort out the minimum ecosystem needed, eg, 14 different strains for 14 different people. Then, the bacteria have to be fed appropriately or else they will be eliminated by selective advantage. The reason fecal transplants work so well is that they are given to the person precisely at the time they are beginning their recovery from a bout with C. difficile colitis. Most significantly, these people have a damaged ecosystem in their gut that is teetering and more vulnerable to elimination. If it’s left alone, it creates an inflammatory environment that most healthy bacteria cannot tolerate, while C. difficile thrives. Now that we understand this, the organisms must be fed properly during this time while we are also introducing antibiotics targeting C. difficile.

Speaking of feeding the organisms, can an individual also experience bacterial effects from frozen vegetables in a “food as medicine” paradigm?

Definitely. This can help indirectly, in the sense that many fruits and vegetables will properly feed your beneficial organisms by providing fiber, and potentially directly, by providing therapeutic-beneficial organisms. The freezing process does not kill everything—organisms with spores, capsules, or strong cell walls can survive and then thrive. For example, in a study presented at the ASM Microbe conference, a small molecule was identified in Lactobacillus that inhibits the growth of antibiotic-resistant organisms. A few years ago, another study identified a small molecule named lactocillin that is made by a different Lactobacillus species that normally lives in the vagina. [The molecule] doesn’t affect healthy bacteria, but it does have potent antibacterial activity against a range of gram-positive vaginal pathogens.

Can you discuss the connection between the microbiome and neurodegenerative disease?

I have followed the work of Dr. Perlmutter [neurologist David Perlmutter, MD, in private practice in Naples, Florida, and author of Grain Brain, among other books]. It’s interesting and worthy of further exploration, but I am concerned with the links he makes between the microbiome and a variety of clinical disorders. These are usually associations, not causation studies. Secondly, if there is a link between the microbiome and depression or Parkinson’s disease, for example, it seems likely that it would be a small contribution, because we are already aware of other factors that are known to be connected. [However,] that doesn’t mean we should not be focusing on it, because it may be one of the things that we can do something about. We cannot typically do anything about a genetic problem, but changes in the microbiome are conceptually simple.

Any other anatomies that are addressed in microbiome research besides the gut?

The first anatomy of microbiome research focus was the mouth. The most common infectious disease in the United States is, in fact, gum disease or oral cavities, but, unfortunately, the research community that studies the mouth typically publishes in different journals and goes to different meetings. They have a long proud tradition. It is unfortunate that there is not more overlap in the research communities. Other non-gut anatomies of focus in microbiome research include the skin and vagina.

What are the next steps for your research?

We are working on several things. We are generally interested in what makes the microbiome stable and what allows it to recover from a disturbance—for example, the introduction of an antibiotic. We do a lot of longitudinal studies involving healthy people, where we observe what happens to the microbiome after a colonic clean-out, antibiotic drug, or diet shift. By looking at many people, we try to find the common features they have for remaining stable.

We are also looking at pregnancy and how [the microbiome] affects gestational outcome. Most significantly, we are finding that a certain kind of microbiome promotes premature labor. Hopefully, one day, we may help to prevent premature delivery, and instead promote full-term, healthy in utero development.
coinfections is antibiotic pressure. Disruption of the gut flora can lead to decreased immunity, which promotes colonization by *Candida* and the presence of the microbe in the blood (candidemia). *C. difficile* can also take advantage of altered gut flora to establish an infection. The 2 infections often occur separately, but they can co-exist. How often that occurs is unclear.

“Our objective was to describe the prevalence and clinical characteristics of candidemia patients with *C. difficile* coinfection and to identify potential risk factors for the development of candidemia-*C. difficile* coinfection in patients with candidemia,” said Sharon Tsay, MD, Mycotic Diseases Branch and Epidemic Intelligence Service, CDC, during an oral abstract session at the 2017 ID Week Conference in San Diego, California.

The coinfection was defined as the diagnosis of *C. difficile* infection within 90 days of the identification of candidemia. The data were from CDC candidemia surveillance surveys from 2014 to 2016 conducted nationwide as part of the agencies’ Emerging Infections Program. Data collected included demographics, microbiology, underlying medical conditions, health care exposures, and death.

Of the 2129 cases of candidemia, 193 (9%) patients were coinfected by *C. difficile* and 1936 (91%) displayed candidemia. About two-thirds of the *C. difficile* infections were detected prior to candidemia diagnosis (median 10 days), with the remaining one-third detected a median of 7 days after candidemia diagnosis. Demographically, the coinfected patients were comparable to their counterparts with candidemia alone with respect to age (19-44, 45-64, and ≥65 years), sex, and black race.

The similarities between the 2 patients group extended to underlying conditions, including liver disease, inflammatory bowel disease, pancreatitis, hematologic malignancy, stem cell transplantation, and HIV. Differences in underlying conditions between the coinfected and candidemia groups included prevalence of diabetes (42% vs 31%; odds ratio [OR], 1.61; 95% CI, 1.19-2.18) and solid organ transplant (6% vs 2%; OR, 4.07; 95% CI, 2.06-8.07).

Comparison of health care exposure revealed difference between the coinfected and candidemia groups concerning hemodialysis (23% vs 12%; OR, 2.19; 95% CI, 1.52-3.16), prior hospitalization (72% vs 57%; OR, 1.89; 95% CI, 1.37-2.62), and central venous catheterization (79% vs 69%; OR, 1.63; 95% CI, 1.14-2.33). The groups were comparable concerning the *Candida* species isolated and the 30-day mortality rate (both 25%).

Multivariate logistic regression analysis revealed 4 risk factors of coinfection: diabetes (OR, 1.41; 95% CI, 1.03-1.92), solid organ transplant (OR, 2.95; 95% CI, 1.46-6.00), hemodialysis (OR, 1.82; 95% CI, 1.24-2.67), and prior hospital stay (OR, 1.74; 95% CI, 1.26-2.43).

Because the data were collected from case report forms, no other information on the *C. difficile* infections including treatment was available.

"In patients with *C. difficile* infection, 1 in 100 developed candidemia. In patients with candidemia, nearly 1 in 10 had *C. difficile* infection. The message for clinicians is to be vigilant. Look for candidemia and *C. difficile* infection occurring together. Clinicians should identify patients at greater risk and review best practice for antibiotic prescribing,” said Dr. Tsay.
ID Week 2017

Health Officials Respond to “Surprising Return” of Hepatitis A

BY KRISTI ROSA

(continued from cover)

“To really understand hepatitis A virus outbreaks, it’s important to understand the global patterns of transmission,” Dr. Foster explained. In the United States, endemicity is very low and outbreaks are uncommon; hepatitis A infection is typically seen in travelers who have visited endemic regions. However, she added, “When outbreaks do occur, they can be large and prolonged.”

The hepatitis A vaccine was first introduced in 1995, according to the CDC, and since then, health care professionals routinely vaccinate all children, travelers to certain countries, and persons considered at-risk for infection. “Since the introduction of the hepatitis A vaccine, reported cases of hepatitis A infection have decreased by 95%,” Dr. Foster shared.

Although incidence has decreased in all age groups, high rates of infection remain in adults: before the vaccine, most outbreaks involved asymptomatic children. As individuals grow older, not only are they more likely to be symptomatic, but the severity of the disease and their likelihood of experiencing adverse consequences increase. Perhaps even more unsettling is that there are no universal vaccination recommendations for adults, and vaccination uptake among at-risk adults, who do have existing vaccination recommendations, remains low.

The 5 largest hepatitis A virus outbreaks in the United States, in the postvaccine era, have occurred within the last 5 years, with over 1400 outbreak cases having been reported to the CDC in just the last 15 months. “And just to put this into perspective,” Dr. Foster stated, “only 459 outbreak cases were reported in the 10 years between 2005 and 2015,” underscoring the severity of the current situation.

“Another distinctive aspect about the recent hepatitis A outbreaks from the past year is that there was a shift to hepatitis A genotype 1B,” Dr. Foster shared. She added that most of the outbreaks that have occurred within the last 5 years have been associated with genotype 1B, including the current outbreak in San Diego.

To this end, Dr. McDonald took the audience on a journey from the beginning of the San Diego hepatitis A outbreak investigation up to current efforts being made to quell it. This outbreak started in early March 2017, when an increase in the number of hepatitis A cases was noted to be above baseline. “From November 2016 through February 2017, between 7 and 9 cases were expected and 19 cases were reported,” he shared.

The San Diego County Health and Human Services Agency investigation approach included:
- The administration of a standard hepatitis A questionnaire addressing potential exposure sources (food, drink, close contact)
- A supplemental questionnaire that looked at drug use, homeless service access, hygiene practice, and restroom use
- Identification of cases with sensitive occupations (food handlers or health care workers)
- Investigating possible sources of the outbreak (food, water, drugs) in conjunction with environmental health workers
- Arrangements to send specimens to the CDC’s Viral Hepatitis branch to confirm presence of hepatitis A virus RNA

“From 2009 to 2016, there were just 24 to 36 cases per year,” Dr. McDonald reported, most likely due to the introduction of the hepatitis A vaccine. However, in 2017, there has been a rise. “As you can see in 2017, we are now at just under 500 cases reported so far.” He confirmed that as of Monday, October 2, 2017, there have been 481 confirmed and probable cases associated with the ongoing outbreak as well as 17 deaths; 70% of those infected required hospitalization. Those infected range in age from 5 to 87 years, with the 5-year-old being the only pediatric case in this outbreak. A total of 33% of those infected are homeless and illicit drug users, 17% are homeless only, and 12% are illicit drug users only. “Most of the cases live in group homes, single-room occupancy hotels, or jail and have shared restroom facilities with one of those 2 at-risk groups,” he added.

“The majority of the cases in the outbreak are genotype 1B, and several of the infected individuals are suffering from a coinfection, with 17.5% of cases coinfected with hepatitis C and 5.8% coinfected with hepatitis B. Unfortunately, despite exhaustive investigation, a common source of the outbreak has yet to be identified.

Health care officials remain vigilant in their efforts to quell the outbreak. Their efforts include:
- Developing an Incident Command System to manage the outbreak
- Conducting case investigations
- Providing postexposure prophylaxis
- Ongoing communication with the United States Department of Housing and Urban Development on housing and sanitation
- Issuing a local health emergency advisory on September 1, 2017

The overall strategy to tackle this outbreak has involved vaccinating individuals who are at risk of infection, promoting proper sanitation and hygiene, and providing education for prevention.

“Hepatitis A is a routine childhood vaccination and children are well immunized in San Diego. However, like most of the country, and as Dr. Foster mentioned, we have lots of room for improvement in adults, particularly in travelers, men who have sex with men, illicit drug users, and people with chronic liver conditions,” Dr. McDonald stressed. A total of 45% of hepatitis A cases are illicit drug users and none had been previously immunized, indicating “major missed opportunities for prevention.” Local recommendations that have been raised to fix the problem have been: vaccinating the homeless, vaccinating those in close contact with the homeless population, and janitorial and sanitation workers.

In addition to these recommendations, efforts are being made on a street level, including mass vaccination events where health care workers take to the streets to make the vaccine available to at-risk individuals. The efforts seem to be working: 54,073 vaccinations have been issued since the outbreak was identified.

Efforts have also been made to improve sanitation. Over 5000 hygiene kits were developed and distributed to educate individuals on proper hygiene practices, and disinfection guidelines have been circulated. Furthermore, 66 handwashing stations were installed in areas with high concentrations of at-risk individuals.

“And we’ve actually researched and provided, to local cities, street sanitation protocols to better address the environmental burden of hepatitis A,” Dr. McDonald added.

More work is underway. Since the presentation at ID Week, Jerry Brown, the governor of California, declared a state of emergency to help direct funds toward controlling the outbreak and providing adults hepatitis A vaccines. In addition, community talks, public ad campaigns, and fact sheets have all been designed and distributed to educate the public, particularly those individuals who are at highest risk for hepatitis A infection.

“We continue to work with community stakeholders to increase vaccination efforts and awareness,” Dr. McDonald concluded in his presentation. The hope is that with these efforts, health officials will be able to turn the tide in the fight against this massive hepatitis A virus outbreak and hold off future infections. ▲

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The State of PrEP in 2017: Recent Data and Current Challenges

Although a once-daily pill to prevent HIV exists, US populations at highest risk have the lowest rates of usage.

BY CHRISTOPHER B. HURT, MD

Since it was approved by the US Food and Drug Administration (FDA) in 2012, preexposure prophylaxis (PrEP) has changed the HIV prevention landscape in the United States. At the end of the first quarter of 2017, an estimated 120,000 Americans were taking emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for PrEP. The number of new prescriptions remained stable at around 11,000 per quarter in 2016. This is good news for domestic prevention efforts, but data presented at the 2017 International AIDS Conference in Paris, France, highlight some of the continued challenges faced in our expansion of PrEP.

Investigators from Gilead Sciences, the manufacturer of FTC/TDF, examined pharmacy fulfillment data from January 2012 through September 2016 to describe trends and patterns in prescribing. In the first 2 years following FTC/TDF’s approval, women made up almost half (42%) of all individuals prescribed FTC/TDF for HIV prevention. Since 2014, the proportion of women has decreased dramatically, currently accounting for only 15% of all recipients. In addition, young adults represent a disproportionately small number of PrEP users relative to their importance as a key risk group; just 11% of men and 24% of women prescribed PrEP were under age 25. Although only 40% of prescriptions had associated race and ethnicity information, the trends seem likely to reflect fundamental inequities in health care access across the United States. In 2015, blacks and Hispanics/Latinos accounted for 45% and 24% of all new HIV diagnoses in the United States, respectively, yet they comprised less than a quarter of all PrEP recipients (13% Hispanic/Latino, 10% black) across the 4 years of available data. (Figure)

Taken together, the unevenness of PrEP’s uptake across at-risk groups highlights the work that remains to be done in implementation and scale-up; bringing attention to these disparities is a necessary first step in bringing about change. However, it is important to keep in mind that although PrEP can have a meaningful impact on HIV incidence, it is by no means a magic bullet.

In fact, modeling data from the Centers for Disease Control and Prevention (CDC) estimate that PrEP implementation can be expected to avert approximately 17,000 new infections over a 5-year period, assuming all the goals of the National HIV/AIDS Strategy are reached. In contrast, 168,000 infections could be prevented if 85% of individuals diagnosed with HIV were linked with care, and 80% of those linked with care are virologically suppressed. Clearly, antiretrovirals used as PrEP and treatment as prevention have an important role to play in controlling the epidemic, but their potential has not yet been fully realized.

Where do we go from here? Gilead’s data suggest that over the past year, the number of new prescriptions for PrEP has plateaued, but there are more than 120,000 people in the United States who are potential candidates for PrEP. Indeed, CDC analyses suggest that 1 in every 4 men who have sex with men, 1 in every 5 individuals who inject drugs, and 1 in every 200 heterosexuals has at least 1 indication for PrEP per the US Public Health Service’s 2014 guidelines, for a total of about 1.2 million Americans.

Those of us in the HIV prevention community need to expand our efforts to introduce and demystify PrEP for frontline providers and members of key, at-risk populations. Across the country, local AIDS education and training centers (NCATEC) have taken up this challenge. At the North Carolina AIDS Training & Education Center (NCATEC), we have partnered successfully with state and local health departments, AIDS advocacy groups, and community-based organizations to work on PrEP expansion. Since our efforts began in late 2014, NCATEC has curated a searchable map of known prescribers, allowing both consumers and providers to identify access points nearby. Examination of our map over time has allowed us to identify geographic gaps in service availability, which largely (and unsurprisingly) fall in rural, impoverished areas. In these communities, access to health care often depends on safety net providers located in community and rural health centers and public health department clinics.

In collaboration with Duke University, we have examined barriers to PrEP expansion into local health departments and are working on localized, tailored solutions to address them. In addition to our work with rural PrEP access, we have partnered with campus health centers across the state’s university system to make sure they are able to provide comprehensive sexual health services to their students. The specific inclusion of historically black colleges and universities has been an important part of our outreach efforts in North Carolina, as well, with trainings on their campuses provided by infectious diseases clinical faculty from both the University of North Carolina and Duke University.

Our success in PrEP implementation in a rural Southern state is a source of pride, but we have much work to do in the years to come. As we gather data on the state of PrEP expansion, we must continue to share our findings with advocacy groups and policy makers to shine a light on the structural inequalities that are restricting access. This is especially true in states that opted not to expand Medicaid, many of which are in the Southeast; the uncertain fate of the Patient Protection and Affordable Care Act has further complicated the situation for some at-risk individuals. Although those living with HIV can leverage a variety of services to help stably engage in care, none of those are available to uninfected, at-risk individuals—even though they often face similar challenges in transportation, employment, unstable housing, and care for mental health or substance use. These are formidable challenges to be sure, but not insurmountable, provided that there is political will and pressure applied from knowledgeable professionals like you.

References are available at ContagionLive.com.
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James S. Lewis, PharmD, FIDSA, Co-Director of Antibiotic Stewardship, Oregon Health and Science University