IDWeek 2017
Antibiotic Therapy for Staphylococcal Bloodstream Infections

A treatment algorithm for staphylococcal bloodstream infections (BSIs) featuring markedly shorter antibiotic therapy than the standard of care produces similar rates of success and serious adverse events—and for complicated infections, the algorithm approach works better. The good news from the randomized, multinational, open-label, adjudicator-blinded trial was presented at IDWeek 2017 in San Diego, California.

“The optimal duration of treatment for staphylococcal bacteremia is unknown. Long-course or short-course treatment may place the patient at risk. If treatment is too prolonged, there is a greater risk of the development of antibacterial resistance and antibiotic-associated adverse events. (continued on page 34)

Multidrug-Resistant Infections

Multidrug-Resistant Pseudomonas aeruginosa Infections: Hard to Treat, But Hope on the Horizon?

By Joshua Garcia, PharmD; Katherine Gruenberg, PharmD; Lynn Nguyen, PharmD; and Conan MacDougall, PharmD

Pseudomonas aeruginosa (P. aeruginosa) is an aerobic, gram-negative bacilli that can be found ubiquitously in soil, plants, and hospital reservoirs of water, including showers, sinks, and toilet water.1 A recent report from the National Healthcare Safety Network, summarizing the health care-associated infections from 4515 US hospitals from 2011 to 2014, reported (continued on page 9)

Antibiotics Prescribed by Dentists May Add to CDI Incidence

Of all the health care-associated infections that plague health officials, health care facilities, and patients alike, Clostridium difficile infection (CDI) is the most common, accounting for upward of 453,000 cases and a staggering excess annual financial burden of $1 million. The threat of C. difficile (C. diff) has investigators worldwide on a mission to learn more about the troublesome bacteria and get a better handle on preventing infections. At IDWeek 2017 in San Diego, California, Maria Bye, MPH, an epidemiologist at the Minnesota Department of Health in St. Paul, provided some concerning conclusions gleaned from an active population- and laboratory-based CDI surveillance survey: (continued on page 35)

IAS 2017

Study: Oral Truvada Safe & Tolerable for Use in Adolescents

With the lofty worldwide goal of ending the AIDS epidemic by 2030, researchers are working to cut back on the number of new HIV diagnoses by strengthening preventive strategies. Adolescents and younger individuals make up a growing share of those living with HIV worldwide, creating a need for preventive efforts specific to this population.

At the 9th International AIDS Society Conference on HIV Science in Paris, France, 2 teams of investigators reported findings related (continued on page 24)

Positive Results Seen in Study of Adolescent Use of PrEP Vaginal Ring

To halt the AIDS epidemic, investigators are looking into more ways to prevent infection in populations that are at particularly high risk, including adolescent girls and young women aged 15 to 24 years. According to the National Institutes of Allergy and Infectious Diseases (NIAID), this group accounted for 20% of new infections among adults worldwide in 2015, even though NIAID states that they make up just 11% of the adult population.

To address the need for preventive efforts tailored for this high-risk (continued on page 31)

5th C. diff Conference

New Tactics to Prevent and Control Clostridium difficile Infections

When it comes to the fight against infectious diseases, many agree that it’s better to prevent infections from happening than finding effective ways to treat them after they make their presence known. Prevention is particularly important when it comes to addressing Clostridium difficile (C. diff) infections (CDIs).

At the 5th Annual International C. diff Awareness Conference & Health Expo in Las Vegas, Nevada, Contagion® sat down with Maureen Spencer, RN, BSN, MEd, CIC, FAPIC, director of clinical implementation at Accelerate Diagnostics, for an exclusive interview on her presentation of strategies to prevent and control the transmission of the disease within health care facilities. (continued on page 32)

Hospital Mattresses: A Vector for Spreading Clostridium difficile

Clostridium difficile (C. diff) is known to cause around 250,000 infections each year, as well as a staggering 14,000 deaths. In response, health care workers everywhere have been channeling their efforts into preventing the life-threatening infection in their facilities. One way to do this is by strengthening disinfection efforts. As one researcher boldly pointed out at the 5th Annual International C. diff Awareness Conference & Health Expo, in Las Vegas, Nevada, one of the biggest vectors for spreading C. diff is largely unrecognized: hospital mattresses.

“You’re at risk for getting C. diff infections if you’re getting antibiotics, on proton pump inhibitors, if people aren’t washing their hands— (continued on page 30)
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A New Year, A New Lead, and New Offerings to Come

It is a pleasure to write you as the new editor-in-chief of Contagion. I have enjoyed watching this publication launch and rapidly scale up its offerings since it began 2 short years ago. I find the newness of Contagion appealing and am excited to help shape this young publication into the go-to resource for infectious diseases (ID) practitioners. It is my hope that Contagion will be a primary platform that practitioners use to stay up-to-date on ID-related news as our contributors summarize and synthesize the wealth of data available.

Since taking the reins, I have moved to expand upon the offerings in Contagion in some areas and refocus others. Two new sections have been created. Monica Mahoney, PharmD, will be leading “In the Literature” (page 8), where contributors provide critical analyses of new studies of importance in ID as they are published. Sara Schulz, MD, will lead our “Case Study” articles (page 36), where cases of diagnostic or therapeutic interest are described and reviewed, with pertinent teaching points highlighted. These sections are being introduced in this issue, and I am confident that they will become highlights of Contagion moving forward.

Each issue contains content in 6 areas, some of which have been refined. Viral Hepatitis has been revised from Hepatitis C to be inclusive of advances in other viral hepatid-leses. Acute Infections has replaced Respiratory Infections to include more acute-onset infections. Multidrug-Resistant Infections has evolved from Health Care-Acquired Infections to expand its scope as well. Stewardship and Prevention has been expanded to accommodate articles addressing the growing importance for antimicrobial stewardship across practice settings. In this issue, Jamie Wagner, PharmD, and Karin Clifford, PharmD, have authored a review of successful stewardship strategies for long-term care facilities. Emerging diseases has been re-titled Emerging and Re-Emerging Infections to make way for articles on both "new" pathogens, like Candida auris, and resurgent infections, such as sexually transmitted infections in the elderly. HIV/AIDS remains a section of importance as new therapies are developed and treatment approaches shift.

This issue of Contagion contains a feature by the team of Conran MacDougall, PharmD, et al, about the treatment of multidrug-resistant Pseudomonas aeruginosa (P. aeruginosa) infections. Pseudomonas is a pathogen that justifiably receives a lot of attention in ID circles, but some practitioners, myself included, have lost a bit of their focus on it as other resistant pathogens, such as carbapenem-resistant Enterobacteriaceae (CRE), have gained prominence. The authors remind us that P. aeruginosa remains the elephant in the room of Gram-negative pathogens in hospitals and take us through the new therapies that treat resistant strains.

As the ever-changing world of ID continues to evolve, so will Contagion, and I look forward to steering the publication to meet the growing demands on our profession to provide you with the most timely and relevant content to improve our practice and patient outcomes.

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

100 Years After Spanish Flu Pandemic, Influenza Research Opportunities Abound

In this issue of Contagion, we mark the 100th anniversary of the Spanish flu pandemic of 1918-1919 (page 16), which is reported to have caused more deaths in a single year than the Black Death that spread across Europe in the 14th century from 1346-1353. The influenza virus infected about 500 million individuals (one-third of the world’s population at the time) and close to 50 million died; 675,000 of these deaths were in the United States.

Researchers in the infectious diseases (ID) field are steadfast in their efforts to predict when the next big outbreak will hit. They agree that there will be another Spanish flu-like pandemic, but worry that we will be unprepared. As Michael Osterholm, PhD, MPH, director of the Center for Infectious Disease Research and Policy at the University of Minnesota laments in the article, “It is going to occur. It’s just a matter of when and where it starts.”

Other health experts from around the world, such as Margaret Chan, MD, former director-general of the World Health Organization, have warned that we have not done enough to prepare for the next pandemic, and countries are vulnerable as their populations grow and globalization increases. The influenza virus evolves from year to year, including those strains that are transmissible from animal to human, such as the H7N9 bird flu. According to Dr. Osterholm, H7N9 and its swine flu cousin, H1N1, are being watched very carefully. Indeed, he expects the next pandemic flu outbreak will be zoonotic in origin. Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, added, “[In 2009, H1N1] was percolating in the swine population for a while. We weren’t monitoring the population particularly well, so we missed it.”

Although there has been progress toward developing a universal flu vaccine, this space represents a tremendous opportunity for innovative research and an entrepreneur-ial approach to develop a response to protect the world’s population against a serious health threat. So much so that Bill and Melinda Gates have provided significant funding, to the tune of $100 million over the next 5 years, to the Coalition for Epidemic Preparedness Innovations. The coalition is aimed at developing vaccines against known diseases, such as influenza, and investing in next-generation technologies.

At a time when many in the health care field are focusing on curing mainstream issues such as diabetes and heart disease, it is important to take a step back and remember that despite all our advances in medicine, we remain vulnerable. Let us take this time, as we mark the anniversary of a devastating pandemic, to remind ourselves to remain vigilant and stay out ahead of problems before they arise. Contagion remains dedicated to keeping our readers informed on the latest news in ID through our print journal, website, and email newsletters.

Stay informed, and thanks for reading!

Mike Hennessy, Sr
Chairman and CEO

REFERENCE
Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Hard to Treat, But Hope on the Horizon?

Two recently approved agents offer significant activity against these hard-to-treat conditions.

BY JOSHUA GARCIA, PHARM.D; KATHERINE GRIENBERG, PHARM.D; LYNN NGUYEN, PHARM.D; AND CONAN MACDOUGALL, PHARM.D
Using a One-Health Approach to Combat Tick-Borne Diseases

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

Infections transmitted by ticks are increasingly recognized as important causes of disease in humans and pets in North America, said Susan Little, DVM, PhD, DACVM (parasitology), Regents Professor of Parasitology, Oklahoma State University, Stillwater, in a recent US Centers for Disease Control and Prevention Clinician Outreach and Communication Activity webinar.

Indeed, the US Department of Health and Human Services (HHS) recently announced the appointment of 14 members to the new Tick-Borne Disease Working Group. This group will provide expertise to help HHS in its efforts to identify unmet needs and research priorities in tick-borne diseases (TBDs) to improve federal coordination of efforts related to this serious public health problem.

Dr. Little noted that the past 3 decades have seen a dramatic rise in the number of certain species of ticks and their geographic distributions worldwide. The expansion in tick populations has led to an increased risk of infection for humans and animals with both established tick-borne agents and newly recognized ones, creating a serious One Health problem.

The introduction of infections to humans in new geographic locations can “catch local physicians off guard because they are not used to seeing certain TBDs in their local areas,” said Dr. Little.

Although the media tends to place much of the focus of TBDs on Lyme disease, Dr. Little stressed that ticks also transmit many other pathogens. In addition to other bacteria, they also transmit helminths and protozoa. “We’re learning more, especially in recent months, about viral transmission,” she added.

Dr. Little highlighted several challenges to controlling tick populations, such as the expanding geographic range of many ticks, and the presence of ideal environmental conditions and plentiful wildlife reservoir that which have allowed the numbers of ticks to increase. She discussed some of the most common tick species associated with dogs in North America. These are 3-host ticks, she noted: Each tick developmental stage feeds on its host and then detaches, molts in the environment, and then reattaches to a new host in the next stage. These ticks include the Lone Star tick (*Amblyomma americanum*) and the brown dog tick (*Rhipicephalus sanguineus*), among others.

According to Dr. Little, the tick stages of the brown dog tick have a strong host preference for dogs and are found everywhere dogs exist. “They are truly a dog phenomenon,” she said. Although these ticks can survive outside, they can also survive indoors and may produce massive infestations in homes that cause serious problems for humans and dogs. These indoor infestations can be difficult to eradicate and can be catastrophic, Dr. Little stressed, adding that owners should expect that environmental treatment efforts will take at least 6 months to eliminate this tick from indoor premises.

The stages of the other tick species may occur on a variety of wildlife hosts and other animal hosts, she said. Typically, these ticks exist and thrive on wildlife in their natural habitats, so the tick populations tend to increase when the wildlife populations increase.

Scientists and clinicians face significant challenges in controlling these tick populations, said Dr. Little. “Geographic expansion is a huge challenge to tick control,” she emphasized, adding that scientists’ ability to limit tick reproduction is also limited.

“Tick myths and misperceptions” also pose challenges to tick control, said Dr. Little. In veterinary medicine, these include underestimation of the risk of infestation for some pets. For example, although most people are by now aware of the risk of tick infestation for dogs, they may not be aware of the risk of cats and thus may not be using any tick control products on their cats.

Dr. Little recommended some strategies to limit TBD transmission to humans and animals in the face of increasing risk of tick infestations. The ideal strategy is to protect the skin, she said. People should wear protective clothing when walking in tick-infested areas and should regularly perform skin checks for ticks on themselves and on their dogs. Dr. Little advised using the “pick them and flick them” approach to removing ticks from the skin.

“All dogs should be on tick prevention products all year round,” said Dr. Little, not only for the dog’s benefit, but also as a public health recommendation, noting that a vaccine is also available for canine Lyme disease. Dr. Little also discussed other helpful strategies for tick control, including preventing pets from roaming, limiting tick habitats (eg, by removing leaf litter and burning debris), excluding and discouraging wildlife from yards and homes, and treating wildlife for ticks.

Dr. Little emphasized that pets are at low risk for TBDs if they receive regular veterinary care and if their owners follow tick prevention recommendations. Simply having pets does not increase the public health risk for TBDs in people, she noted.

“The good news is that comprehensive tick control is really the best way to minimize the risk of tick infestation” for people and pets, concluded Dr. Little.
Tenofovir Also Acts on Herpes
By Laurie Salaman, MS

Having genital herpes (herpes simplex virus [HSV]) increases the risk that someone will contract or spread HIV during sexual intercourse, and it also can lead to worse health outcomes for those already infected with HIV. Because herpes is a cofactor for HIV, scientists are eager to develop strategies that will target both HIV and HSV in one fell swoop.

Several clinical trials investigating tenofovir for the prevention of HIV and HSV have been conducted, with varying results. The CAPRISA 004 study found that a vaginal microbicidal gel containing tenofovir reduced HIV acquisition by 39% and reduced HSV acquisition by 51%. The VOICE study, which used oral tenofovir and vaginal microbicidal gel, was halted ahead of schedule due to an inability to show that tenofovir reduced disease transmission rates, possibly due to low adherence. Two other studies that had subjects take a form of tenofovir were unable to demonstrate a reduction in transmission rates for HIV and HSV.

These mixed clinical results led a group of Belgian researchers to conduct an in vitro trial to see how tenofovir (a first-line candidate against HIV) and PMEO-DAPy (an investigational antiviral agent) affected the herpes virus.

“Tenofovir inhibits the action of the enzyme reverse transcriptase in HIV, but HSV does not have that enzyme so the drug must be affecting something else,” Contagion® Editorial Board Member Kirk E. Hevener, PharmD, PhD, assistant professor in the Department of Pharmaceutical Sciences at the University of Tennessee College of Pharmacy in Memphis, who was not part of the study, told Contagion®. “The team hypothesized that the target of these drugs in HSV was the DNA polymerase enzyme, a common HSV drug target. To prove this, they exposed human embryonic lung cells infected with the herpes virus to both drugs. The selective pressure resulted in the emergence of resistant viral mutants.”

The scientists then performed sequencing on the gene encoding the HSV DNA polymerase enzyme in the mutants to show that the resistance was due to amino acid changes (mutations) in the DNA polymerase enzyme that affected the drugs’ ability to bind to the enzyme. “They confirmed this by testing both drugs against the lab- and clinic-derived viruses with known DNA polymerase mutations to show that the 2 drugs were also less effective against these,” Dr. Hevener said.

The scientific community is eager to come up with new strategies that can prevent both viruses in humans. “Genital herpes, a highly prevalent sexually transmitted disease, is recognized as one of the most common causes of genital ulcers in developed and developing countries,” the authors wrote. However, while herpes presents its own risks, one of its most insidious aspects is its association with HIV. “Because infection with HSV-2 has been associated with an increased risk for HIV-1 infection and often worsens the clinical outcome of HIV disease, strategies to prevent transmission of both HIV-1 and HSV are highly desirable,” the authors wrote.

The researchers noted that because clinical study subjects seem to have difficulty adhering to a regimen that includes microbicidal gels, scientists are in the early stages of developing intravaginal rings that offer easy delivery of tenofovir. More work is needed, however. “Taking into account that the target of all approved anti-HSV drugs is the DNA [polymerase] and that a single mutation in this viral enzyme may confer resistance to many anti-HSV drugs, there is an urgent need to develop novel classes of anti-HSV drugs,” they wrote.

Although this study is encouraging, the fact that it was conducted in vitro does not necessarily translate to success in human subjects. “There is no evidence provided here that inhibiting HSV by these drugs translates into clinical efficacy,” Dr. Hevener said. He also pointed out that the study team could have gone further than sequencing only the enzyme DNA polymerase under the assumption that this was the drugs’ target. “It did turn out to have mutations in the HSV-resistant virus, so they were probably right, but they should have confirmed this by sequencing the rest of the virus’ genome to make sure there were no mutations elsewhere—which could indicate another possible drug target. I suspect we’ll be seeing some follow-up studies on this soon.”

First Efficacy Study Launched for Investigational Mosaic HIV-1 Preventive Vaccine
By Danielle Mroz

The first efficacy study for an investigational mosaic HIV-1 preventive vaccine was initiated by Janssen Pharmaceutical Companies and several global partners.

A total of 2600 women between the ages of 18 and 35 in 5 countries in Sub-Saharan Africa will be enrolled in the large-scale proof-of-concept efficacy study, Imbokodo (HVTN 705/HF002008), which will evaluate whether the investigational mosaic HIV-1 preventive vaccine is safe and able to reduce infection compared with placebo. Clinical research sites in South Africa have already started administering vaccines to participants, and sites in Malawi, Mozambique, Zambia, and Zimbabwe are waiting on their regulatory approvals.

The initiation of this trial marks the first time in more than 10 years that 2 vaccine efficacy studies are occurring at the same time. According to Janssen parent company, Johnson & Johnson (J&J), a concurrent study HVTN 702 “is currently underway in South Africa to evaluate a different vaccine candidate.”

The quest for a vaccine against HIV has been a challenging one, partly because of the virus’ “ability to mutate rapidly and its global genetic diversity with multiple strains and subtypes prevalent in different parts of the world,” stated J&J in a press release. Despite these complications, experts such as Anthony S. Fauci, MD, director of the National Institute of Health’s National Institute of Allergy and Infectious Diseases, have stated that we are not going to see an end to the AIDS epidemic without a vaccine. In a recent commentary, Dr. Fauci further elaborated on this, stating, “Although an estimated 19.5 million of the estimated 36.7 million HIV-infected people globally are receiving anti-HIV therapy, an extraordinary accomplishment, more than 17 million people are not receiving therapy. This leaves a substantial treatment gap.” In addition, he cited the sheer cost of providing antiretroviral therapy (ART) for all of those infected as another factor to consider when thinking that the epidemic could be eradicated via therapy alone. “The cost of providing pre-exposure prophylaxis and other preventive services to the millions of people who are at risk for HIV infection is substantial,” he said. It is for these and several other reasons that Dr. Fauci says that “we will actually need an HIV vaccine to achieve—and I want to underscore a very important word—a durable end to the HIV pandemic.”

The United Nation’s Program on HIV/AIDS has set a high bar end date for the epidemic with their 90-90-90 program, which states that 90% of those living with HIV/AIDS will be aware of their status, 90% will be receiving ART, and 90% of those on ART will have viral suppression—all by 2020. And while many countries have made great strides toward reaching these goals, with an estimated 1.8 million individuals newly infected with the virus in 2016—790,000 of which were reported in eastern and southern Africa—much work is still needed to be done.

To this end, Johan Van Hoof, MD, Janssen Vaccines & Prevention B.V. and Therapeutic Area Head, R&D, Infectious Diseases & Vaccines, stated in the press release: “Having a preventive vaccine would be a vital tool in a comprehensive global strategy to end the HIV pandemic. Our investigational vaccine is based on mosaic antigens that have been engineered using genes from a wide range of different HIV subtypes. The ultimate goal is to deliver a ‘global vaccine’ that could be deployed in any geographic region to help protect vulnerable populations at risk of infection.”
Antimicrobial resistance (AMR) is sadly not a new threat, and despite Alexander Fleming’s warnings about resistant bacteria rising up because of the frequent and misuse of antibiotics, only fairly recently have individuals truly started to pay attention. Not only is there a growing threat of resistant bacteria, but the development of new antibiotics has been woefully insufficient. A recent report found that “of the drugs in development, only 12 have the potential to address the most critical Gram-negative pathogens on the World Health Organization’s antibiotic-resistant priority pathogens list: carbapenem-resistant Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii (see Table for complete list.) Furthermore, bacteria resistant to 1 antibiotic in a class are more likely to be resistant to others in that class and only approximately 1 in 4 antibiotics represent new drug classes or mechanisms of action to combat bacteria that are constantly evolving.”

The challenges of drug research and development are startling in light of the predictions for AMR: 10 million deaths worldwide per year by 2050 and $100 trillion lost between now and then in terms of global production. Current data indicate that there are approximately 23,000 deaths in the United States already each year, and about $20 billion in excess direct health care costs (see Figure).

What is to be done? There are several initiatives, like the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), that seek to infuse life into the research and development of new drugs. There is also a push on health care providers and agriculture to reduce the use of antimicrobials. But these are all long-term solutions that may take years or decades to implement. Although long-term plans are critical, if you were hospitalized today with a highly resistant infection, what would be the short-term plan of action your health care providers would take?

One strategy that’s gathering momentum as an alternative to antibiotics is the use of bacteriophages (or phages), which are viruses that infect good bacteria and use them to produce more phages that continue the assault on the bacteria. Phages replicate quickly, and phage therapy is becoming a more viable approach because it has a narrow host range. This may not sound like a good thing, but the very specific bacterial targeting...
that certain phages have (and more phages exist than stars in the universe) means they can be used for a targeted approach. Not all bacteria are bad, and part of the problem so frequently seen with infections, like Clostridium difficile, is that antibiotics kill off a lot of good bacteria in the process of killing the bad. Phage therapy has the capacity to selectively kill specific bacteria within an ocean of bacteria. Harnessing phages that can attack certain bacteria with almost laser-like precision is exactly what is needed in when tackling resistant bacteria. Imagine a room full of people with 1 villain. Would you rather have a snipr capable of taking out just the villain or a shotgun that could potential harm innocent bystanders? Phage therapy has a sniper-like selectivity that makes it extremely effective, but without the negative adverse effects so often seen with antibiotics.

A recent application of this approach to resistant infections was seen for the first time in the United States, when a patient with a severely resistant and systemic infection was treated with intravenous (IV) bacteriophages. The patient was near death, but recovered after the treatment and is now a model for the success of phage therapy. Team member, Robert Schooley, MD, chief of the Division of Infectious Diseases at the University of California San Diego School of Medicine noted, “We don’t yet fully understand the potential—and limitations—of clinical bacteriophage therapy, but it’s an unprecedented and remarkable story, and given the global health threat of multidrug-resistant bacteria. Harnessing phages that can attack certain bacteria with almost laser-like precision is what is needed when tackling resistant bacteria. Imagine a room full of people with 1 villain. Would you rather have a sniper capable of taking out just the villain or a shotgun that could potential harm innocent bystanders? Phage therapy has a sniper-like selectivity that makes it extremely effective, but without the negative adverse effects so often seen with antibiotics.

Dr. Chan discussed his research, the potential of phage therapy, and what it means for health care providers. “Bacteriophage therapy is an approach that could be especially valuable in tackling AMR because [phages] self-amplify/limit in the presence [or] absence of susceptible hosts (ie, bacteria), they can be used alongside chemical antibiotics, they have killing mechanisms distinct from currently used chemical antibiotics, they can readily be isolated from the environment should bacteria become resistant to a particular phage, and they can also select for reduced virulence and antibiotic sensitivity by forcing evolutionary trade-offs in pathogenic bacteria. My experience in treating 2 people suffering antibiotic-resistant infections was pretty straightforward, as there is an efficient and functional process for applying for permission from the US Food and Drug Administration.”

Given the capacity for phage therapy to treat extremely resistant infections, I was curious as to Dr. Chan’s suggestions and words of wisdom for medical providers. “For medical providers, I would suggest that they carefully evaluate their patients as candidates for this treatment at this stage because we are in the dangerous territory of a single case going poorly and the medical community responding with a, ‘See? We told you it wouldn’t work’ and phage therapy being killed as a potential therapeutic. Once phage therapy becomes more accessible, I’d suggest that practitioners carefully review the pros and cons of phage therapy. While they are certainly antibacterial, they are distinct in several ways [that] should be understood before undertaking this approach to infection management.”

AMR is a difficult problem that stems from so many industries and poor practices. A solution will require a multitude of tactics and approaches, of which bacteriophage therapy has the potential to save lives as we search for prevention.

References available at ContagionLive.com.
Short-Course Antibiotic Therapy for Enterobacteriaceae Bloodstream Infections

By Monica V. Mahoney, PharmD, BCPS, AQ-ID

The duration of antibiotic therapy has garnered attention recently, particularly after the aptly titled BMJ article, “The Antibiotic Course Has Had Its Day,” by Llewelyn and colleagues was published. Although the media interpreted the article to mean that patients did not have to finish their prescribed course of antibiotics, the true message of the paper was that duration of therapy for many common infections is not rigorously studied and individual patient responses should guide their unique durations. Over the past few years, more studies have challenged the concept that longer infection treatment durations are better. Some more recent evidence supports the use of 4-day courses for source-controlled intra-abdominal infections and 7 days for hospital- and ventilator-associated pneumonias. Until recently, there was no good data to determine whether shorter courses of therapy could be used for bloodstream infections as well.

Chotiprasitsakul and colleagues retrospectively identified 4967 unique patients 18 years or older with Enterobacteriaceae bloodstream infections admitted to 1 of 3 hospitals. Following strict exclusion criteria, patients were stratified as receiving short-course treatment of 6 to 10 days (n = 385) or prolonged-course treatment of 11 to 16 days (n = 1384). Patients additionally underwent propensity matching, for a final cohort of 770 patients. The primary outcome was 30-day posttreatment mortality. Secondary outcomes included recurrent bloodstream infections with the same organism, Clostridium difficile (C. diff) infection, and emergence of multidrug-resistant Gram-negative colonization or infection. Patients were approximately 60 years of age, mostly black or white, and evenly split between male and female. The source of bloodstream infection was from a urinary source in 35% to 40% of patients. Escherichia coli, Klebsiella pneumoniae, and Enterobacter species were the most common organisms isolated. Adequate source control was achieved in more than 97% of patients.

A short course of antibiotic therapy was not associated with an increased risk of 30-day mortality (9.6% vs 10.1%, respectively; HR, 1.12; 95% CI, 0.70-1.80). Additionally, no reduction in mortality was seen for each additional day of antibiotics administered. A urinary source of the bloodstream infection was found to be protective, while a higher Pitt bacteremia score and end-stage liver disease were found to be associated with higher 30-day mortality in a multivariate model. There were no differences found in terms of infection relapse, C. diff infection, or isolation of multidrug-resistant organisms. The authors concluded that in uncomplicated (aka source controlled) Enterobacteriaceae bloodstream infections, short courses of 6 to 10 days of antibiotic therapy resulted in rates of 30-day mortality similar to those seen with prolonged courses.

This article adds to the growing body of literature that points toward individualization of duration of therapy for each patient. Prompt and adequate source control is vital to the success of any therapy. Once this is achieved, therapies can be shortened from what is traditionally thought. In light of the many critical ongoing antibiotic drug shortages, reducing the length of therapy is one method of preserving our armamentarium of medications for those who truly require them.

References are available at ContagionLive.com.

Antibiotic Prophylaxis Prior to Dental Procedures in Patients With Orthopedic Implants

By Margaret Cook, PharmD, BCPS

Over 1 million primary hip and knee arthroplasties are performed in the United States each year. The reported risk of periprosthetic and deep implant infections ranges from 0.3% to 8.3%. Although dental procedures may result in transient bacteremia, there is no controlled evidence to suggest an association between bacteremia following dental procedures and prosthetic joint infection. Lingering historical concerns have led to inconsistent practices in antibiotic prophylaxis in this population. In 2015, the American Dental Association (ADA) published guidelines that advised against the use of antibiotic prophylaxis prior to dental procedures in patients with orthopedic implants due to the lack of evidence associating dental procedures with prosthetic joint infections (PJIs) and the absence of data supporting a benefit of antibiotic prophylaxis.

In an attempt to reconcile practice inconsistencies, the American Academy of Orthopedic Surgeons (AAOS) and the ADA published Appropriate Use Criteria (AUC) for antibiotic prophylaxis prior to dental procedures in patients with orthopedic implants. In addition, the AAOS/ADA AUC have been translated into an online tool to facilitate antibiotic decision assessment and more targeted prophylaxis.

In the absence of randomized controlled data, this Web-based inventory provides guidance on antibiotic prophylaxis decisions using readily accessible patient risk factors that, independent of dental procedures alone, have been suggested to increase the risk of PJIs (Table). The online AUC tool accounts for 64 clinical scenarios and in most cases (61%) advises against the use of antibiotic prophylaxis (eg, “Prophylaxis is rarely appropriate”). In the remaining scenarios, prophylaxis is deemed reasonable (eg, “May be appropriate”) in 27% of cases or recommended (eg, “Appropriate”) in 12% of cases based on risk factors, such as underlying severe immunosuppression or history of PJIs.

The AAOS/ADA inventory is available on the AAOS website and may be a valuable tool to target antibiotic prophylaxis, reduce the burden of unnecessary antibiotic exposure, and possibly reduce the risk of, or a concern for, associated infections.

References are available at ContagionLive.com.
Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Hard to Treat, But Hope on the Horizon?

Two recently approved agents offer significant activity against these hard-to-treat conditions.

By Joshua Garcia, PharmD; Katherine Gruenberg, PharmD; Lynn Nguyen, PharmD; and Conan MacDougall, PharmD

(continued from cover)

to be the sixth most common nosocomial pathogen overall and second most common pathogen in ventilator-associated pneumonia (VAP) in US hospitals. On a national level, *P. aeruginosa* was found to have resistance or intermediate susceptibility to at least 1 carbapenem in 19.3% (4365/22,593) of isolates, resistant to at least 1 aminoglycoside in 9.7% (2631/27,197) of isolates, resistant to either cefepime or cefazidime in 10.3% of isolates (2763/26,772) resistant to at least 1 fluoroquinolone in 21.6% (5808/26,897) of isolates, resistant to piperacillin/tazobactam in 10.0% (2378/23,662) resistant to piperacillin/tazobactam in 10.0% (2378/23,662) of isolates, and multidrug resistant (MDR) in 14.2% (3871/27,289) if isolates.

This high level of resistance is attributable to the multiple intrinsic resistance mechanisms that *P. aeruginosa* may express, including beta-lactamase production, efflux-mediated and porin-related resistance, and target site modification. These mechanisms are often present in combination, causing a broad range of antibiotics to be rendered ineffective against a given *P. aeruginosa* isolate. The production of beta-lactamase enzymes represents one of the most prominent resistance mechanisms utilized by *P. aeruginosa*. AmpC beta-lactamase in *P. aeruginosa* is a chromosomally mediated beta-lactamase that is naturally induced by the presence of some beta-lactams and beta-lactam inhibitors, conferring natural resistance to lower level penicillins and cephalosporins. Although the induction of AmpC beta-lactamase confers resistance to a number of beta-lactam antibiotics, it is the hyper production, or "derepression," of AmpC through chromosomal mutation, which confers resistance to a number of antipseudomonal agents, such as piperacillin/tazobactam.

For *P. aeruginosa* to acquire resistance to agents such as carbapenems and cefepime, other mechanisms of resistance are usually present in combination with hyper production of AmpC beta-lactamase, such as overexpression of efflux pumps (carbapenems), production of other beta-lactamases, or down-regulation of porin production (carbapenems and...
KATHERINE GRUENBERG, PHARMD

Dr. Gruenberg is an assistant professor of Clinical Pharmacy at the University of California, San Francisco (UCSF) School of Pharmacy. She received a doctor of pharmacy degree from UCSF and completed postgraduate training at Northeastern Memorial Hospital (PGY-1) and UCSF (PGY-2 Infectious Diseases Education). She is an active member of SIDP.

...BUT, THERE'S HOPE ON THE HORIZON?

Two recently approved agents offer significant activity against multidrug-resistant *P. aeruginosa* infections. In addition, 2 agents in phase II/III trials may expand the armamentarium further. The Table describes the stage of development of these 4 agents, the mechanism of enhanced activity of these agents against *P. aeruginosa*, and the in vitro potency of the agents. Notably, 1 newly approved agent (meropenem–vaborbactam) and several agents in development (aztreonam–avibactam, finafloxacin, plazomycin) generally have activity against *P. aeruginosa* but offer little added activity against MDR isolates. Below we discuss the available clinical data for the recently approved agents.

RECENTLY APPROVED AGENTS WITH ENHANCED ACTIVITY AGAINST *P. AERUGINOSA*

### Cefazidime-Avibactam

**Clinical Trials**

In 2015, the FDA approved ceftazidime–avibactam for the treatment of complicated intra-abdominal infections (cIAIs) in combination with metronidazole and complicated urinary tract infections (cUTIs), including pyelonephritis, in adult patients. The FDA-approved dose for both indications is 2.5 grams every 8 hours in patients with creatinine clearance greater than 50 mL/minute. In phase III cIAI trials, ceftazidime–avibactam demonstrated cure rates of at least 90% for both cefazidime-susceptible and ceftazidime-resistant *P. aeruginosa* infections, with no statistically significant difference observed compared with the meropenem arm.2,6

### Cefepime

Finally, *P. aeruginosa* can express resistance to non-beta-lactam antibiotics through antibiotic target modification. The 2 more prominent antibiotic classes susceptible to this resistance mechanism are fluoroquinolones and aminoglycosides.4

### Table: Newly Approved and Late-Stage Investigational Agents With Activity Versus Multidrug-Resistant *P. aeruginosa*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications Approved Or Under Study</th>
<th>Mechanism of Enhanced Antipseudomonal Activity</th>
<th>Percent Susceptibility or MIC90 of P. aeruginosa by Resistance Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazidime/avibactam (Avycaz)</td>
<td>Approved 2014 (cUTI, cIAI); phase 3 (HAP)</td>
<td>Potent inhibition of AmpC beta-lactamase by avibactam</td>
<td>Cefaz-NS: 80%6; Cefaz/pip-tazo/mero-NS: 70% 6</td>
</tr>
<tr>
<td>Cefepidoxame/tazobactam (Zerbaxa)</td>
<td>Approved 2015 (cUTI, cIAI); phase 3 (HAP)</td>
<td>Increased affinity for PBP, greater stability vs AmpC hydrolysis</td>
<td>Cefep-NS: 77%3; Cefep/pip-tazo/mero-NS: 70% 3</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>Phase 3 (HAP, MDR organisms); phase 2 (UTI)</td>
<td>Enhanced penetration through outer membrane by siderophore transport, greater stability vs AmpC hydrolysis</td>
<td>Amikacin/cipro/mero-NS: MIC&lt;sub&gt;90&lt;/sub&gt;: 1 mg/L5; Amikacin/cipro/mero/cef-tazo-NS: MIC&lt;sub&gt;90&lt;/sub&gt;: 2 mg/L5</td>
</tr>
<tr>
<td>Imipenem–cilastatin–relebactam</td>
<td>Phase 3 (HAP), phase 2 (cUTI)</td>
<td>Potent inhibition of AmpC beta-lactamase by relebactam</td>
<td>Imipen-NS: 81%3</td>
</tr>
</tbody>
</table>

Table indicates ceftazidime; cefepide; cefepidoxame/tazobactam; cIAI, complicated intra-abdominal infection; cip, ciprofloxacin; cipro, ciprofloxacin; cist, complicated urinary tract infection; HAP, hospital-acquired pneumonia; mero, meropenem; MIC<sub>90</sub>, minimum inhibitory concentration for 90% of isolates; NS, nonsusceptible; PBP, penicillin-binding protein; pip-tazo, piperacillin/tazobactam; PsA, Pseudomonas aeruginosa.

In phase 3 cUTI trials, *P. aeruginosa* was isolated rarely (~5% of isolates), with microbiological response rates for *P. aeruginosa* infections similar between the ceftazidime/avibactam and doripenem arms.3 REPRISE was a pathogen-directed phase 3 trial that specifically enrolled patients with ceftazidime-resistant *enterobacteriaceae* and *P. aeruginosa* cUTIs and cIAIs.4 For cUTIs due to *P. aeruginosa*, the microbiological response was 79% and 60% with ceftazidime/avibactam and best available therapy (most commonly a carbapenem), respectively. Two patients in the study had cIAIs due to *P. aeruginosa* (one in each treatment arm); both had a favorable microbiological response. REPROPE was a recently completed phase 3 trial comparing ceftazidime/avibactam to meropenem for nosocomial pneumonia.12 The second most common Gram-negative pathogen was *P. aeruginosa*, isolated from approximately 30% of patients. Ceftazidime/avibactam demonstrated noninferiority to meropenem for the primary endpoint of clinical cure across all patients (per-pathogen analysis is not yet available).

### Experience for MDR *P. aeruginosa*

One case series described the successful treatment of 2 patients with extremely drug-resistant (XDR) *P. aeruginosa* infections using the combination of ceftazidime/avibactam and colistin. The first patient had XDR *P. aeruginosa* bacteremia with septic emboli to the lungs. The second patient had XDR *P. aeruginosa* sinusitis and meningitis. Both patients were previously treated with meropenem in combination with colistin, without clinical improvement, before they were started on ceftazidime/avibactam at 2.5 g/8 h plus colistin at 2 MU/8 h. Both patients demonstrated clinical and radiological resolution with ceftazidime/avibactam.12

### Cefotolozane-Tazobactam

Clinical Trials

Cefotolozane-tazobactam was approved by the FDA in 2014, shortly before ceftazidime–avibactam was approved for the same indications. The FDA-approved dose for both indications is 1.5 g/8 h in patients with creatinine clearance greater than 50 mL/minute. In the phase 3 ASPECT-cIAI trial, cefotolozane/tazobactam plus metronidazole demonstrated noninferiority to meropenem in the primary endpoint of clinical cure rate at the test of cure visit; for infections due to *P. aeruginosa* specifically, clinical cure rates were 100% with cefotolozane/tazobactam and 93.1% with meropenem.13 In the phase 3 ASPECT-cUTI trial, cefotolozane/tazobactam was studied against levofloxacin; in infections due to *P. aeruginosa* specifically, microbiological eradication was higher with cefotolozane/tazobactam (85.7%) compared with levofloxacin (58.3%), although statistical conclusions could not be drawn based on the small sample.14 A phase 3 trial for nosocomial pneumonia is in progress (NCT02070757), where cefotolozane/tazobactam will be studied at a higher dose of 3 g/8 h and patients in the comparator arm will receive meropenem.

### Experience for MDR *P. aeruginosa*

Clinical experience with cefotolozane/tazobactam for MDR *P. aeruginosa* has been described in several case series and retrospective studies, primarily with pneumonia. In a retrospective review of 21 patients treated with cefotolozane/tazobactam for MDR *P. aeruginosa* infections (86% with pneumonia), the clinical success rate was 71%. The emergence of resistance to cefotolozane/tazobactam was found in 3 patients and occurred as quickly as 8 days into therapy.21 In a retrospective review of 12 patients with MDR *P. aeruginosa* infections, salvage therapy with cefotolozane/tazobactam resulted in microbiological eradication within 30 days in 83% of patients. However, 2 of those patients subsequently grew *P. aeruginosa* resistant to...
ceftolozane/tazobactam, 1 of whom experienced clinical recurrence.16 In another case series of 3 patients, ceftolozane/tazobactam was used successfully in the treatment of health care-associated and VAP secondary to MDR P. aeruginosa. All patients had previously been treated with meropenem or ciprofloxacin, and all isolates were susceptible to ceftolozane/tazobactam with a minimum inhibitory concentration (MIC) of 1 mcg/mL or less. Ceftolozane/tazobactam was dosed at 3 g/8 h and all 3 patients were cured with microbiological eradication.17 Although the data are more limited, ceftolozane/tazobactam has also been used in the treatment of bloodstream infections,18,19 skin and soft tissue infections,20,21 osteomyelitis,22 mycotic pseudoaneurysm,23 a left ventricular assist device infection, and a cystic fibrosis pulmonary exacerbation (at a dose of 3 g/8 h) due to MDR P. aeruginosa.24

COMPARATIVE ACTIVITY OF CEFTAZIDIME/AVIBACTAM AND CEFTOLOZANE/TAZOBACTAM

Ceftolozane/tazobactam appears to have greater in vitro activity against P. aeruginosa than that of ceftazidime/avibactam, particularly against strains with meropenem resistance. Two studies comparing the activity of these agents against meropenem-resistant P. aeruginosa have been published.25,26 Both studies reported MIC distributions demonstrating more potent activity with ceftolozane/tazobactam than with ceftazidime/avibactam. A higher proportion of isolates had ceftazidime/avibactam MICs at the susceptibility breakpoint (8 mg/L) compared with ceftolozane/tazobactam MICs. In contrast to the large surveillance studies, which report susceptibility rates greater than 85% for both agents, much lower susceptibility rates were described in an evaluation of beta-lactam resistant P. aeruginosa patient isolates from Los Angeles-area hospitals.27 As expected, a greater proportion were susceptible to ceftolozane/tazobactam than to ceftazidime/avibactam, but susceptibility rates were more modest than previously reported (72.5% vs 61.8%). These findings highlight the importance of using local susceptibility data to guide decision making, as susceptibility rates can vary greatly depending on local resistance patterns. Of note, only 9% of ceftolozane/tazobactam-resistant isolates were susceptible to ceftazidime/avibactam, whereas 36% of ceftazidime/avibactam resistant isolates were susceptible to ceftolozane/tazobactam, again suggesting that ceftolozane/tazobactam may have greater utility as a last-line treatment option against MDR P. aeruginosa.25

There appears to be a modest potency advantage and more clinical experience with ceftolozane/tazobactam for MDR P. aeruginosa than with ceftazidime/avibactam. However, of particular concern are the multiple reported cases of the emergence of resistance to ceftolozane/tazobactam. Whether or not this is a problem with ceftazidime/avibactam is largely unknown given the paucity of data for its use in MDR P. aeruginosa infections. The possibility of resistance development should be considered in patients who have recurrence or poor response to therapy. References are available at ContagionLive.com

Note: This is an edited version of an upcoming paper in Current Infectious Diseases Reports.

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New Initiatives for HIV Taking Off This Year

Advances in antiretroviral therapies increase opportunities for patients with HIV to have more successful treatment outcomes.

BY JENNIFER BAILEY, PHARM.D.; MARY SANOUB, PHARM.D.; AND DEVANG PATEL, MD

Advancements in the management of HIV over the past several decades have led to remarkable improvements in patient survival and quality of life. Yet, disparities in diagnosis, retention in care, and treatment failure continue to hinder the goal of disease eradication, hence propelling new initiatives. A multifaceted approach to global HIV control now routinely involves such strategies as pre-exposure prophylaxis (PrEP) in high-risk populations, widespread screening, treatment as prevention, and ongoing efforts to dispel the stigma of living with the disease. Maximizing antiretroviral (ARV) potency, convenience, and tolerability is another constantly moving target. In 2017, significant progress in HIV treatment was achieved with approval of the first 2-drug maintenance regimen for select patients with HIV and the early clinical success of long-acting injectable therapy. Additional October patients with HIV and the early clinical success of regimens consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent from a different therapeutic class to maximize antiviral efficacy. However, as patients now initiate treatment earlier and live longer, they also become more vulnerable to long-term medication toxicities. This has led to a re-emerging interest in simplified, drug-sparing regimens. Secondary benefits of these regimens may include antiretroviral therapy (ART) preservation, improved convenience, fewer drug interactions, and reduced costs.

In November 2017, the US Food and Drug Administration approved the first 2-drug regimen to treat HIV. JULUCA is a fixed-dose regimen that contains the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) and the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV). This is the first complete single-tablet regimen that does not incorporate NRTIs, thus sparing patients potential toxicity from these agents. Clinical use of this regimen likely preceded its formal approval, as published data of real-world application populates the literature.6 The data behind the approval of this regimen come from 2 open-label, multicenter phase 3 clinical trials, SWORD 1 and SWORD 2, presented at the 2017 Conference on Retroviruses and Opportunistic Infections.7 All patients (N = 1024) enrolled in this study were suppressed, with HIV-1 RNA <50 cells/mL for at least 12 months with no history of virologic failure. Patients either continued their cART suppressive regimen or switched to DTG / RPV. Results demonstrated noninferiority of viral suppression for the 2-drug regimen at 48 weeks compared with traditional 3- or 4-drug regimens.

DTG / RPV does not necessarily translate into success of all simplified regimens. Other published attempts at 1- or 2-drug regimens produced varying results or unclear applicability. A prime example was the initial promise of DTG monotherapy. However, in a randomized trial comparing DTG with cART in virologically suppressed patients, several patients experienced virologic failure with DTG alone, prompting premature study discontinuation.8 Subsequently, phase 1 investigation of DTG with lamivudine has shown greater promise in select virologically suppressed patients, although further study is needed.9

THE FORMULATION FRONTIER—LONG-ACTING ART

Despite a multitude of available fixed-dose regimens, adherence to daily lifelong ART still challenges many patients. The development of long-acting (LA) ARVs to facilitate HIV treatment and prevention seems intuitive and mimics modern approaches to many other chronic disease states. Transdermal, injectable, and implantable drug delivery options may reduce pill fatigue and thus improve adherence, overcome oral bioavailability concerns, and potentially expand options for medication access. In a study of patient attitudes toward LA ARVs, 84% of patients indicated they would “definitely” or “probably” try injectable therapy offered on a monthly basis.10 Although properties such as aqueous solubility, metabolism, elimination, and dosing volume limit the repertoire of potential injectables, several ARVs have recently entered advanced clinical study for emerging use. Physiologically based pharmacokinetic modelling simulations have been applied and validated to identify and characterize candidate drugs.11 Most favorable at this time is the novel combination of cabotegravir (GSK1265744; CAB) and RPV, 2 ARVs with physicochemical compatibility, yet unique mechanisms of action that lack significant pharmacokinetic interactions.12,13 CAB, an experimental INSTI and DTG analogue, was first evaluated as an oral tablet and later as an injectable nanosuspension.14 Depot-formulated CAB was studied in a dose-escalation manner as both intramuscular and subcutaneous injections given monthly or quarterly.15 Rilpivirine LA injection is also a nanosuspension formulation.16 The Long-Acting Antiretroviral Treatment Enabling (LATTE) trial was a phase 2b, randomized, parallel-group study in treatment-naïve adult patients with HIV-1 infection treated with oral CAB plus dual NRTIs (abacavir/lamivudine or tenofovir/emtricitabine) as induction therapy, followed by oral CAB plus RPV maintenance therapy.17 The comparator group was efavirenz plus the dual NRTI backbone. Viral suppression was comparable in the efavirenz arm during both phases, with a numerically higher response rate and shorter time to viral suppression with CAB. Subsequently,
in the randomized, open-label, noninferiority LATTE-2 trial, LA intramuscular CAB plus RPV, given in 4- or 8-week intervals (following a 20-week oral induction period) was compared with oral CAB plus abacavir/lamivudine in HIV-1 positive adults to maintain viral suppression. Pre-specified efficacy criteria were met for virologic suppression was achieved in 94% of the 4-week group and 95% of the 8-week group, compared with 91% of the oral treatment group at 32 weeks, and remained so through 96 weeks. Mild to moderate injection-site pain was the most common adverse event (AE), which lasted for a median duration of 3 days. No serious AEs were considered to be related to study treatment. The authors concluded that LA CAB plus RPV offers high efficacy and acceptable safety for maintenance therapy in virologically suppressed patients living with HIV, thereby supporting advancement to future randomized controlled-trials.

For patients who wish to avoid the burden or stigma of taking daily oral ARVs or for those who struggle with the responsibility, LA injectables may be preferable. However, there are downsides to consider. In patients with a well-controlled viral load who may only require twice-annual office visits, the need for more frequent visits for drug administration may pose a barrier to adherence. Although AEs were generally mild with CAB plus RPV, any AE may be compounded by the fact that the offending agent has a long half-life and cannot be rapidly eliminated. Moreover, resistance is concerning if the agents are discontinued due to declining drug levels. At least 1 patient in the LATTE-2 trial developed an integrase mutation Q148R, imparting phenotypic resistance to CAB. This was also a concern when CAB was studied for PrEP.

Finally, the clinical trials all require oral lead-in periods that will necessitate careful management and clear understanding between patients and providers.

CONCLUSION

Recent advances in ART simplification, including the approval of the first 2-drug HIV maintenance therapy and early success of LA parenteral ARVs hold potential to significantly increase the likelihood of sustained success for patients receiving treatment for HIV. The Joint United Nations Programme on HIV/AIDS has set forth a goal for 2020: to have 90% of people living with HIV know their diagnosis, to have 90% of that group on ART, and to have 90% of those on treatment be virally suppressed (90-90-90). These new treatment strategies could potentially have a significant impact on reaching the goal of 90-90-90.

References are available at ContagionLive.com.

Table. Highlights of Updates to the US DHHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents Living With HIV

<table>
<thead>
<tr>
<th>SECTION UPDATED</th>
<th>SUMMARY OF GUIDELINE RECOMMENDATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of antiretroviral therapy</td>
<td>• Initiation of immediate ART on the day of HIV diagnosis may be considered as a strategy to increase engagement in care and achievement of viral suppression</td>
<td>• This is a resource-intensive initiative requiring interdisciplinary care coordination</td>
</tr>
<tr>
<td>What to start: Initial combination regimens for the antiretroviral-naive patient</td>
<td>• Recommended (AI) regimens for most patients: - DTG/ABC/TFC* - DTG plus TFV/FTC* - EVG/COBI/TFV/FTC* - RAL plus TFV/FTC* - INSTI-based regimens are recommended for most people with HIV for their high efficacy and overall greater tolerability compared with agents from other drug classes</td>
<td>• In certain clinical situations, other regimens may be preferred for various reasons (refer to Table 6 of the DHHS guidelines)</td>
</tr>
<tr>
<td>Management of the treatment-experienced patient</td>
<td>• Several updates were made to Table 10 of the DHHS guidelines related to antiretroviral options for patients with virologic failure</td>
<td>• DRV has been moved to a recommended regimen in certain clinical situations, primarily because of greater tolerability of the INSTIs</td>
</tr>
<tr>
<td>Considerations for antiretroviral use in patients with coinfections</td>
<td>• Due to the risk of HBV reactivation in persons with HBV infection during interferon-free HCV treatment, all patients initiating HCV therapy should be tested for HBV</td>
<td>• Greater evidence has mounted that TAF has less bone and kidney toxicity than TDF, while TDF is associated with lower lipid levels (clinical significance unclear)</td>
</tr>
<tr>
<td>Limitations to treatment safety and efficacy</td>
<td>• Adherence to the continuum of care should include regular assessment of linkage-to-care and adherence to ART and clinic appointments</td>
<td>• Postmarketing reports of neuropsychiatric adverse events associated with INSTIs; further studies are needed to identify the true incidence and differentiate risk between agents; a pathophysiological mechanism is not defined</td>
</tr>
<tr>
<td>• Address barriers to adherence to ART and appointments before initiation of therapy and regularly thereafter</td>
<td>• Those not immune to HBV infection should be vaccinated</td>
<td></td>
</tr>
<tr>
<td>• Patients with adherence concerns should be placed on regimens with high barrier to resistance</td>
<td>• Tables describing the compatibility between HCV direct-acting antiviral agents and HIV ART were updated in the guidelines to contain newer anti-HCV therapies</td>
<td></td>
</tr>
<tr>
<td>• The approach to improved adherence should be tailored to the individual and done through a multidisciplinary approach</td>
<td>• Adherence to the continuum of care should include regular assessment of linkage-to-care and adherence to ART and clinic appointments</td>
<td></td>
</tr>
</tbody>
</table>

Ai indicates strong rating of recommendation with data from randomized controlled trials; AIi, strong rating of recommendation with data from other (non-randomized controlled) studies; TFC, tenofovir; ABC, abacavir; ART, antiretroviral therapy; COBI, cobicistat; DHHS, Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

References are available at ContagionLive.com.
In 2017, research on 3 drug combinations for the treatment of hepatitis C virus (HCV), which were in phase 2 studies, was discontinued, meaning that there are no longer direct acting antivirals (DAAs) in the pipeline for HCV treatment and cure in the foreseeable future. Thankfully, in 2017, 2 new drug therapies, Vosevi (sofosbuvir/velpatasvir/voxilaprevir; Gilead) and Mavyret (glecaprevir/pibrentasvir; AbbVie) were approved by the US Food and Drug Administration (FDA) for the treatment and cure of HCV.1,2

Vosevi, a combination of sofosbuvir and velpatasvir, previously approved drugs, with the new drug voxilaprevir, offers a new treatment option for patients who previously failed regimens that included a nonstructural protein 5A (NS5A) drug or sofosbuvir without an NS5A inhibitor.4 In clinical studies, Vosevi was compared in adults with HCV genotypes 1 through 6 against placebo and in adults with genotypes 1 through 3 against sofosbuvir and velpatasvir.1 In both trials, approximately 96% of the patients who received Vosevi were considered cured, which was defined as having undetected viral levels within the blood after 12 weeks of treatment.1

The release of Vosevi on the market as a fixed-dose, 1-pill, once-daily regimen is significant in the fact that it provides another therapy option that effectively cures hard-to-treat patients infected with the most common genotypes of HCV (see Table 1 for indications).4 This newly developed drug is unique in being the only drug available on the market for treatment-experienced patients with genotypes 4 through 6 who previously failed a DAA.5 It also stands out from Harvoni (ledipasvir/sofosbuvir) in its inclusion of patients with genotype 3. Overall, it has become the recommended drug of choice for DAA treatment-experienced patients with genotypes 1, 3, 4, 5, and 6 per American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updates on the HCV Guidelines website.5 However, Vosevi is not recommended in the guideline updates in treatment-experienced patients with genotype 2; Epclusa (sofosbuvir/velpatasvir) remains the preferred recommendation.5 It is also important to note that unlike Harvoni, Vosevi is only approved for patients without cirrhosis or with compensated cirrhosis, whereas Harvoni can be used to
In clinical trials, when Mavyret was used to treat patients with cirrhosis, the virus was detected in the blood of patients treated with either a NS5A inhibitor or a nonstructural protein 3/4A (NS3/4A) protease inhibitor. It is important to note that the indication for previous treatment does not affect sustained viral response rates. Thus, depending on indication, the duration varies for these 3-pill, once-daily regimens, as depicted in Tables 2 and 3.

In the fall of 2017, Merck announced its decision to discontinue 2 of its drug combinations for hepatitis C, MK3682B (grazoprevir/razuvar/uprifosbuvir) and MK3682C (razuvar/uprifosbuvir) in the midst of phase 2 trials. In their first phase 2 study, the C-CREST trial observed the safety and efficacy of MK3682B in patients with genotypes 1, 2, and 3 with or without cirrhosis. With 8 weeks of treatment with MK3682B, patients with genotypes 1, 2, and 3 had cure rates of 96%, 86%, and 95%, respectively. Efficacy was comparable between patients with and without cirrhosis. Merck was investigating the treatment of patients with genotype 1 who failed previous therapy with Harvoni or Zepatier (elbasvir/grazoprevir) in the C-SURGE trial, a phase 2 study. In 1 treatment arm, patients received MK3682B with ribavirin for 16 weeks, while the other arm included patients treated with MK3682B alone for 24 weeks. Because the trial is not yet completed, the final results will be presented at a future scientific congress, according to Merck’s website. Both C-CREST and C-SURGE preliminary results indicated that MK3682B was a potential pathway for Merck to release a drug combination for both treatment-naïve patients who previously failed a DAA treatment. If C-SURGE results show success in treating patients with genotype 1 who have failed treatment with Harvoni or Zepatier, MK3682B could have shared a niche with Vosevi for that hepatitis C indication. However, given that there are several drugs on the market for similar indications in other HCV target genotypes/studied endpoints, Merck ultimately decided to halt its pursuit of new HCV drug marketing while allowing the C-SURGE trial to progress to completion for other potential indications.

Additionally, Janssen announced that it will no longer develop its HCV treatment regimen JNJ-4178, which consists of 3 DAAs: AL-335, odalasvir, and simeprevir. During phase 2 trials, Janssen announced that the OMEGA-1 study will be completed as planned, but their focus will shift to developing treatments for hepatitis B. This decision was made after consideration of the vast availability of treatment regimens on the market for HCV, while there are significantly less manufacturers studying drugs for hepatitis B.

Perhaps these discontinuation announcements signal a slower development in new therapies to be released in the upcoming year due to competition in the HCV field. The new drugs, sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir, released during 2017 offer additional options for HCV, especially for treatment-experienced patients.

References are available at ContagionLive.com.

### Table 1. Indications and Treatment Durations for Vosevi

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Previously Treated Regimen</th>
<th>Vosevi Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, 3, 4, 5, 6</td>
<td>A nonstructural protein 5A (NS5A) inhibitor</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a or 3</td>
<td>Sofosbuvir without an NS5A inhibitor</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

### Table 2. Mavyret Therapy Duration for Treatment-Naïve Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>Compensated Cirrhosis (Child Pugh A)</td>
</tr>
<tr>
<td>1, 2, 3, 4, 5, 6</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

### Table 3. Mavyret Therapy Duration for Treatment-Experienced Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Previous Treatment</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>Compensated Cirrhosis (Child Pugh A)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Nonstructural protein 5A inhibitor</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Nonstructural protein 3/4A inhibitor</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1, 2, 4, 5, or 6</td>
<td>Interferon, pegylated interferon, ribavirin, and/or sofosbuvir</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

With strong support from the AASLD and IDSA, as well as a brief 8-week treatment duration, Mavyret is likely to be used more frequently in the future.
The Spanish Flu Pandemic 100 Years Later: Are We Ready for Another One?

The lack of a universal flu vaccine and the ease with which borders are crossed means a fast-spreading virus could be devastating.

BY LAURIE SALOMAN, MS

Ms. Saloman is a health writer with more than 20 years of experience working for both consumer- and physician-focused publications. She is a graduate of Brandeis University and the Medill School of Journalism at Northwestern University. She lives in New Jersey with her family.

The influenza pandemic that gripped the world from 1918 to 1919 sickened 500 million individuals and killed almost 50 million, many of them young and otherwise healthy. A quarter of the US population took ill, and entire cities shut down to try to halt the disease’s spread. Deaths were swift and harsh as fluid filled victims’ lungs, and funeral homes and cemeteries were inundated with coffins that piled up faster than they could be buried.

One hundred years later, we have not experienced anything like the pandemic that shook the world in the early 20th century. But are we being complacent? Is another pandemic lurking in our future, and are we ready for such an event?

For at least 1 infectious disease researcher, the next deadly epidemic is an everyday worry. “It is going to occur,” Michael Osterholm, PhD, MPH, director of the Center for Infectious Disease Research and Policy at the University of Minnesota and an author of Deadliest Enemy: Our War Against Killer Germs (Little, Brown and Company, 2017), told Contagion: “It’s just a matter of when and where it starts. The possibility that we could have a 1918-type pandemic again is actually very real.” The reason, he says, is that pandemics go back to ancient times; like hurricanes, they’ve occurred on a regular basis throughout history, with varying levels of severity. Recent outbreaks include H1N1 (swine flu), which killed about 8600 people worldwide in 2009, and H7N9 (avian flu), which has infected individuals throughout the current decade and, according to Dr. Osterholm, is being watched “very carefully” in China right now. As with swine and avian flu, he expects the next flu affecting a large number of humans will be zoonotic in origin.

Although the world has seen advancements in infectious-disease control since the Spanish Flu pandemic, including the creation of the seasonal flu vaccine, Dr. Osterholm says that certain facets of modern life make it more, not less, likely that another pandemic could be deadly. “We live in a global just-in-time economy,” he said. “A pandemic could put a screeching halt to that.” Because so many medical products used in the United States are made overseas, Dr. Osterholm explained, any interruption in the process of manufacturing and shipping goods would have an immediate impact on emergency departments’ ability to care for patients. Viruses also have the ability to spread in a way they didn’t 100 years ago, thanks to the millions who fly every day. “[Aviation] is a really a very accelerated way to move the virus that’s unprecedented in human history,” he said.

As far as readiness for a pandemic, Dr. Osterholm feels we’re unprepared. The biggest obstacle? The lack of a universal flu vaccine that covers all strains of influenza and protects people for several years. If scientists are able to develop one, he said, “we could...probably create the greatest public health victory in human history.” Governments, pharmaceutical companies, and philanthropic organizations all need to be working toward a universal flu vaccine, because although the current seasonal flu vaccine may help in the event of a pandemic, it also may be no match for whatever virus causes the next outbreak.

The delay in the development of a universal flu vaccine is rooted in money, according to Dr. Osterholm. Although diseases like HIV and cancer are funded to the tune of billions of dollars, significantly less is allocated to flu research. And while eradicating HIV and
cancer are important goals, he feels an infectious-disease outbreak has the potential to be far more destructive than those conditions. Writing in the *New York Times* last year, he said an influenza epidemic “could be more devastating than an atom bomb.”

**CONCERN, BUT NOT PANIC**

The prospect of another flu pandemic is worrisome, agreed Anthony Fauci, MD, head of the National Institute of Allergy and Infectious Diseases, who said we almost certainly will have another outbreak. “We have a history of pandemics,” he told Contagion®, “We’ve recently had a pandemic [H1N1]. The good news is, it wasn’t too severe.” Will the next pandemic be catastrophic? “Certainly, it’s possible,” he said. “[But] it would likely be mitigated by certain tools and interventions we have now that we didn’t have in 1918. We have antibiotics to treat the complications of bacterial pneumonia. We did not have any degree of capabilities of intensive care [in 1918].” He allowed that it’s possible that should a severe pandemic occur, the supply of tools we have now, such as respirators and medications, could be overwhelmed by the demand for them.

Dr. Fauci maintained that when pandemics occur, and how severely, are variables that are very difficult to predict (see Table). Given that almost all influenzas are zoonotic in nature, “you can at least keep an eye on what’s happening in the animal kingdom,” he said, citing birds and pigs specifically. “[In 2009, H1N1] was percolating in the swine population for a while. We weren’t monitoring the swine population particularly well, so we missed it.”

A universal flu vaccine would be a big help, Dr. Fauci agreed. “If we develop a universal flu vaccine that has at least some protection against any and all strains, then we will be much more ready than we are right now,” he said, cautioning that a society can never be truly ready for a catastrophic pandemic. A chart put out by the Centers for Disease Control and Prevention (CDC) that compares pandemic flu to seasonal flu highlights the particular risks of a pandemic, including the fact that most people will have almost no immunity to a virus to which they haven’t been exposed previously. Healthy individuals frequently suffer serious complications (as opposed to the seasonal flu, which disproportionately targets babies, older people, and those with preexisting conditions), and there is likely to be global economic disruption due to travel restrictions and business closings.

![Table: Pandemic Versus Seasonal Flu](#)

| **Table:** Pandemic Versus Seasonal Flu² |
| **FREQUENCY:** |
| Pandemic: Infrequent—pandemics occurred 3 times in the 20th century |
| Seasonal: Yearly, peaking in the winter |
| **IMMUNITY:** |
| Pandemic: Most people have little to no immunity |
| Seasonal: Many people have some immunity |
| **VACCINE AVAILABILITY:** |
| Pandemic: Limited availability; 2 doses may be needed |
| Seasonal: Available; 1 dose needed |
| **COMPLICATIONS:** |
| Pandemic: Moderate to high risk of complications and death among both sick and healthy individuals; deaths since 2010 number between 12,000 and 56,000 |
| Seasonal: Low risk of complications in healthy people; higher risk among vulnerable groups; estimated death toll in the United States during 1918 was 675,000 |
| **IMPACT:** |
| Pandemic: May have a major impact on society and the economy |
| Seasonal: Very little day-to-day impact on society and the economy |

**TIPS TO STAY SAFE**

Although it’s clear that nothing is guaranteed to stave off influenza in the event of a pandemic, there are steps individuals can take to protect themselves. Citizens can take advantage of antiviral drugs or pandemic vaccines, if those are available (they will likely be limited). Government officials, schools, and employers can encourage individuals to avoid traveling or gathering in public spaces to reduce the chance of infection. Well individuals should be separated from those who are ill and, as with the seasonal flu, should be vigilant about hand washing. Because a flu pandemic can last for months, all government and businesses entities ideally will have a plan in place to address every contingency so surprises are minimized.³

References are available at ContagionLive.com
The world of infectious diseases is dynamic, with threats that vary temporally, geographically, and by practice setting. The objective of this article is to highlight notable pathogens that may be relevant for infectious diseases clinicians in the United States in 2018. To provide a clinical and not purely epidemiological perspective, the diseases were considered on the basis of their unique and potentially alarming features in addition to changing incidence. This year, the infectious diseases community should watch out for:

**CANDIDA AURIS**

*Candida auris* (*C. auris*) is an emerging fungal species that has been identified as the causative pathogen in an increasing number of invasive fungal infections.1 It is unique among *Candida* species in that it is often multidrug resistant, is challenging to identify through the yeast identification methods used in many clinical microbiology laboratories, and is prone to causing outbreaks in health care facilities because of its ability to persist on environmental surfaces after application of quaternary ammonium disinfectants.1-3

Since its initial identification in Japan in 2009, *C. auris* has spread through international travel to several countries. In the United States, 203 *C. auris* cases have been reported as of December 2017.7 The geographic distribution in the United States demonstrates a predominance in New York and New Jersey, but fewer cases in Illinois, Massachusetts, and Florida. *C. auris* is associated with invasive infections and a high mortality rate, particularly from bloodstream infections in patients with serious underlying comorbidities and indwelling devices.7 Most isolated strains of *C. auris* in the United States are resistant to azoles but susceptible to echinocandin antifungals, although treatment-emergent echinocandin resistance has been reported.6 Echinocandins remain the empiric treatment of choice for suspected *C. auris* infection.

Given the serious implications for both patient care and infection control, the US Centers for Disease Control and Prevention (CDC) provides support and recommendations for the identification of *C. auris* in clinical laboratories.7 In addition to species-level detection from sterile sites, the CDC recommends that *Candida* identified in nonsterile sites be identified to the species level in patients with potential risk factors for *C. auris* infection or in facilities with known *C. auris* cases. *C. auris* should be suspected among patients who have experienced an overnight admission to a health care facility in affected regions, including India, Pakistan, South Africa, Kenya, Columbia, and Venezuela.5,8 Because of structural similarities and omission from current databases, *C. auris* is commonly misidentified by biochemical identification systems; for example, Microscan results may indicate *C. lusitaniae*, *C. guilliermondii*, *C. parapsilosis*, or *C. famata*, and Phoenix results may indicate *C. haemulonii* or *C. catenulata*.7 Furthermore, clinical laboratories utilizing matrix-assisted laser desorption ionization/time of flight may require research use-only databases to accurately identify *C. auris*. Facilities are encouraged to work with their local health departments if *C. auris* is suspected and to review recommendations specific to their diagnostic platforms if unusual *Candida* species are identified.
ELIZABETHKINGIA ANOPHELES

Elizabethkingia anopheles (E. anopheles), a common environmental Gram-negative bacilli, caused an outbreak of infections in the Midwest between 2015 and 2016 that affected at least 65 patients. Although this outbreak was contained, the event is notable because it was almost exclusively community acquired with- ing the gene implicated in human infections, including also found in Virginia, Tennessee, Michigan, and New Jersey and Maryland. Human isolates were of resistance in Gram-negative isolates.12

Transfer of mcr-1–containing plasmids to carbapenem-resistant Enterobacteriaceae has the potential to lead to truly pan-resistant infections with dire consequences. Treatment options for such pathogens would be experimental at best, based on in vitro data examining bacterial kill with different combinations of antimicrobials.20

In a recently published study utilizing a hollow-fiber infection model, the combination of amikacin, aztreonam, and polymyxin B was the most effective combination against E. coli coharboring mcr-1 and blagms.20 Research into therapeutic options and prevention of mcr-1 transfer are high priority research areas in the coming year.

VECTOR-BORNE DISEASES: THE LONE STAR TICK

Amblyomma americanum (A. americanum), colloquially referred to as the Lone Star tick, is characterized as an especially aggressive tick inhabiting the southeastern and eastern United States.21 Lone Star ticks have been associated with transmission of Ehrlichia spp., which causes human ehrlichiosis, Heartland virus, tularemia, and southern tick-associated rash illness.22 Recently, a CDC investigation of ticks collected in northwestern Missouri suggested that A. americanum is also a vector of Bourbon virus to humans.22

Bourbon virus clinical infections remain exceedingly rare, having been definitively identified in 5 individuals since the first reported case in Bourbon County, Kansas, in the spring of 2014.25 The most recent report of Bourbon virus infection occurred in the summer of 2017, affecting an employee of a state park in Missouri.24 Of particular concern, Bourbon virus has been rapidly fatal in immunocompetent adults, with no known cure and with a variable prevalence among ticks within the affected geographic area.25 Health care providers may suspect Bourbon virus among patients in the Midwest who experience fever, thrombocytopenia, and leukopenia after recent tick exposure and who test negative for other known tickborne illnesses.

Heartland virus infections are relatively more common, with over 30 reported cases occurring in the midwestern and southeastern United States as of July 2017.25 Similar to Bourbon virus, Heartland virus should be suspected in tick-exposed patients in affected geographical areas who present with fever, fatigue, nausea, diarrhea, and anorexia that do not respond to treatment with doxycycline. Rarely, Heartland involves thrombocytopenia, leukopenia, and transaminitis.25 Clinicians should be aware that evidence of Heartland virus in wildlife has been discovered in wide geographic areas of the South and Northeast, indicating that it may be more prevalent throughout the eastern United States than previously believed.26

ZOONOTIC FLU VIRUSES

Zoonotic flu viruses are not a new human threat, with various hosts assuming a position of risk over the years. Persistent zoonotic influenza threats include highly pathogenic strains of avian H7N9, H5N1, and H5N6, and swine influenza viruses H1N1, H1N2, and H3N2.27 Avian cases have occurred in patients with close contact with poultry, particularly in Africa, Europe, and Asia where influenza H5 subtypes are commonly identified in birds. Human-to-human avian influenza transmission is thought to be unlikely based on epidemiological and virologic evidence. Swine influenza cases continue to be reported in the midwestern and western United States among patients with direct exposure to swine; a recently reported case suggests that limited human-to-human transmission of influenza H3N2 may be possible.27

A potentially emerging zoonotic influenza strain to watch for is avian influenza H7N2, given its demonstrated ability to infect humans in contact with infected domestic animals.28 The vast majority of previous human infections with avian flu viruses resulted from direct contact with infected birds. The reported case of human H7N2 affected a veterinarian who had close unprotected exposure with H7N2-infected cats at an animal shelter in New York City.29,30 Investigations into the outbreak suggest that human transmission risk is low, however, and that the disease is generally self-limiting, but the possibility of a more widespread problem must be considered in light of the unique transmission history.

These infectious diseases are notable in their unique and potentially alarming behavior.

Diseases of concern for US infectious diseases clinicians in the coming year are difficult to predict, but historic data suggest continued heterogeneity in the types and presentations of emerging pathogens. Atypical vectors, such as Lone Star ticks harboring novel viruses and domestic felines harboring avian influenza, must be considered. Previously unknown pathogens, such as C. auris and Gram-negative organisms expressing mcr-1 colistin resistance, will require particular diligence from both clinicians and clinical microbiologists. Hopefully, the lessons learned from recent infections with C. auris, E. anopheles, mcr-1–mediated colistin-resistant E. coli, Bourbon virus, and avian influenza will prepare healthcare providers for future threats. References available at Contagionlive.com.
Long-term care facilities (LTCFs) help to provide both medical and personal care services to millions of Americans each year. As the population of adults over age 65 increases, this number is predicted to rise to 21% of the US population by 2040; there will be a corresponding increase in patient enrollment in LTCFs.

LTCF residents are at an increased risk of developing infections due to many underlying comorbid conditions, frequent use of invasive devices, age-related physiologic changes, and institutional exposure. These risk factors lead to approximately 1 million to 3 million infections occurring each year in LTCF residents, consisting mostly of urinary tract infections, respiratory tract infections, skin and soft tissue infections, and gastroenteritis. Roughly 63% of all LTCF deaths can be attributable to infections. Approximately 79% of all residents of these facilities receive systemic antibiotics each year, with close to 75% of these antibiotics inappropriately prescribed. This results in an increased number of adverse drug events (second only to antipsychotics), including development of antibiotic resistant organisms and Clostridium difficile (C. diff) infection. It is also well documented that LTCF residents have a high rate of colonization and infection with antibiotic-resistant organisms and C. diff. Isolation of antibiotic-resistant organisms is more common in LTCFs than in acute care facilities, further emphasizing that LTCFs serve as reservoirs for these difficult-to-treat organisms in the community.

Recently, there have been a number of resources released from the US Centers for Disease Control and Prevention (CDC), American Society of Consultant Pharmacists (ASCP), and the Agency for Healthcare Research and Quality (AHRQ) to aid LTCFs in creating antimicrobial stewardship programs (ASPs). Additionally, the Centers for Medicare & Medicaid Services issued a mandate in October 2016 stating that all LTCFs must fully implement an ASP by November 2019. However, many facilities lack access to the resources that are available to help them develop a strong program. This limitation can be the result having clinical providers located off-site, which leads to difficulty in appropriately diagnosing infections; relying on front-line staff to provide information on which to base clinical decisions; and lacking access to lab and microbiology reports and sufficient funding to hire staff, both physicians and pharmacists. Other barriers to optimizing antimicrobial use in

Successful Stewardship Strategies in Long-Term Care Facilities

One successful model takes an engineering approach to patient safety outcomes focusing on work system improvements.

BY JAMIE L. WAGNER, PHARMD, BCPP; AND KALIN M. CLIFFORD, PHARMD, BCPP, BCGP

Jamie L. Wagner, PharmD, BCPP

Dr. Wagner is a clinical assistant professor at the University of Mississippi School of Pharmacy. She received a PharmD from Midwestern University–Chicago College of Pharmacy, completed a PGY1 residency at Henry Ford Hospital, and an infectious diseases pharmacotherapy outcomes fellowship at Wayne State University / Henry Ford Hospital. She serves on the SIDP Antimicrobial Stewardship Committee and is chair of the Long-Term Care Stewardship Subcommittee.
Antimicrobial stewardship programs that take a multifaceted approach are more likely to be successful.

LTCFs include frequent antibiotic use in end-of-life patients, with up to 42% still receiving antibiotics despite a lack of evidence for relief of discomfort. Additionally, patients and family members expect antibiotic prescriptions to ease the suffering, thus making appropriate antibiotic prescribing difficult. These factors, along with minimal evidence of effective LTCF stewardship strategies, have prevented many facilities from implementing ASPs. Additionally, although each facility should be able to customize their stewardship programs to meet their individual needs, there is still a lack of standardization of stewardship program components for all LTCFs.

Reports of successful strategies to implement antimicrobial stewardship in LTCFs are starting to emerge within the review literature. A recent integrative review by Gurses and colleagues used the Systems Engineering Initiative for Patient Safety (SEIPS) model, an engineering approach to patient safety outcomes focusing on work system improvements. They reviewed tools, technologies, tasks, organizational condition, person(s), and environments to determine which aspects of workflow improvements it made more sense to modify to implement an ASP. Based on their approach, they were able to identify the following areas as fruitful aspects of an ASP: integrating postprescriptive recommendations into prescribers’ workflow; utilizing consultants in the infectious disease field; multidisciplinary education, and integrating preprescriptive data into nurses’ workflow. Previous ASPs focused on providing education through a variety of methods. Schwartz et al trained their physicians and nurses on recent guideline updates and created pocket cards of new guideline recommendations. By doing this, they found they decreased overall antibiotic use and have maintained that decrease for 2 years post intervention. Monette and colleagues provided antibiotic prescribing guidelines to all their physicians, but also supplied a report to the physicians in the intervention group of their antibiotic prescribing habits and indicated if each prescription complied with the current prescribing guidelines. They found that the physicians who received the feedback, in addition to the prescribing guidelines, were more likely to follow the antibiotic prescribing recommendations. Zimmerman et al evaluated training sessions for nurses and staff of multiple nursing homes. As part of the training session, they developed pocket guides and medical referral forms for the nursing staff to use. Nurses and prescribers also were given ongoing feedback regarding their antibiotic prescribing rates and habits. Results of this study showed that the overall rate of antibiotics used decreased.

A common theme for ASPs is that a multimodal approach is likely to be more successful. If a facility is only adding services, including education to patients, caregivers, and nursing staff, but not providing additional reinforcement, the knowledge gained from the educational sessions will not be retained. Furano et al evaluated the use of developing a nursing home-specific antibiogram as a tool. They found a modest increase in appropriate antibiotic prescribing after implementation of the antibiogram (32% vs 45%), but as it was not accompanied by recurrent education, the benefit was less than expected. The programs that identified greater decreases in their inappropriate antibiotic use incorporated a variety of methodologies, including development of pocket cards with new antibiotic prescribing recommendations, nursing communication forms that contained specific checkbox information to identify patient-specific symptoms, and 72-hour bundle policies, in accordance with CDC recommendations, that allow for re-evaluation of antibiotic orders and reassessment of symptoms and microbiological culture results to highlight key areas still needing improvement. Kassett and colleagues evaluated a multimodal program that included changes to 4 key areas: the use of ASP guidelines and policies, audit and feedback between physicians and clinical pharmacists, creation of information technology tools, and educational sessions. These programs were implemented in both their hospital and LTCF. This specific analysis did not note any significant decrease in number of antibiotics prescribed, but there was a sizeable drop in prescribed days of therapy and actual days of therapy counts, which led to decreases in overall antibiotic exposure.

At this time, the literature has not identified a single approach to LTCF ASPs as the gold standard approach. The literature has not yet identified a single approach to LTCF ASPs as the gold standard approach.

References are available at ContagionLive.com.
Although persistent symptoms have been observed in patients with a history of Lyme disease, the causes and management of these symptoms, as well as the challenges in conducting effective research studies, remain controversial among researchers. Improvements in research design and congenial collaboration among experts will be important for answering these questions, according to experts who participated in a recent Contagion® Peer Exchange Panel.

Controversies Surrounding the Causes and Management of Persistent Symptoms Related to Lyme Disease

BY GINA BATAGLIA, PHD

Although persistent symptoms have been observed in patients with a history of Lyme disease, the causes and management of these symptoms, as well as the challenges in conducting effective research studies, remain controversial among researchers. Improvements in research design and congenial collaboration among experts will be important for answering these questions, according to experts who participated in a recent Contagion® Peer Exchange Panel.

LONG-TERM MANIFESTATION OF SYMPTOMS

Peter L. Salgo, MD, and Leonard Sigal, MD, noted that many patients who receive antibiotics soon after infection will have symptom improvement; however, Samuel Shor, MD, FACP, pointed out that 39% of patients in the SLICE study treated early with antibiotics did not return to their pre-Lyme disease health status after 6 months. Dr. Shor noted that the findings in the SLICE study suggest persistence of symptoms after antimicrobial therapy in some patients, but whether they still harbor the Borrelia burgdorferi (B. burgdorferi) bacteria is controversial among scientists.

Some experts, including Robert C. Bransfield, MD, DLFAPA, suggest that patients carry the infection in a latent manner for several years and that an event, such as a co-infection with another pathogen, can re-activate the B. burgdorferi. “Co-infection is a complicated thing,” said Bransfield. “It can be a complex interactive infection, co-infection with other tick-borne or non-tick-borne pathogens that might be in the body and are opportunistic, like viruses.”

Dr. Sigal pointed out that past research has demonstrated that the proinflammatory B. burgdorferi-derived debris may persist after treatment with antibiotics, even if no live organism is present, and contribute to the persistent symptoms observed after treatment. Dr. Bransfield disagreed, stating that the persistent inflammatory reaction associated with symptoms likely lasts longer than the presence of the pathogen-derived debris. Bransfield also noted that patients who have received adequate treatment have relatively stable symptoms, whereas others have symptoms that worsen over time, likely caused by immune system provocation, although more research is needed to determine whether persistent infection is contributing to this immune system provocation.

MANAGEMENT CONSIDERATIONS

The panelists also debated the effective management of individuals with suspected Lyme disease, considering the notoriously inaccurate diagnostic laboratory testing, particularly for cases that have gone undiagnosed for several years. According to Dr. Bransfield, the 2-tiered system...
of serologic testing with an enzyme-linked immunosorbent assay (ELISA), followed by a confirmatory western blot test if the ELISA is positive, may be somewhat useful if a patient was infected a few months ago but is not standardized to test individuals who were infected 5 to 10 years ago. Furthermore, Dr. Sigal stated that the relationship between lingering symptoms and infection status is often unclear for many patients.

“I saw a gentleman 15 years after an erythema migrans who came in with Lyme arthritis,” said Dr. Sigal. “He was very seropositive. If somebody comes in with something that is not clinically likely to be Lyme disease and you have the blood test that’s positive, you don’t know if there’s any relationship between the two or if this is one of those lucky individuals who get bitten by a tick, their immune response deals with [it], and they seroconvert because there is an organism inside and available to their immune system.”

Dr. Shor noted that although some experts state that the antimicrobials improve symptoms by providing an anti-inflammatory effect, they may also induce an inflammatory response, such as a Jarisch-Herxheimer reaction. He also described a recent study in which researchers had *Borrelia* naïve ticks feed off mice that had been infected with *B. burgdorferi* and subsequently treated with antibiotics and showed that the ticks transmitted the pathogen to a group of *Borrelia* naïve mice, suggesting that antibiotics may not be sufficient to clear the infection.

**RESEARCH CHALLENGES**
The existence of chronic Lyme disease is a contentious debate among experts, and this controversy may be due to gaps in the types of research being funded, according to Patricia V. Smith. She stated that the lack of rigorous studies and the researchers that discount the relationship between persistent symptoms and Lyme disease is frustrating for many patients.

“After 33 years, I can say if it wasn’t for the International Lyme and Associated Diseases Society, most of the patients I have seen across the country...would not have anyone to turn to, to try to help them figure out just exactly what they do have,” she said.

To support the notion that funding for Lyme disease research is biased, she recalled her experience in 2012 at Congressional hearings of the House Foreign Affairs Committee, stating that a prominent researcher testified that there were “serious issues” with the grant process at the National Institutes of Health (NIH).

“If someone wanted to do a study and said they were looking at chronic Lyme, those grants were just not considered,” said Ms. Smith. “Apparently, those who sat in peer review didn’t really want to look at chronic Lyme because they had another bias. The same kinds of studies were funded year after year...instead of the kinds of research that really needed to be done; for example, research on new cutting-edge testing.”

Dr. Sigal argued that the NIH grants were appropriately awarded and used by the recipients, but were rarely sufficient to conduct all needed research and consider multiple viewpoints.

“There’s an undercurrent to many of these conversations that, somehow, there’s this nefarious self-interest amongst people who are getting funds for research,” said Dr. Sigal. “That’s really not true. These are scientists who are trying to do their best. There are other people who believe in a very different approach to Lyme disease...They are welcome to approach the NIH to get funds for their research as well. If...the paper is written properly, if the grant is written properly—they’ll be taken into consideration.”

**REACHING A CONSENSUS**
Most of the panelists agreed that a 2- to 4-week course of antibiotics for patients with suspected Lyme disease is an appropriate first step of treatment. However, they noted that the clinical response will likely vary among individuals, particularly if there is a complex infection, multiple pathogens, or life-threatening clinical manifestations, such as meningitis.

For the subset of patients who do not respond to 6 weeks of antibiotics, the panelists agreed that a careful differential diagnosis and empathetic review of a patient’s clinical picture should be performed. However, Dr. Shor pointed out that the secondary assessment will probably vary among clinicians based on their perception of the incidence of active Lyme disease.

As for prolonging antibiotic use in patients who do not have symptom improvement at first, Dr. Shor stated that they should be continued if clinicians feel that there is still an active infection. “By not [continuing antibiotics], you potentially run the risk of not having adequate therapeutic gains.”

The panelists also agreed that more collegial peer discussions among experts can help to reconcile differences in viewpoints and develop a specific universal definition of Lyme disease. However, several barriers have precluded these research projects and collaborations, including a climate of fear surrounding physicians, who have been subject to sanctions in the past for long-term treatment of patients with Lyme disease, and the reluctance of physicians and patients to participate in clinical trials due to poor responses to long-term antibiotic use in previous trials.

However, Dr. Sigal added that the duration of many of these long-term antibiotic trials was likely insufficient to see the desired outcomes and Shor noted that the trials had multiple confounding variables, such as the inclusion of patients with long-duration illness who had previously received the protocols being tested and the failure to identify co-infections. The panelists concluded that improving the quality of scientific research on clinical biomarkers and testing, along with a better consensus among experts about study design, goals, and endpoints, could help improve the perceived value among experts of study results in trials of persistent symptoms following Lyme disease infection. ▲
Study: Oral Truvada Safe & Tolerable for Use in Adolescents

BY CONTAGION® EDITORIAL STAFF

Although the number of participants who took Truvada as prescribed was lower than the number who opted in and this number decreased over time, nearly 40% of the participants were adherent by the end of the study.

According to a press release, this phase 2 study evaluated the “safety, acceptability, and use” of Truvada, which contains 2 anti-HIV drugs, tenofovir and emtricitabine, as part of a prevention package for adolescents. This marked the first time that girls were included in a clinical trial of the daily oral tablet as a means of preexposure prophylaxis (PrEP) in the adolescent population, according to the release, which also noted that Truvada has yet to receive approval “by any national regulatory body for use as oral PrEP in adolescents.” However, the tablet is already used for prevention in adults.

The study enrolled 148 sexually active adolescents and young adults (99 females and 49 males aged 15 to 19 years) from Cape Town and Johannesburg, South Africa. None were infected with HIV at time of enrollment and all were deemed otherwise healthy. All participants were instructed to take oral Truvada daily for at least 3 months, with the option to take it up to 1 year. According to the press release, all participants received an HIV preventive package consisting of:

- HIV testing
- Management of sexually transmitted infections
- Access to condoms
- Postexposure prophylaxis
- Counseling on infection risk reduction (including, for males, circumcision) and ongoing need for oral PrEP

The participants also were provided with 3 preventive components tailored for their population:

- Option to receive daily/weekly reminder text messages to take their tablet
- Adherence clubs—meeting with community health care worker for counseling and support for taking the tablet as PrEP
- Option to receive real-time reports on blood level of tenofovir during study visits

Most participants chose to take the oral tablet, which proved “safe and tolerable” for this population, according to the investigators. “Although the number of participants who took Truvada as prescribed was lower than the number who opted in and this number decreased over time, nearly 40% of the participants were adherent by the end of the study,” they said. Furthermore, just 1 participant (aged 19) became infected during the trial; she reportedly stopped taking the tablets 3 months prior to her diagnosis. Throughout the first 3 months, the participants were required to make monthly visits to health care providers; after that, they went quarterly. At each visit, participants could choose to opt out or continue taking the tablets. In addition, blood samples were periodically drawn and analyzed for evidence of adherence. The participants were monitored for 1 year.

At the 3-month mark, the investigators found tenofovir in the blood of 57% of the participants, providing evidence that they were adhering to the regimen. A total of 82% of the participants opted to continue treatment. However, at the 6-month mark, tenofovir was detected in just 38% of participants, and just 64% opted to continue treatment. By the end of 1 year, 38% of participants tested positive for tenofovir. The most commonly cited reasons for stopping treatment were either headaches or nausea.

“The trend toward lower adherence to Truvada for PrEP as study visits became less frequent parallels what was observed in a study of PrEP in adolescent gay and bisexual boys, suggesting that monthly study visits may support greater adherence to oral PrEP among adolescents over time,” Protocol Chair and International AIDS Society President Linda-Gail Bekker, MBChB, PhD, commented in the press release.

The investigators said they hope that the results will help support the development of evidence-based guidelines for the use of Truvada as oral PrEP in adolescents.

The National Institute of Allergy and Infectious Diseases contributed funding to the study.
Indication and Usage for JULUCA

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

Important Safety Information

CONTRAINDICATIONS

JULUCA is contraindicated in patients:

• with previous hypersensitivity reaction to dolutegravir or rilpivirine.

• receiving dofetilide, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, systemic dexamethasone (>1 dose), St. John's wort, and proton pump inhibitors (e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole).

*HIV-1 RNA <50 copies/mL on a stable antiretroviral therapy for at least 6 months.
Discontinue JULUCA immediately if signs or symptoms of severe skin and hypersensitivity reactions develop (such as severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, mucosal involvement, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, and difficulty breathing), as a delay in stopping treatment may result in a life-threatening reaction. Clinical status, including laboratory parameters with liver aminotransferases, should be monitored and appropriate therapy initiated.

### Important Safety Information (cont’d)

**WARNINGS AND PRECAUTIONS**

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

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

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

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Please see additional Important Safety Information for JULUCA on the previous page.
Please see Brief Summary of Prescribing Information for JULUCA on the following pages.
Grades 1 to 4 adverse reactions of ≥2% frequency were diarrhea, 2% vs <1%, and headache, 2% vs 0% (JULUCA vs continued baseline ART, respectively). Discontinuations due to adverse events were 4% for patients who switched to JULUCA and <1% for patients who continued baseline ART in the pooled analyses.

*Based on a pooled analysis of the SWORD 1 and SWORD 2 trials, 2 identical designed, randomized, multicenter, open-label, parallel-group, noninferiority trials comparing JULUCA (n=513) vs continuation of current stable ART (INSTI, NNRTI, or PI + 2 NRTIs; n=511) in treatment-experienced, virologically suppressed (HIV-1 RNA <50 copies/mL; on stable suppressive uninterrupted therapy for ≥6 months prior to screening) adults (≥18 years) with HIV-1. At baseline, 11% of patients had CD4+ T-cell counts <350 cells/mm² and 11% were CDC Class C (AIDS).

Baseline third agents were: 54% NNRTIs, 26% PIs, and 20% INSTIs. Patients were excluded if they had a history of treatment failure, known substitutions associated with resistance to dolutegravir or rilpivirine, any degree of hepatic impairment, positive for hepatitis B virus (HBV), or with an anticipated need for hepatitis C virus (HCV) therapy during the study.

Primary endpoint was proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 using FDA snapshot analysis.

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

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

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

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

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

**DOSAGE AND ADMINISTRATION**

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

**Juluca**
dolutegravir 50 mg/
rilpivirine 25 mg tablets

Visit www.julucahcp.com to learn more.
BRIEF SUMMARY

**JULUCA** (dolutegravir and rilpivirine) tablets

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

**CONTRAINDICATIONS**

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

**Drug Class** | **Clinical Comment**
--- | ---
Antithyroid: Deltolate | Potential for serious and/or life-threatening events due to the potential for increased deltolate plasma concentrations.
Anticonvulsants: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin | Potential for significant decreases in rilpivirine plasma concentrations due to CYP3A enzyme induction, which may result in loss of virologic response.
Antimycobacterials: Rifampin, Rifapentine | Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.
Glucocorticoids: Dexamethasone | Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.
Glucocorticoids: Dexamethasone (more than a single-dose treatment) | Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.
Proton Pump Inhibitors: e.g., Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Ranitidine | Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.

**WARNINGS AND PRECAUTIONS**

Skin and Hypersensitivity Reactions: Hypersensitivity reactions have been reported with dolutegravir and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase 3 clinical trials of rilpivirine, treatment-related rash was at least Grade 2 severity were reported in 3% of subjects. No Grade 4 rash was reported. Discontinue JULUCA immediately if signs or symptoms of severe skin or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, mucosal involvement [oral blisters or lesions], conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including laboratory parameters with liver amonitransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with JULUCA after the onset of hypersensitivity may result in a life-threatening reaction. Hepatitis: Hepatic adverse events have been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations. Additionally, in some patients receiving dolutegravir-containing regimens, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity including elevated serum liver biochemistries and hepatitis have also been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to acute liver failure has been reported with dolutegravir-containing products, including liver transplant with Tivicay (abacavir, dolutegravir, and lamivudine). Monitoring for hepatitis is recommended. Depression: Depressive Disorders: Depressive disorders (including suicidal ideation, attempt behavior, or completion) have been observed in patients treated with dolutegravir plus rilpivirine. These changes are not considered to be clinically relevant. Serum Lipids: In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QTc interval of the electrocardiogram. Consider alternatives to JULUCA when coadministered with a drug with a known risk of torsade de Pointes. See the Drug Interactions section for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with JULUCA; review concomitant medications during therapy with JULUCA, and monitor for the adverse reactions associated with the concomitant drugs.

**ADVERSE REACTIONS**

The safety assessment of JULUCA in HIV-1–infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine was based on the pooled primary Week 48 analyses data from 2 identical, international, multicenter, open-label trials, SWORD-1 and SWORD-2. A total of 1,024 adult HIV-1–infected subjects who were on a stable suppressive antiretroviral regimen containing 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine, were randomized and received treatment. Subjects were randomized 1:1 to continue their current antiretroviral regimen or be switched to dolutegravir plus rilpivirine administered once daily. In the pooled analyses, the proportion of subjects who discontinued treatment due to an adverse event was 4% in subjects receiving dolutegravir plus rilpivirine once daily and was <1% in subjects who remained on their current antiretroviral regimen. The most common adverse events leading to discontinuation were psychiatric disorders: 2% of subjects receiving dolutegravir plus rilpivirine and <1% on their current antiretroviral regimen. The most common adverse reactions (grades 1 to 4) reported in at least 2% of virologically suppressed subjects with HIV-1 infection in SWORD-1 and SWORD-2 trials (week 48 pooled analyses) in either treatment arm – JULUCA (n=513) vs current antiretroviral regimen (n=511), respectively: diarrhea (2%, <1%), headache (2%, 0). Less Common Adverse Reactions occurred in less than 2% of subjects receiving dolutegravir plus rilpivirine or are from studies described in the prescribing information of the individual components, Tivicay (dolutegravir) and EVORA21 (rilpivirine). Some events have been included because of their seriousness and assessment of potential causal relationship. General Disorders: Fatigue. Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, nausea, upper abdominal pain, vomiting. Hepatobiliary Disorders: Cholelithiasis, hepatitis. Immune System Disorders: Immune reconstitution syndrome. Metabolism and Nutrition Disorders: Decreased appetite. Musculoskeletal Disorders: Myalgia. Nervous System Disorders: Dizziness, somnolence. Psychiatric Disorders: Depressive disorders including depressed mood, depression, suicidal ideation, attempt behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Other reported psychiatric adverse reactions include anxiety, insomnia, sleep disorders, and abnormal dreams. Renal and Urinary Disorders: Glomerulonephritis membranous, glomerulonephritis mesangio proliferative, nephrolithiasis, renal impairment. Skin and Subcutaneous Tissue Disorders: Pityriasis rosea. Adverse Reactions section for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with JULUCA; review concomitant medications during therapy with JULUCA, and monitor for the adverse reactions associated with the concomitant drugs.

**Interactions**

Concomitant use of JULUCA and other drugs may result in known or potentially significant drug interactions, some of which may lead to: Loss of therapeutic effect of JULUCA and possible development of resistance; Possible clinically significant adverse reactions from greater exposures of concomitant drugs. In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QTc interval of the electrocardiogram. Consider alternatives to JULUCA when coadministered with a drug with a known risk of torsade de Pointes. See the Drug Interactions section for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with JULUCA; review concomitant medications during therapy with JULUCA, and monitor for the adverse reactions associated with the concomitant drugs.
tests in the rilpivirine group is not known. Postmarketing Experience: The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or rilpivirine-containing regimen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Muscloskeletal Disorders: Arthralgia, myalgia. Hepatobiliary Disorders: Acute liver failure, hepatotoxicity. Renal and Genitourinary Disorders: Nephrotic syndrome. Skin and Subcutaneous Tissue Disorders: Severe skin and hypersensitivity reactions including DRESS.

Drug Interactions
Concomitant Use With Other Antiretroviral Medications: Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. Potential for JULUCA to Affect Other Drugs: Dolutegravir, a component of JULUCA, inhibits the organic cation transporters (OCT1) and multidrug and toxic extrusion transporter (MATE1); thus it may increase plasma concentrations of drugs eliminated via OCT1 or MATE1 such as dolutegravir and metformin. Potential for Other Drugs to Affect the Components of JULUCA: Dolutegravir is metabolized by uridine diphosphate (UDP)-glucuronosyltransferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegravir is also a substrate of UGT1A1, UGT1A6, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro. Drugs that induce these enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir. Rifampin, Rilpivirine: Rifampin is primarily metabolized by CYP3A, and drugs that inhibit or induce CYP3A may affect the clearance of rilpivirine. Coadministration of JULUCA and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Coadministration of JULUCA and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Coadministration of JULUCA with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. QT-Prolonging Drugs: In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QT interval of the electrocardiogram. Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes. Established and Other Potentially Significant Drug Interactions: Information regarding potential drug interactions with dolutegravir and rilpivirine are provided below. These recommendations are based on either drug interaction trial results of individual components or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. Alterations in dose or regimen may be recommended based on drug interaction trials or predicted interactions with JULUCA:

- Antacids: e.g., aluminum or magnesium hydroxide, calcium carbonate - administer JULUCA 4 hours before or 6 hours after taking antacids.
- Antiarrhythmics: dofetilide - coadministration is contraindicated with JULUCA.
- Anticoagulants: carbamazepine, oxcarbazepine, phenytoin - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- Antidiabetics: metformin - with concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or JULUCA. When starting or stopping JULUCA, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of JULUCA is recommended.
- Antimycobacterials: rifampin, rifapentine - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- Antivirals: carbonic anhydrase, sucralfate, or buffered medications - Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.
- Macrolide or luteolate antibiotics: clarithromycin, erythromycin, telithromycin - Where possible, consider alternatives, such as azithromycin.
- Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing products or laxatives, sucralfate, or buffered medications - Administer JULUCA 4 hours before or 6 hours after taking products containing polyvalent cations.

Narcotic analgesics: methadone - No dose adjustments are required when starting coadministration of methadone with JULUCA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
- Oral calcium and iron supplements, including multivitamins containing calcium or iron (non-antacid) - administer JULUCA and supplements contain calcium or iron together with a meal or take these supplements 4 hours before or 6 hours after taking JULUCA.
- Proton Pump Inhibitors: e.g., esomeprazole, lanzoprazole, omeprazole, pantoprazole, rabeprazole - coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations.

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

Use in Specific Populations
Pregnancy: Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JULUCA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. There is insufficient prospective pregnancy data from the APR to adequately assess the risk of birth defects and miscarriage. Given the limited number of pregnancies exposed to dolutegravir-containing regimens reported to the APR, no definitive conclusions can be drawn on the safety of dolutegravir in pregnancy, and continued monitoring is ongoing through the APR. Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population.
- Lactation: The Centers for Disease Control and Prevention recommend that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether JULUCA or components of JULUCA are present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir and rilpivirine were present in milk. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving JULUCA.
- Pediatric Use: The safety and efficacy of JULUCA have not been established in pediatric patients.

Hepatic Impairment: Clinical trials of JULUCA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in administration of JULUCA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- Renal Impairment: No dosage adjustment is necessary for patients with mild or moderate renal impairment (creatinine clearance greater than or equal to 20 mL/min).

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

by:

GlaxoSmithKline

ViiV Healthcare

Research Triangle Park, NC 27709

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Hospital Mattresses: A Vector for Spreading Clostridium difficile

BY KRISTI ROSA

(continued from cover)

those kinds of things have been well recognized. But the big risk to inpatients is the mattress,” Edmond A. Hooker, MD, DrPH, professor in the Department of Health Administration at Xavier University, told Contagion® in an exclusive interview. “Patients are exposed to the mattress; they’re lying on it for hours on end, and these mattresses cannot be cleaned. With the current cleaning methods being used today, they are not being cleaned adequately enough, and we need to change [that].”

Even after terminal cleaning, the mattresses are not clean, Dr. Hooker stressed in his presentation, and he listed at least 30 peer-reviewed studies that supported his statement. This research begs the question of why the mattresses are not being disinfected properly. According to Dr. Hooker, one of the answers is time. Many hospitals ask environmental services workers to turn a room over in just 20 minutes, which, Dr. Hooker said, makes it impossible to clean all of items in the room.

“If you are truly cleaning and disinfecting every part of that room, it takes almost 30 minutes just to clean the bed,” he explained. “You’ve got to wipe the top of the mattress, the sides, the bottom, the bed deck, the handrails, up underneath, the wheels—all of that is potentially contaminated. And [they’re] not doing that. They usually spend about 3 minutes on the bed. Three minutes to disinfect a major piece of equipment."

Properly cleaning a mattress is a multistep process that requires rinsing, something that health care staff just don’t have time for.

“I can tell you right now, there’s not a hospital on the planet rinsing after they clean, then disinfecting, and then rinsing again,” Dr. Hooker said. “Nobody’s doing that; it would take them an hour just to clean the bed. They would be tied up for an hour, and that hospital has patients coming out of the operating room, patients in the emergency [department (ED)]. I had 50 in-patients being held in my [ED] just last week—50.”

The other problem is the chemicals that are being used in hospitals to clean the mattresses. “Hospital hard surfaces are a lot easier to clean because the chemicals were made for hard surfaces,” Dr. Hooker told Contagion®. “Unfortunately, the mattress [has] a soft, porous surface; it was intended to be that to stop all of the bed sores. And so, if you think about a 1970s car with a vinyl seat—you sat in it, you sweated, and you stuck to it, and that was miserable. Well, that’s not good for a patient either, and that’s what mattresses used to be like.”

Now, mattress developers are using “breathable fabric,” which allows for the moisture to get away from the patient, according to Dr. Hooker. However, the problem with this is, the chemicals that are being used to clean the mattresses were developed to be used on hard surfaces. “All of the chemicals that are being used are the wrong chemicals; they don’t work, and they damage the fabric, which causes cracks and crevices where C. diff and other nasty bugs can go down and hide,” Dr. Hooker stressed.

To make matters worse, regulatory agencies, such as the Food and Drug Administration, the Environmental Protection Agency, and the Centers for Disease Control and Prevention (CDC), appear to be “turning a blind eye” to the issue, according to Dr. Hooker.

“They are great organizations with wonderful people working there, but they just haven’t done anything. The CDC has not updated their guidance since 2008 in the cleaning of mattresses, and the 2008 guidance didn’t really change much from the 2003 guidance. The CDC could say, ‘Effective immediately: Clean these beds to a high level every single time,’ but instead they call it a noncritical surface; they say it’s noncritical because it doesn’t touch nonintact skin,” Dr. Hooker said. “The last time I checked, every single patient has nonintact skin; they’ve got an intravenous line in; they’ve got dermatitis; they’ve got a pressure ulcer; they just had an operation on their hip—that’s nonintact skin. And yet, we lay the patient on the mattress as if they’re being laid on a perfectly clean space, and it’s not clean. They put it in the noncritical category, which means that you can use low-level disinfection.”

As per current practice in hospitals, unless a patient has documented multidrug-resistant organisms or C. diff, they get “normal” cleaning, which is a 1-step process using a quaternary ammonia cleaner. “Quaternary ammonium compound is the most commonly used disinfectant; it does not work for C. diff. It has been shown not to work for C. diff on hard surfaces, and it clearly isn’t going to work on soft surfaces,” Dr. Hooker explained.

Dr. Hooker reminded conference goers of the chemicals that do work against C. diff. These are mainly bleach (for log 5 to log 5 reductions) and H2O2/Peracetic acid (for log 4 reduction). He pointed out that use of UV light only yields a log 1 reduction.
Hydrogen peroxide vapor is another option that gives a log 5 reduction, but it takes hours to work, and, again, the chemicals available to kill *C. diff* only work for hard, porous surfaces. So, how do you kill *C. diff* on soft, porous surfaces, such as hospital mattresses?

Dr. Hooker discussed the use of a launderable mattress cover known as the Trinity Guardian Patient Barrier System, which is made of knit polyester fabric with a polyurethane coating on the patient side—the same breathable materials used in high-end mattresses. The cover was designed to prevent the penetration of bodily fluids and microorganisms, and, according to Dr. Hooker, it’s cost-effective, easy to use, and works against *C. diff*.

“You need a verifiable process that’s repeatable and doesn’t depend on workers doing things right or wrong,” Dr. Hooker explained. Here’s how it works:

- **Put the cover on the mattress.** This takes 30 seconds to 1 minute. The cover is reverse-rolled, so that the patient contact surface is inside, which means nothing touches the mattress.

- **When the patient leaves, roll the cover up and take it to the laundry.** There are multiple health care laundries around the United States now, and they can all do this. You clean it, you rinse it, and then you wash with chlorine. “We wash with chlorine, which is normally dangerous for mattress surfaces, but it’s not in this case because we rinse it off and we use lower concentrations of it,” Dr. Hooker explained. “Chlorine works, even at that lower 150 parts per million (ppm); this means that I’m not putting that 5000 ppm all over the mattress.” Then, you rinse it again.

- **Dry it with heat.** Heat makes chlorine much more effective, according to Dr. Hooker, and bacteria do not like heat. The heat also works to kill the bacteria.

- **Inspect every mattress, every time.** “Just like operating room linens are inspected because we can’t have cracks in those, this is the same idea,” Dr. Hooker explained. The cover is barcoded, which means workers can tell how many times it has been used and when it’s at the end of its life, where it’s going, and where it’s supposed to be. “We’ve shown that we can run it through at least 150 times without degradation,” he added.

- **Repeat.**

The mattress cover is made for each specific manufacturer’s bed, and it has clips to ensure that it stays in place; it can even be used on ED or operating room stretchers. “They cost about $450 dollars. And so, if you say 150 uses, that’s about $3 a turn—that’s not bad. It costs about $5 to $6 to clean them because they’ve got to be cleaned well. Obviously, you don’t want to just take them and wipe them off. Then you’ve got the same problem that you had before,” Dr. Hooker said.

Dr. Hooker and colleagues conducted a recent study to test the effectiveness of the mattress covers in 2 long-term acute care hospital settings; one facility had 74 beds, the other had 30 beds. The investigators changed the cover after each patient and then laundered them using hot water, detergent, and chlorine. They proceeded to compare *C. diff* infection rates by using Poisson regression between the 16 months before using the covers and the 14 months after using them. The results? Use of the mattress covers helped reduce *C. diff* infections by 47.8% in the first hospital and 50% in the second.

“The mattress is the highest touch point in the room; you lay on that thing 23 hours a day or more, and yet we clean the toilet better than we clean what you lay on,” Dr. Hooker stressed. “And the sheet won’t protect you; the bacteria can go right through a sheet; blood can come right through a sheet; *C. diff* can come right through a sheet.”

Launderable mattress covers may provide a potential solution to an ongoing problem faced by health care facilities everywhere. One thing is for certain: the current cleaning methods leave much to be desired, and so something needs to change.
MEETING COVERAGE

5th Annual International C. diff. Awareness Conference

New Tactics to Prevent and Control C. Difficile Infections

BY CONTAGION® EDITORIAL STAFF

(continued from cover)

Contagion®: Are there newer strategies being explored to prevent CDIs in facilities?

We have very interesting technology. A new one that I just learned about is dried hydrogen peroxide; it’s actually a system that can be put up in your ventilation system and it will take the moisture and turn it into hydrogen peroxide and continually disinfect the room. There are lights that run 24/7 with UV light and they will disinfect the environment, even when you’re not in the room; they’ll actually put on a higher level of disinfection activity when the room is vacated. And because of that, those facilities are sporicidal for environmental cleaning, even paint. Sherwin-Williams has paint that can have an antibacterial effect and will kill bacteria on the wall if you use that particular kind of paint. And so, there’s a lot out there.

C. diff is one of the biggest causes of nosocomial infectious diarrhea, which, in turn, can lead to lengthier hospital stays, increased financial burden, and higher morbidity and mortality rates among those infected. Therefore, the use of appropriate thorough disinfection practices is critical in health care facilities. However, in the haste to turn over rooms quickly after patient discharge, effective disinfection can fall through the cracks, allowing C. diff spores to remain in the room for the next patient.

Contagion®: Can you share some statistics regarding surface contamination?

Years ago, Phil Carling, MD, did a study that included 23 acute care hospitals where he used a fluorescent gel that he had developed. He solicited IPs in these hospitals to stamp high-touch surfaces in patients’ rooms, such as bed rails, bedside tables, commodes, and bathrooms. The IPs returned the next day and used a black light to see whether the fluorescent gel was still there or if it had been removed by EVS. What they found was that, overall, only approximately 49% of the surfaces in the hospitals were cleaned.

There are a couple of reasons for that. We don’t have enough EVS workers in hospitals; it’s not uncommon for that position to get downsized when hospitals are having financial issues. We also don’t have well-trained EVS workers. Many of the hospitals don’t even have training programs or manuals available on how to clean and disinfect unless they’re outsourced to a company that is a...
cleaning company. And so, we have rooms that are not being cleaned and disinfected; in fact, if you are admitted to a room where a prior occupant had any of the following multidrug-resistant organisms [MDROs]—methicillin-resistant Staphylococcus aureus, Acinetobacter, Pseudomonas, C. diff—your risk of picking up the infection from just being in the room increases 2- to 4-fold. That's our challenge.

For prevention interventions, we use a lot of innovative EVS equipment. Some of it's really cutting edge and new, while others, like UV robots, have been around for a while. Hospitals are looking at that technology to treat the room after patients with CDIs are discharged.

There's also technology that is purifying the air. That's really new over the last 2 years. We never really had that before. This is especially important because we know that C. diff spores can be aerosolized. We have new light fixture technology that disinfects the air using filters and UV light that purifies the air 24/7. That's a future goal for a lot of vendors: to create technology for self-disinfecting rooms to help in our battle against environmental issues and the fact that we don't have enough workers to clean the rooms.

There are many risk factors for CDI, which include underlying conditions/comorbidities; individuals with disease states, such as cardiopulmonary disease and diabetes; and, arguably most importantly, antibiotic exposure.

**Contagion**: As an IP, can you explain the importance of prevention, especially when it comes to a health care-associated infection like C. diff?

A lot of our job should be prevention, but we still end up handling infection control efforts. They changed our title years ago from infection control practitioners to IPs, and yet when you hear most of the things being spoken about at conferences, we're talking about the control of the environment, of people using precautions, and of treating patients' infections.

The prevention aspect is to stop the inappropriate use of antibiotics. If we didn't use so many antibiotics, we wouldn't have conditions like this developing. That's the prevention piece of it—the antimicrobial stewardship program [ASP], and having IPs actively involved in taking on antimicrobial resistance and assisting the ASP program members with reducing the number and length of treatments or days of therapy with the antibiotics. That is what causes these MDROs and C. diff.

**Contagion**: What's a major way to prevent CDIs?

Decreasing the use of antibiotics. Many laboratories are using older, traditional methods of doing cultures, and it can take anywhere from 2 to 3 days to get not only the culture itself specified out and colonies picked off, but to put it into some identification [ID] system—whether it be polymerase chain reaction (PCR) or some other kind of rapid technology. Then they go on to do sensitivities that can take anywhere from 2 to 4 to 5 days, depending on the specimen. In the interim, patients are on antibiotics waiting for the results. I feel that it's the No. 1 problem we have in hospitals—delayed lab results.

For example, you've got somebody in septic shock in the ICU. We are wiping out all the good flora in their mouth, their colon, and their skin, being on antifungal, anti-Gram-positive, anti-Gram-negative, and even sometimes double therapy, while physicians are covering their tails. The physician doesn't know what infection the patient has and so they want to give them everything. We call that empiric therapy. After physicians get the lab results, they can de-escalate the patient and then get to more targeted therapy. For instance, rather than use imipenem, which is more expensive, the physician can maybe switch to gentamicin based on a sensitivity result and have the patient on something that's safer and less expensive.

To help with faster lab results, there is new technology that has come out that's available. These are fast ID and susceptibility systems, and IPs have to work with the lab to support them. [Adopting these technologies] should be driven from the clinical side, with IPs supporting the lab to get this technology. What often happens, though, is a disconnect between IPs and the lab, because everything goes into electronic medical records [EMRs]. And so, IPs get EMRs in their offices, and they're able to look at all the cultures from there. In the old days, we would go to the lab in the morning, find out what was going on with gram stains and blood cultures and any unusual organisms, then head up to the ICU and see all the sickest patients and do our rounds. Now, the IPs are chained to their desks, doing surveillance for the CDC's National Healthcare Safety Network [NHSN], and not going out doing what they should be doing—which is surveillance out on the floors consulting, providing education, and visiting departments. It's created a big crisis in infection prevention, the NHSN system, without the support IPs should have had for data analysts to help us navigate the system.

The laboratory needs support, too, probably through the ASP committee. Through that committee, we can all make a case for the lab to get a very rapid system. If we have the pharmacist showing the days of therapy and how they could reduce it, the IPs reducing the adverse outcomes, and nursing and critical care and sepsis coordinators all making a business case so that the lab—whose budget is going to go up—can be left alone, then we can say, 'We're going to support you clinically.' But that's not what happens. Often, it's left to the lab, and the lab gets shut down.

There's also a new machine available that will do a blood culture from [half of a cc] of positive blood, the Accelerate Pheno System. It will automatically identify an organism and its sensitivity within 7 hours, whereas typically you wait anywhere from 2 to 5 days. When that kind of technology comes out and starts to get adopted in more hospitals, then patients—who are getting more savvy these days—can say, "You didn't use the more rapid [and] fast technology, and I got an infection because I sat waiting for days. I got C. diff on top of it." There are now some legal suits that are going along those lines. Patients are feeling that they're not having the advantage of some of this more rapid and fast technology for either ID of the organism alone or the antimicrobial sensitivity. This new system combines the 2 together.

**Contagion**: Can you speak to the importance of teamwork when it comes to the fight against C. diff?

[The fight] requires a team, and the team should include, or at least try to get, members from the chief of surgery, [since they're going to be doing colectomies on patients who have CDI]; the chief of gastroenterology, since we see a higher correlation of CDIs with proton pump inhibitors and with endoscopy procedures; and nurse managers, especially the nurse manager of the unit that might deal with more of the patients coming in from long-term care and being on [contact] precautions. [The team should] have members of the microbiology lab there, too, as well as the IPs, and the quality department, since they're responsible for all the penalties that we are getting from the Centers for Medicare & Medicaid Services for CDI cases. Also, EVS should be there, if there is some of this innovative technology that they would have to know or you intend to install special lights and fixtures.

What the team should do at first is get everybody on the same page with education. There are a couple of good epidemiology articles on CDIs to provide everyone with, to ensure they understand this national crisis with C. diff. Then, from there, developing different tasks and projects for the group members and reviewing different cases are important as well. Talk about, "Why did this person likely get a CDI? Does it look like it was due to the antibiotics? Or could this [patient] have been somebody who wasn't on antibiotics, but picked it up while they were in the hospital as a cross-contamination case?" That would be the role of the IP: to bring those cases forward and present them to the committee.
Antibiotic Therapy for Staphylococcal Bloodstream Infections: Doing the Same With Less

By Brian Hoyle, PhD

The co-primary end points were efficacy assessed as test of cure following treatment and safety. The prespecified secondary end point was days of antibiotic therapy in patients able to be evaluated who did not have complicated BSI. An independent external adjudication committee established the primary efficacy outcome and assessed the significance of any potentially effective nonstudy antibiotic. An echocardiography lab conducted a blind review of all endocardiograms.

The 509 patients were randomized to receive standard of care (n = 254) or the algorithm-based therapy (n = 255). In each group, 4 patients were excluded when the bacteria were identified as being other than Staphylococcus. There were 190 CoNS patients in the standard of care group and 194 in the algorithm group. The respective numbers for S. aureus were 59 and 57. Of the CoNS infections in the standard of care group, 124 were simple, 52 were uncomplicated, and 15 were complicated. In those with S. aureus, 45 infections were uncomplicated and 14 were complicated. In the algorithm group, the CoNS infections were simple in 136 patients, uncomplicated in 39, and complicated in 19. For those with S. aureus infections, 34 were uncomplicated and 23 were complicated.

The 2 groups were balanced at baseline concerning age, sex, race, body mass index, risk factors (injection drug use, diabetes mellitus, immunosuppression, chronic renal insufficiency), and the setting of infection (nosocomial, community health care–associated, community acquired). Treatment was similarly successful in the 2 groups; 207 of the 254 patients (81.5%) in the standard of care group and 209 of 255 (82.0%) in the algorithm-based therapy group (absolute difference 0.5%; 95% CI, –5.2 to 6.1). “Algorithm-based therapy was as successful as the standard of care,” Dr. Holland said.

Treatment success was similar for simple, uncomplicated, and complicated CoNS, as well as for uncomplicated S. aureus infections. For complicated S. aureus infections, treatment was successful for just 35.7% of standard of care patients compared with 82.6% for the algorithm-based therapy group (absolute difference 46.9%; 95% CI, 22.1-71.6). The treatment groups were similar in terms of treatment success for both methicillin-susceptible methicillin-resistant S. aureus and CoNS.

The standard of care and algorithm-based groups displayed comparable rates of serious adverse events (28.3% vs 32.5%) and mortality (5.9% vs 6.7%). The comparability extended to the duration of treatment.

“Use of the treatment algorithm for staphylococcal bacteremia shortens therapy without compromising outcomes. In cases of complicated S. aureus bacteremia, improved outcomes were evident with the algorithm-based therapy,” Dr. Holland said. “This algorithm provides a means to accurately identify those patients with staphylococcal BSI for whom a short course therapy is appropriate.”
Antibiotics Prescribed by Dentists May Add to CDI Incidence

BY KRISTI ROSA

(continued from cover)

Dentists are contributing to the incidence of these infections. In her presentation, Dr. Bye stressed that antibiotic exposure is a major risk factor for CDI, and, unfortunately, dentists have been left out of antibiotic stewardship programs. They shouldn’t be, she said: Recent data found that in 2013, dentists prescribed about 10% of antibiotics—more than 24 million prescriptions—in the outpatient setting in the United States. “In dentistry, antibiotics are indicated to treat oral infections, such as tooth abscesses,” Dr. Bye said. “Historically, recommendations for antibiotic prophylaxis have been created for 2 specific groups of patients: those with heart conditions that may predispose them to infective endocarditis, and those with prosthetic joints who may be at risk for developing an infection at the site of the prosthesis.”

However, prophylaxis guidelines regarding invasive dental procedures for patients with congenital heart disease and prosthetic joints have evolved over the years. The American Dental Association recommends prophylaxis for patients with specific heart conditions only, rather than all congenital heart conditions, and it is no longer recommended for patients with prosthetic joints. Still, some dentists continue to prescribe prophylaxis.

For example, Minnesota dentists included in a 2015 survey reported prescribing antibiotics for these clinical reasons: for patients with high-risk conditions (84% of dentists), to battle localized swelling (70%), and for patients experiencing gum pain (38%). They also prescribed for nonclinical reasons, such as precautionary (38%) or legal concerns (24%). Fewer than half of the surveyed dentists were concerned about patients experiencing adverse events, antibiotic resistance, or CDI.

In their survey, Dr. Bye and colleagues compared the characteristics of individuals with community-associated CDI (CA-CDI) who took antibiotics for a dental procedure with CA-CDI cases who took antibiotics for nondental reasons. The analyses were conducted with chi-square tests using SAS 9.4. The investigators identified a total of 2176 CA-CDI cases between 2009 and 2015; of these, 75% were confirmed via interview, and more than half (57%) reported taking prescribed antibiotics in the 12 weeks prior to diagnosis. Although upper respiratory infections were the most common indication of antibiotics, dental procedures came in second, with urinary tract infections close behind.

Of the 926 individuals with CA CDI who reported taking antibiotic use, 48% of those who received antibiotics for a dental procedure were prescribed clindamycin, which is commonly associated with CDI, and just 30% had it listed in their medical records. Collectively—between drugs prescribed and reported in interviews and those noted in medical records—50% of cases reported taking clindamycin compared with 10% of those who took nondental antibiotics.

In July 2015, the investigators started collecting dental antibiotic indications in addition to prescriber information. To date, 76 cases of dental antibiotic use have been identified, with top indications including tooth infections/abscesses (43%), oral surgery prophylaxis (35%), and prophylaxis for dental cleaning (13%). Dr. Bye drove home this point: “Sixty-seven percent of the 76 cases were prescribed antibiotics by dentists.”

The investigators next collected data related to patients with heart conditions or who had received joint replacements. Of the cases prescribed dental-related antibiotics, 4 had heart conditions (1 had a valve replacement) and 4 had joint replacements. “Of these 8 cases, only the valve replacement potentially warranted antibiotic prophylaxis under current guidelines,” Dr. Bye said.

The study had 2 notable limitations: The dental records were not reviewed, and the investigators cannot attribute CDI to dental prescribing when other antibiotics are prescribed for different indications,” Dr. Bye added.

“Our analysis suggests that antibiotics prescribed by dentists are contributing to CDI,” Dr. Bye said in conclusion. Although overall antibiotic prescribing has decreased, dental prescribing is actually increasing. “A recent review indicates that taking any antibiotic can increase a person’s chances of getting CDI by 7 times,” she added. “When taking clindamycin, you increase the chances by 20 times.”

To help ward off these issues, Dr. Bye provided the following recommendations:

- Dentists must be included in stewardship programs.
- Dentists need to consider risk of CDI when prescribing antibiotics.
- Clarification and consistency is needed across professional associations regarding dental prophylaxis for joint replacement.
- More research is needed to better understand the risk of adverse events linked with dental procedures.

“Everybody plays a role in antibiotic stewardship,” Dr. Bye stressed. “Dentists should follow ADA guidelines for antibiotic prophylaxis and treatment, as well as counsel patients about the risk and symptoms of C. difficile and other complications of antibiotic use.”

Fewer than half of the surveyed dentists were concerned about patients experiencing adverse events, antibiotic resistance, or CDI.
A Peculiar Finding in an Unfamiliar Patient

A rare metallo-ß-lactamase makes its way into the United States via an 84-year-old patient.

BY ADRIENNE T. TERICO, PHARMD, BCPS; AND WILLIAM C. PACE, MD

PREVALENCE AND IMPACT OF CARBAPENEM RESISTANCE AND METALLO-ß-LACTAMASE–PRODUCING ORGANISMS IN THE UNITED STATES

Over the past decade, carbapenem resistance in Enterobacteriaceae has become more prevalent worldwide, and the United States has been no exception. In the latest report compiled by the CDC, there were an estimated 9300 infections caused by carbapenem-resistant Enterobacteriaceae (CRE) annually, resulting in 610 deaths.1 These data are largely driven by the Klebsiella pneumoniae carbapenemases (KPCs), which are serine-based carbapenemases that have been reported in every state of the United States except for Idaho. Metallo-ß-lactamases (MBLs), which are dependent on zinc for the hydrolysis of ß-lactams, occur more frequently in other countries, such as Greece, India, and across the Middle East.2 New Delhi metallo-ß-lactamase-1 (NDM-1) is an MBL that has become widespread in India over the past decade and is rarely encountered in the United States. As of June 2017, only 230 NDM isolates had been reported in the United States, in addition to the 41 and 30 reported isolates of Verona integron–encoded metallo-ß-lactamase (VIM)– and inosine-5’-monophosphate (IMP)–producing CRE, which are also MBLs. Only 3 NDM-1 isolates were reported in the state where the patient discussed was evaluated.3 These numbers likely underestimate the prevalence of MBL-producing organisms, as laboratory testing is not always accessible or optimal and there is no mandatory reporting of carbapenem resistance in every state.4

IDENTIFICATION OF CARBAPENEM RESISTANCE

Carbapenem resistance in gram-negative bacteria can be attributed to production of carbapenemases or may be the result of multiple resistance mechanisms at work—such as altered permeability of the cell wall preventing carbapenem entry, along with cephalosporinase production that would additionally confer resistance to penicillins and cephalosporins.5,6 Even when carbapenemase production is the suspected mode of resistance, multiple factors affect the ability of currently available antimicrobials to eradicate these organisms. These include the class of the carbapenemase (zinc or serine based), antibacterial minimum inhibitory concentrations, the level of expression of the gene encoding for the carbapenemase, the bacterial inoculum, and the ability to achieve adequate antibacterial concentrations to eradicate those inoculums at the site of infection.7

Because of the many possible mechanisms for carbapenem resistance, MBL production cannot be identified on a susceptibility panel alone. Since aztreonam is hydrolyzed by serine-based carbapenemases, such as KPC but not MBL, an organism resistant to all ß-lactams except aztreonam may raise suspicion for an MBL-producing organism. However, many MBL-producing organisms possess other modes of antibacterial resistance, including extended spectrum ß-lactamases (ESBLs) or cephalosporinases, which would confer resistance to aztreonam. Similarly, an organism resistant to cefazidime–avibactam and meropenem–vaborbactam, which are active against many serine carbapenemase producers but not MBLs, may prompt further investigation.7 These suspicions should be confirmed by molecular testing, such as polymerase chain reaction with sequencing.7 Molecular tests may not be readily available in clinical laboratories, warranting outsourcing to other labs, increasing the time to results and, inevitably, time to appropriate treatment of patients.

CASE: Presence of New Delhi Metallo-ß-lactamase-1 in a Female Patient

Early August 2017

• An 84-year-old woman presented to the emergency department (ED) with chief complaint of trouble breathing, lower abdominal pain, and diarrhea for 4 days.
• Afebrile, vital signs within normal limits, white blood cell (WBC) count of 8.5 K/µL.
• Urinalysis results: positive nitrite, small leukocyte esterase, 7 to 20 WBCs per high power field.
• Discharged from ED with prescription for trimethoprim/sulfamethoxazole for a urinary tract infection.

Mid-August 2017

• Patient returned to ED, complaining of shortness of breath, left-sided chest pain, and a nonproductive cough.
• Urine culture from early August ED visit reviewed: Escherichia coli resistant to penicillins, cephalosporins, carbapenems, fluoroquinolones, and trimethoprim/sulfamethoxazole found; retained susceptibility to aztreonam.
• Concerning for possible metallo-ß-lactamase (MBL) production.
• Patient was admitted for observation because of chest pain, and a consult to the Infectious Diseases (ID) service was obtained.
• ID evaluation:
  ° Patient denied urinary complaints.
  ° No findings to support diagnosis of an acute bacterial infection; afebrile, WBC count 8.5 K/µL.
  ° Repeat urine culture sent with additional testing requested:
    – Identical organism grew—susceptible to aztreonam, tigecycline, nitrofurantoin, and colistin.
    – E-test for fosfomycin showed activity.
    – Resistant to ceftazidime–avibactam, also consistent with MBL production.
    – Two outside laboratories confirmed the presence of the New Delhi metallo-ß-lactamase-1 (NDM-1) enzyme by polymerase chain reaction.
  ° Thorough history obtained to determine where patient may have acquired this organism.
    – Neither patient nor close contacts including family, friends, and visiting health care workers traveled internationally.
  ° Review of accessible records revealed 10 courses of antibiotics over the past 4 years.
  ° Decided to observe patient off antibiotics.

Plan to start fosfomycin if she developed symptoms of cystitis.

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TREATMENT OPTIONS FOR MBL-PRODUCING ORGANISMS

When it comes to treatment of MBL-producing organisms, the antimicrobials that are currently available are less than ideal. The agents most frequently associated with preserved activity are colistin, tigecycline, and fosfomycin. Their use is frequently limited by narrow therapeutic indices, intermediate susceptibility, or sources of infection where drug concentrations achieved are suboptimal. Newly approved therapies such as ceftazidime–avibactam and meropenem–vaborbactam are active only against serine carbapenemases and possess no activity against MBL producers.

A majority of the data surrounding treatment of CREs lie in combination therapy with antibacterials from multiple classes. Most of these studies include KPC producers, with few studies evaluating treatment of MBL-producing organisms. A review of 907 patients with systemic infections, 188 of whom were infected with isolates producing the MBL VIM enzyme, demonstrated that combination therapy with 2 or more agents was superior to monotherapy and associated with a survival benefit (27.4% vs 38.7% with monotherapy; P<.001). The lowest rate of mortality (18.8%) was observed in patients who received carbapenem therapy as part of their combination regimen.

The data on treating NDM MBLs are largely limited to case reports. Clinical success was described in a neutropenic patient on active chemotherapy with NDM-1 K. pneumoniae bacteremia was treated with polymyxin B in combination with aztreonam, at which point an extended infusion of meropenem was substituted for aztreonam. Petersen-Morfín et al describe a burn patient who became bacteremic with a susceptible Pseudomonas aeruginosa and an NDM-1 K. pneumoniae. The patient was initiated on colistin, amikacin, and enteral rifampin and died 3 days later.

Fosfomycin has retained activity against many MBL blood and urinary isolates in vitro, but its oral preparation is the only formulation available in the United States at this time, precluding its use in systemic infections because of suboptimal concentrations in sites other than the bladder. Therefore, its use, like nitrofurantoin, is largely limited to uncomplicated urinary tract infections (UTIs). The remaining cases reported in the literature on treatment of NDM isolates are of patients who were treated with oral fosfomycin or nitrofurantoin for UTIs. A pediatric patient from New Delhi who developed a UTI with NDM-1 was initiated on tigecycline for 5 days with transition to 1 dose of oral fosfomycin, which sterilized her urine. Rosa et al described 2 cases of NDM Enterobacteriaceae causing complicated UTIs in renal transplant patients successfully treated using the “double carbapenem” strategy plus oral fosfomycin. Both patients improved clinically, and urine cultures were sterilized. Rogers et al described treatment of 2 isolates, 1 eradicated by nitrofurantoin monotherapy, while colistin and rifampin were used for the second infection, as no oral options remained active. Both patients achieved clinical cure. Although aztreonam is a theoretical treatment option, as the drug is not hydrolyzed by MBLs, there is a lack of evidence utilizing aztreonam as monotherapy for infections caused by MBL-producing organisms. However, aztreonam–avibactam specifically targets MBLs and is currently being studied in phase 2 trials. When avibactam is added to aztreonam, it also restores activity against other β-lactamas that may be expressed simultaneously, such as ESBLs or serine-based carbapenemases. In vitro studies demonstrate potent activity against CREs, serine carbapenemase– and MBL-producing organisms alike, with more than 98% of Enterobacteriaceae isolates being inhibited. Results from recent research have shown that using ceftazidime–avibactam paired with aztreonam may be synergistic. This novel strategy has been used with clinical success, including in 1 patient who was bacteremic for 26 days on alternative therapy but cleared cultures hours after initiation of this regimen.

There are 2 more therapies targeted for MBLs in the pipeline. Cefiderocol is a siderophore cephalosporin that is stable against carbapenemases, including MBLs. In vitro, it has shown excellent activity against KPC and MBL strains, including NDM. LYS228 is a monobactam with activity against an array of drug-resistant organisms. In vitro, it has demonstrated potent activity against carbapenemase-producing organisms, including MBLs.

In conclusion, evidence for treatment of infections caused by MBL-producing organisms is scarce. With each case, benefits and risks of treatment must be considered. Site of infection, source control, ability to optimally dose antimicrobials without compromising safety, and severity of illness should play a role in the decision of which antimicrobials to initiate. The clinical successes described in the limited available evidence may be multifactorial and should be interpreted carefully. An important consideration when evaluating this literature is that it may be confounded by the fact that acquisition of resistance genes frequently comes at a fitness cost for organisms, which may make them less virulent. There is great anticipation for newer agents in the pipeline that are specifically targeted for MBLs.

References are available at ContagionLive.com.
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