EMERGING & RE-EMERGING INFECTIONS

Influenza Virus Is Primed for Continual Emergence and Pandemic Potential

The broad host range and natural reassortment of the influenza virus has played an instrumental role in previous pandemics, and the virus is poised for future large-scale outbreaks.

BY RYAN P. MCNAMARA, PHD; AND RODNEY E. ROHDE, PHD, SV/SM/MB(ASCP)SM, FACSC

It remains to be seen whether the 2021-2022 flu season will be a return to pre-COVID-19 numbers.

The ability of any infectious agent to maintain constant transmission enables it to be an ongoing threat to public health. These agents include organisms from viruses to helminths. Transmission ability can be enhanced by an agent's ability to infect and transmit in a broad range of hosts. However, few pathogens have achieved greater success at ongoing transmission potential than the influenza virus.

The influenza virus causes an acute infection of the respiratory tract. The duration of the virus replication in a human host is usually limited to 7 to 21 days after symptom onset, with peak virus shedding occurring within the first 10 days. The typical seasonal

(continued on page 12)
Progress Has No Deadline

AS CONTAGION® EDITOR-IN-CHIEF Jason Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS discusses in his letter this issue, a future involving COVID-19 is imminent. Our best vaccine-derived immunity to date is indefinite; our current therapies are beneficial, not curative; and our societal tendencies are simply not going to absolutely curb the virus. Pandemic, endemic—whatever it may be defined as going forward—COVID-19 will most likely be a fixture of future virus risks.

This conclusion does not denote our response to COVID-19 as a complete failure. Yes, there have been faults in messaging, public trust, resourcing, and many other facets of strategy. But our resolve to prioritize funding and focus, to develop novel pharmacological responses, and to work collaboratively across networks of care centers and laboratories have all but assured we did not lose to the pandemic.

And really, the public’s most common issue with COVID-19 is our proof that there’s still a chance to win, to eventually mitigate the virus: it’s not over yet.

Consider the highlights of IDWeek 2021, the major infectious disease meeting which does as good a job as any in keeping perspective on what’s accomplishable in virus mitigation. HIV, which is approaching its fifth known decade of prevalence and burden in the US, still headlines many of IDWeek’s sessions. Their discussions about long-acting PrEP and possible HIV vaccine candidates are ambitious but earned after years of breakthroughs and persistent research.

In influenza, we still seek a universal vaccine. In hepatitis, we set goal dates for eradication. Very few infectious diseases are fully defeated, but we have never been defeated, neither. There is no deadline for the end of COVID-19, unless our progress in diagnosing, treating, and preventing it dictates so.

Thank you for reading Contagion®.

Mike Hennessy Sr
Chairman and founder
MJH Life Sciences™

EDITOR-IN-CHIEF’S LETTER

Time to Prepare People to Accept COVID-19 Endemicity

SARS-COV-2 has taken us on a roller-coaster, and not just on graphs of case counts. The natural tendency to project linearity to trends makes each hill and dip feel unnatural. The media exacerbates perceptual changes with its hyperfocal attention on each new development, even expected ones like breakthrough infections. People feel they are being jolted around.

The early efficacy results of the mRNA vaccines from Pfizer-BioNTech and Moderna were positively stunning. Demonstrating more than 90% vaccine effectiveness against symptomatic infection when the goal was a 50% reduction in severe disease caught people off guard. It was the first bit of good news in quite a while, coming at a time when school buildings were shut in much of the country and we adapted to e-school, working from home, and the awkwardness of Zoom happy hours. When vaccines started to be given in December 2020, people began to envision a world without COVID-19.

Things have not turned out that way. Despite commanding the greatest portion of vaccine supply and getting a head start, vaccinations in the US have fallen behind that of most high-income countries; at this writing, the US is at the bottom of the G7 and 60th in the world in percentage vaccinated. However, that is only part of the picture. The virus has not waited for us to vaccinate the world’s population— it keeps evolving towards more transmissible variants. In the Delta variant, SARS-CoV-2 has transformed into not just a highly transmissible variant, but one of the world’s most transmissible infectious diseases. We are fortunate that Delta came to the US after vaccines became widely available or we would be looking at a very different society right now.

The combination of Delta and vaccine hesitancy has cost many lives, but it also highlights the need to reset expectations on the COVID-19 endgame. Herd immunity may never have been a realistic goal, but it seems clear it is an impossibility. Once the several years, everyone is likely to be infected with SARS-CoV-2. With the attenuation that vaccination provides, most vaccinated people will have asymptomatic, mild, or moderate infection. Unvaccinated people with previous COVID-19 will have less severe reinfection, and the ever-decreasing number of unvaccinated people without previous COVID-19 will be susceptible to severe disease.

The continued spread of immunity, whether acquired by vaccination or infection, will drive overall cases down. However, the incomplete nature of immunity and future mutations in SARS-CoV-2 will allow it to remain a circulating human pathogen like other endemic human coronaviruses.

One of the most apparent issues that the pandemic has revealed is ineffective communication. To increase vaccine uptake, ‘get vaccinated and you’re good’ became the narrative. People listened. When Delta became pervasive and changed things again, momentum towards a ‘post-pandemic’ dream was harder to change. Therefore, it is time to prepare people for a future with endemic COVID-19 now. We won’t be masked forever, but we aren’t wiping the virus off the earth either.

Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS

SARS-COV-2
Influenza Virus Is Primed for Continual Emergence and Pandemic Potential

The broad host range and natural reassortment of the influenza virus has played an instrumental role in previous pandemics, and the virus is poised for future large-scale outbreaks.

RYAN P. MCNAMARA, PHD; AND RODNEY E. ROHDE, PHD, SV/SM/MB(ASCP)SM, FACS
Review the historical background on tetracycline discovery, emerging resistance, mechanism of action, and their spectrum of activity.

Learn about pharmacokinetic and pharmacodynamic similarities and differences of tetracyclines.

Discuss the clinical data supporting tetracycline use for common bacterial infections.

Identify applications for tetracycline-class antibiotics after assessing a patient case.
Role of Immunosuppression on Community-Acquired *Clostridioides difficile* Risk

BY JONATHAN LAPIN, PHARM.D

Overall rates of *Clostridioides difficile* infection (CDI) have steadily declined over the past 10 years. This decline is thought to be primarily driven by a decreased rate of health care–associated CDI because of improved antimicrobial stewardship and infection control efforts in the inpatient setting. Rates of community-acquired CDI, however, remained unchanged over the past decade, with less robust antimicrobial stewardship initiatives found in the outpatient setting. Although this is a positive trend, CDI remains an urgent public health threat and continues to be the most frequent cause of diarrhea among hospitalized patients and overall hospital-acquired infection in the United States. Because of high CDI recurrence rates—estimated to be approximately 25% after an initial episode—and without widespread preventative strategies, identifying patients most at risk of CDI is of paramount importance. The most commonly identified risk factors for CDI include exposure to health care settings, advanced age, and comorbidities such as malignancy, solid organ transplant, chronic kidney disease, inflammatory bowel disease, and HIV.

Several drug-related risk factors have also been documented including antibiotics, acid-lowering medications, such as proton pump inhibitors (PPIs) and H2-receptor antagonists, and potentially nonsteroidal anti-inflammatory drugs. Although a link between the use of immunosuppressive medications and increased risk for CDI has been suggested, risk was historically associated with the frequent need for antimicrobial therapy and exposure to health care environments. Risk of CDI in immunosuppressed patients is also mediated by a blunted antibody response to *C difficile* toxins, resulting in colonization and recurrent infections. In this trial, Varma and colleagues sought to further characterize the associated risk for CDI with various classes of immunosuppressant medications.

Patients were included in this single-center retrospective cohort trial if they were tested for community-acquired CDI (CA-CDI) within 72 hours of hospital admission. The primary outcome in this study was incidence of CA-CDI. At this institution, the diagnostic testing algorithm for CDI included a single-step nucleic acid amplification test for toxin gene. Patients who received immunosuppression were determined through medication reconciliation upon inpatient admission. Patients were then stratified by immunosuppressant class: systemic corticosteroids, calcineurin inhibitors, antimetabolites, tumor necrosis factor a inhibitors, anti-CD20 monoclonal antibodies, and other classes.

Ultimately, 10,992 patients were enrolled in the study, with 1795 testing positive for CA-CDI. The infection was more common in patients who received immunosuppressants, were older than 75 years, had a Charlson Comorbidity Index of 4 or greater, experienced prior hospitalizations within 90 or 365 days prior to the index CDI episode, and used PPIs.

The most common immunosuppressant classes were systemic steroids and calcineurin inhibitors. Interestingly, CA-CDI was less frequent among patients who were exposed to antibiotics, relative to patients who tested negative.

In a multivariate analysis that adjusted for demographic and clinical considerations, calcineurin inhibitors were the only class of immunosuppressants found to independently increase risk of CA-CDI (OR, 1.19; 95% CI, 1.01-1.44). Further, in a sensitivity analysis intended to assess for additive or multiplicative effects of different classes of immunosuppressants, patients on 3 or more classes of immunosuppression had increased odds of CA-CDI (OR, 1.35; 95% CI, 1.25-1.47). When stratified by indication for immunosuppression and adjusted for baseline demographic and clinical variables, only solid organ transplantation (SOT) was associated with an increased risk of CA-CDI (OR, 1.25; 95% CI, 1.08-1.45).

Suggested explanations for immunosuppression-mediated CDI risk—including a blunted antibody response to *C difficile* toxin, intestinal dysbiosis leading to a loss of gut microbial resistance, or drug-induced damage to the gut epithelium through *C difficile*–toxin mediated effects—would theoretically increase risk for CDI. However, study results suggested that this risk may not be shared across all classes of immunosuppressants. These data showed that among hospitalized patients, calcineurin inhibitors may increase the risk for CA-CDI compared with other classes of immunosuppression, and risk may also be increased among patients receiving multiple classes of immunosuppressants—especially patients on 3 or more classes. Unsurprisingly, when stratified by indication for immunosuppression, SOT was associated with increased risk for CA-CDI, which is among the most common indications for calcineurin inhibitors.

This study offers an interesting addition to our understanding of risk factors for CDI, although the findings were sometimes inconsistent with known risk factors for CDI, including administration of antibiotics. The retrospective nature of the study limited a full appreciation for true antibiotic exposure and immunosuppressant exposure prior to admission. Also, the CDI diagnostic testing algorithm included only a single-step polymerase chain reaction–based assay, which is unable to differentiate between active CDI and *C difficile* colonization. Despite mentioning that the study center accepts only unformed stool samples, the authors did not elaborate on efforts either to distinguish symptomatic from asymptomatic patients, or procedures to rule out other etiologies for diarrhea on presentation. Lastly, the authors did not delineate the degree of CDI severity or incidence of fulminant CDI.

As noted in this study, patients receiving immunosuppressants are more likely to have more comorbidities and health care exposure relative to patients not on these medications, in addition to the potential additive risk of the medication itself, suggesting a multifactorial risk profile for patients receiving these medications. For clinicians with patients on calcineurin inhibitors, the key takeaway is that it would be prudent to be mindful of these patients’ increased risk profile for CDI. In the presence of clinical symptoms, it may be reasonable to have increased suspicion for CDI.
What Is the Ideal Duration of Daptomycin and Ceftaroline Combination Therapy for MRSA Bacteremia?

BY NICHOLAS PALISANO, PHARM.D

S taphylococcus aureus is the leading cause of bloodstream infections worldwide, associated with a high incidence of metastatic infections such as infective endocarditis.1,2 The Infectious Diseases Society of America clinical guidelines for the management of MRSA infections endorse the use of vancomycin or daptomycin as standard therapy for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia.3 However, recent studies have shown that a combination of standard therapy plus an antistaphylococcal β-lactam (eg, nafcillin, cefazolin) may enhance bactericidal activity and improve outcomes, such as reduced duration of bacteremia, recurrence, and mortality in patients with persistent MRSA bacteremia.4-6 Proposed mechanisms include β-lactam—induced reduction in cell wall cross-linking, which allows increased daptomycin and vancomycin binding and β-lactam synergy with cationic host defense peptides against MRSA.7

Ceftaroline has emerged as a preferred β-lactam combination agent because of its intrinsic activity against MRSA. A growing body of literature supports dual therapy with daptomycin and ceftaroline for persistent MRSA bacteremia. Results of an in vitro study by Werth et al showed that combination of daptomycin plus ceftaroline had rapid and sustained bactericidal activity against MRSA by enhancing daptomycin-induced depolarization and organism killing.7 The authors proposed that the rapid and complete reduction in high bacterial inoculum may facilitate de-escalation to monotherapy, which may be preferred for infections that require weeks of treatment. However, large studies have yet to confirm these theories.

Results of a retrospective study comparing daptomycin/ceftaroline therapy to standard of care monotherapy in MRSA bacteremia found numerically lower 30-day mortality in patients switched to combination therapy within 72 hours of index culture compared with standard of care (8.3% vs 14.2%, P < .05).8 However, the median duration of positive blood cultures was 9.5 vs 4.8 days for combination and standard of care groups, respectively. Further analysis showed that combination therapy was initiated on day 6, with a mean duration of bacteremia of 3.3 days after initiation, leading the investigators to conclude that early initiation of daptomycin plus ceftaroline may benefit patients at high risk of mortality. Although combination therapy with daptomycin and ceftaroline has been shown to reduce bacterial burden and improve clinical outcomes, the ideal duration of therapy has yet to be elucidated.

Nichols and colleagues attempted to clarify whether continued combination therapy with daptomycin and ceftaroline following bacteremia clearance is preferred over de-escalation to monotherapy.9 All patients received at least 72 hours of combination therapy. The combination group was defined as receiving 10 or more days of therapy, and the monotherapy group received 3 to 10 days of combination therapy before de-escalation to vancomycin, daptomycin, or ceftaroline monotherapy. Notable exclusion criteria included de-escalation before blood culture clearance, transition to hospice, no bacteremia clearance before death, fewer than 10 days of total antibiotic therapy, polymicrobial bacteremia, recurrent MRSA bacteremia, and combination therapy within 1 year prior to admission. The primary outcome was a composite of inpatient infection-related mortality, 60-day readmission, and 60-day bacteremia recurrence. Secondary outcomes included a comparison of adverse drug events and hospital length of stay.

The study included 140 patients—66 (47%) in the combination group and 74 (53%) in the monotherapy group. In the monotherapy group, 18 patients took ceftaroline; 30, daptomycin; and 26, vancomycin. Although more patients in the combination group had a history of intravenous (IV) drug use (58% vs 36%; P < .01), higher rates of endocarditis (56% vs 35%; P = .01) and pulmonary septic emboli (47% vs 27%; P < .01), and positive MRSA sputum cultures (36% vs 19%; P < .01), severity-of-illness scores were similar. The median duration of combination therapy before de-escalation in the monotherapy group was 4.5 days.

The median total antibiotic duration was 56 days for the combination group vs 45 days for the monotherapy group (P = .5). There was no statistically significant difference in the primary composite outcome between the combination and monotherapy groups (21% vs 24%; P = .66) nor after multivariable logistic regression controlling for IV drug use (OR, 2.24; 95% CI, 0.93-5.43) and chronic kidney disease (OR, 2.20; 95% CI, 0.87-5.57). Readmission rates were similar in the combination group vs monotherapy group (20% vs 18%; P = .75). Recurrence of bacteremia occurred in 2 patients in the combination group and 5 patients in the monotherapy group (3% vs 7%; P = .45). Inpatient infection-related mortality was 2% in the combination group compared with 5% in the monotherapy group (P = .10). No statistically significant differences in adverse drug events or inpatient length of stay were observed between groups.

This is the first in vivo study to evaluate the duration of combination therapy with daptomycin and ceftaroline for persistent MRSA bacteremia showing no significant difference in clinical outcomes when patients are de-escalated to monotherapy within 3 to 10 days after blood culture clearance. Although up to 10 days of combination is generous for a definition of “monotherapy,” most patients only received 4.5 days prior to de-escalation, with inference of blood culture clearance. It’s worth noting that there was no report of antimicrobial dosing regimens or vancomycin therapeutic drug monitoring. The institution did not have an outpatient parenteral antimicrobial therapy program before 2017, which may have presented barriers to continuing therapy after discharge, such as insurance coverage and therapeutic drug monitoring. Regardless of these limitations, this study’s results support de-escalation from combination to monotherapy 3 to 10 days after MRSA bacteremia clearance. Given the high administration burden and costs that may be associated with combination therapy, future analyses of adherence and pharmacoeconomic outcomes may provide further insight into the appropriate timing of de-escalation to monotherapy for MRSA bloodstream infections. ▲

References are available at ContagionLive.com.
Flu Vaccination Could Lessen Impact of COVID-19 Effects

BY KEITH A. REYNOLDS

The American College of Physicians (ACP) has issued new policies supporting the government’s COVID-19 vaccination mandate for health care employers receiving federal funds. According to a news release, ACP recommends employers and schools may appropriately require proof of vaccination against highly transmissible diseases such as COVID-19. ACP said the requirements should be complemented by support offered through education, outreach, and paid time off for vaccination and to deal with adverse effects of the shots. The support is important to offer to marginalized populations who may be subject to racism and discrimination, the ACP stated.

The ACP also stated that although those who have medical contraindications should be exempt from these requirements, allowing exemption based on nonmedical reasons poses a risk to public health. “Vaccines are safe and effective—they help prevent serious illness, hospitalizations, and death. Increasing the vaccination rate for COVID-19 is foundational in helping to bring infection rates under control and to keep them under control,” George M. Abraham, MD, MPH, FACP, FIDSA, president of ACP, said in the news release. “We need to ensure that as many members of our society are vaccinated as possible to protect the most vulnerable among us.”

The organization also recommends all health care workers be immunized for the safety of patients and the public unless there is a clear medical contraindication or legal exemption. The ACP supports employers requiring all health care workers be vaccinated against highly transmissible diseases as a condition of employment and has previously supported requirements for COVID-19 vaccines in health care workers, according to the release.

“Health care workers have an obligation to protect the health and well-being of their patients, [and] getting recommended immunizations, including the COVID-19 vaccine, is key that protection,” Abraham said in the release. “Throughout the pandemic, physicians and other health care workers have repeatedly demonstrated their dedication to caring for the patients who need them. Vaccination is a critical part of caring for patients, their families, and loved ones. Immunizations are essential in our fight against COVID-19 and other communicable diseases.”

The ACP has taken a more hands-on approach in the push for vaccination in recent weeks, and Abraham spoke out against COVID-19 misinformation.

“While ethical and responsible discussions of evidence and science to inform patient care and scientific and public policy are necessary and appropriate, clinicians—including physicians—must not contribute to spreading misinformation that can be harmful to patients,” Abraham said in a statement. “Physicians have an ethical obligation to put patient care and best interests above self-interest and to provide patients and the public with accurate information about health care. We agree with the US Surgeon General that health misinformation is a serious threat to public health.”

Vaccines Remain Effective Against Delta

BY JOHN PARKINSON

The Centers for Disease Control and Prevention (CDC) has released data showing the 3 COVID-19 vaccines (Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen) being administered in the United States are demonstrating a high level of vaccine efficacy (VE), especially against severe infection.

The data came from reporting done using 32,867 medical encounters in 187 hospitals and 221 emergency departments (ED) and urgent care clinics (UC) in 9 states from June through August 2021. Reporting began on the date the Delta variant reached 50% of sequenced isolates in each medical facility’s state.

“VE of all 3 authorized COVID-19 vaccines combined remained high against hospitalization (86%) and ED/UC encounters (82%),” the CDC wrote in its Morbidity and Mortality Weekly Report.

The study demonstrates the value of vaccination during the Delta surge this summer.

“Among adults with ED/UC encounters for COVID-19-like illness (18,231; median patient age 43 years, interquartile range [IQR] 29-62 years), laboratory-confirmed SARS-CoV-2 infections were identified among 28.9% (3145 of 10,872) of unvaccinated and 7.0% (512 of 7359) of fully vaccinated patients,” the CDC wrote.

There were some significant statistical differences in the effectiveness of the different vaccines. “VE was highest among Moderna vaccine recipients (92%), followed by Pfizer-BioNTech vaccine recipients (77%), and was lowest (65%) for Janssen vaccine recipients,” the CDC noted.

The authors reported 3 limitations in their study: VE per time since patient vaccination was not examined, VE for partial vaccination was not assessed, and the findings might not be generalizable to the US population.

“These findings reaffirm the high protection of COVID-19 vaccines against moderate and severe COVID-19 resulting in ED, UC, and hospital visits and underscore the importance of full COVID-19 vaccination and continued benefits of COVID-19 vaccination during Delta variant predominance,” the CDC concluded in its report.
Investigational Ebola Vaccine Regimen Shows Immune Response in Children, Adults

BY JOHN PARKINSON

Johnson & Johnson reported its Ebola vaccine regimen, Ad26.ZEBOV (Zabdeno) and MVA-BN-Filo (Mvabea), generated humoral immune responses in children aged 1 to 17 years and adults with the immune responses persisting in adults for at least 2 years.

The data came from the phase 3 EBOVAC-Salone (NCT02509494) clinical trial that was conducted in Sierra Leone. Results were published in The Lancet Infectious Diseases.

These peer-reviewed data support the prophylactic use of the Johnson & Johnson Ebola vaccine regimen to protect people at risk of Ebola, which is essential to our vision of preventing Ebola outbreaks before they can begin,” Paul Stoffels, MD, vice chairman of the executive committee and chief scientific officer at Johnson & Johnson, said in a statement.

PHASE 3 STUDY PARAMETERS
The study was conducted to determine the safety and immunogenicity of the 2-dose, heterologous vaccine regimen. The Ad26.ZEBOV vaccine was administered intramuscularly as the first dose followed 56 days later by the MVA-BN-Filo dose.

The study was divided into 2 stages. There were 443 adult participants (43 in stage 1 and 400 in stage 2) enrolled: 341 participants received the Ad26.ZEBOV and MVA-BN-Filo regimen, 102 participants received a single dose of meningococcal quadrivalent conjugate vaccine (MenACWY) and placebo regimen.

In stage I, 43 adults 18 years or older were vaccinated to gain information about the safety and immunogenicity of the 2-dose vaccine regimen. In stage II, 400 adults plus 576 children or adolescents (including 192 in each of the 3 age cohorts of 1 to 3, 4 to 11 and 12 to 17 years) were vaccinated. Consenting adults participating in stage I of the study were administered an A26.ZEBOV booster dose 2 years after the first dose.

“Vaccine-induced humoral immune responses were observed in 41 (98%) of 42 stage I participants (geometric mean binding antibody concentration 4784 EU/mL [95% CI, 3736-6125]) and in 176 (98%) of 179 stage II participants (3810 EU/mL; 95% CI, 3312-4383) at 21 days after the second vaccination,” the investigators wrote in the study.

OUTBREAKS
Ebola has been a persistent and mysterious disease processes. Individuals who survive Ebola may have lingering symptoms, including eye problems such as blindness, neurological issues, and muscular and joint pain. The symptoms can be debilitating to the point of leaving individuals unable to work.

In one study, investigators identified survivors in East Sierra Leone, and the enrolled survivors then identified household contacts. Both groups were administered a questionnaire assessing self-reported symptoms and were given physical exams. Investigators were looking for patterns within the wide variety of symptoms that Ebola survivors presented with to see if they fit known disease processes.

“Using multiple modalities of statistical analysis of reported symptoms and physical exam findings we found clusters of symptoms that occur together,” Sarah Talia Himmelfarb, MD, resident in Internal Medicine and Pediatrics at Tulane University and a presenting author of the study told Contagion. “This work has significance for the thousands of Ebola survivors who emerged from the 2014-2016 epidemic in Western Africa. It also contributes a small but growing body of knowledge of post-viral sequelae.”

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Both the DRC and Guinea had smaller outbreaks in 2021. The DRC outbreak, which was the country’s 12th, was announced in February. In total, there were 12 cases (probable and confirmed) and 6 deaths reported in the DRC outbreak.

The 2021 DRC outbreak was over by early May. “CDC commends the DRC Ministry of Health and partners whose work helped bring this outbreak to an end,” Rochelle P. Walensky, MD, MPH, director of the Centers for Disease Control and Prevention, said at that time. “We are proud to have been part of the effort and remain committed to supporting the DRC’s efforts to assist outbreak survivors, prevent future outbreaks, and quickly detect and respond to any new cases of Ebola. Our hearts are with the families who lost loved ones due to this deadly disease.”

Knowing that these outbreaks will continue keeps Johnson & Johnson motivated to work with countries in Africa. “Recent and ongoing outbreaks in Africa underscore that the threat of Ebola is not going away, which is why we collaborated to develop a vaccine regimen capable of inducing long-term immunity against Ebola and are now working to ensure that it is accessible to people in need,” Stoffels stated.

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Monoclonal antibodies have recently been developed as therapeutic options for the treatment of and potential prophylaxis for COVID-19. These specific proteins are made to simulate one of the many defenses of the human immune system. Multiple different monoclonal antibodies have been developed that bind to the spike protein of the SARS-CoV-2 virus, which helps prevent viral attachment and entry into human cells. In contrast with convalescent plasma, which consists of many antibodies collected from patients who have recovered from infection, monoclonal antibodies are directed toward specific targets. Monoclonal antibodies were developed to help reduce viral load to decrease the risk of developing serious symptoms in patients infected with the SARS-CoV-2 virus. Currently, 3 monoclonal antibody products have authorized usage for COVID-19.

Bamlanivimab was the first monoclonal antibody given an emergency use authorization (EUA) by the FDA in November 2020 to treat mild to moderate COVID-19 in outpatients at high risk of developing severe COVID-19, as further described in Table 1. This is a neutralizing human IgG1κ monoclonal antibody that targets the spike protein of SARS-CoV-2, preventing the attachment of the protein with the human cell-surface ACE2 protein.¹ The phase 2 BLAZE-1 trial (NCT04427501) in patients with mild to moderate COVID-19 showed an effect of bamlanivimab on viral loads, but more importantly, the treatment group also had less patients progress to COVID-19–related emergency department visits and hospitalization.² This effect was particularly pronounced in a high-risk subgroup of patients (body mass index > 35 or aged > 65 years). However, an increase in circulating COVID-19 viral variants resistant to antibody that targets the spike protein of SARS-CoV-2, preventing the attachment of the protein with the human cell-surface ACE2 protein.¹
Sotrovimab is the third monoclonal antibody currently available for the treatment of COVID-19 since its EUA was announced May 26. A product of GlaxoSmithKline, sotrovimab was created from an antibody identified in 2003 in a survivor of severe acute respiratory syndrome (SARS). Sotrovimab is directed against the spike protein of SARS-CoV-2. Distributed together as a cocktail under the brand name REGEN-COV, casirivimab and imdevimab are administered via intravenous infusion or as subcutaneous injections. The FDA issued an EUA for the use of casirivimab and imdevimab in the treatment of COVID-19 infection in November 2020. The EUA was more recently revised on July 30 to extend its use for postexposure prophylaxis of COVID-19 as well. Both uses are intended for mild to moderate disease in the outpatient setting (Table 1). For use as postexposure prophylaxis, patients with a significant exposure to someone with SARS-CoV-2 infection are eligible if they are either not fully vaccinated or are fully vaccinated but expected to have had an inadequate immune response to vaccination because of an immunocompromising disease or medication use. In a phase 3 treatment study (NCT04425629), more than 4000 nonhospitalized patients with mild to moderate COVID-19 and at least 1 risk factor for severe disease were randomized to receive either casirivimab-imdevimab or placebo. The casirivimab-imdevimab treatment groups demonstrated a 70% risk reduction in hospitalization or death in patients who received the combination treatment. In June, the CDC identified an 11% increase in frequency of the COVID-19 Gamma and Beta variants in the United States, which are not effectively treated by either bamlanivimab or etesevimab. This led the US Department of Health & Human Services to halt distribution of these antibodies that month. However, because bamlanivimab and etesevimab are active against the currently dominant Delta variant, distribution was resumed in September.

The second authorized therapeutic consists of the 2 monoclonal antibodies casirivimab and imdevimab. As with bamlanivimab and etesevimab, casirivimab and imdevimab are directed against the spike protein of SARS-CoV-2. Distributed together as a cocktail under the brand name REGEN-COV, casirivimab and imdevimab are administered via intravenous infusion or as subcutaneous injections. The FDA issued an EUA for the use of casirivimab and imdevimab in the treatment of COVID-19 since its EUA was announced May 26. A product of GlaxoSmithKline, sotrovimab was created from an antibody identified in 2003 in a survivor of severe acute respiratory syndrome (SARS). It is administered as a single intravenous infusion given over 30 minutes. As with the above-mentioned therapies, sotrovimab is indicated for mild to moderate infection in those who are at risk for progression to severe disease. Its use is currently limited to the outpatient setting in patients meeting the criteria in Table 1. The ongoing, randomized, controlled phase 3 COMET-ICE trial (NCT04545060) is investigating the use of sotrovimab in nonhospitalized patients with symptomatic COVID-19 infection and risk factors for disease progression. The primary end point being investigated is hospitalization for more than 24 hours or death within 29 days. An interim analysis of 583 patients showed that risk of progression was reduced by 85% in those treated with sotrovimab compared to placebo.

Though similar in their current indications, the available antibody therapies have several differences. Casirivimab-imdevimab is currently the only monoclonal antibody formulation with an EUA for use as postexposure prophylaxis. It is also the only therapeutic currently available as a subcutaneous injection. Route of administration is important to consider because the need for infusion may limit the access to and feasibility of obtaining treatment in a timely fashion, and it can limit capacity at infusion centers compared to a more quickly administered formulation. Sotrovimab for intramuscular injection is currently under investigation in a phase 3 clinical trial (NCT04913675) and could further improve the logistics of administering monoclonal antibody therapy. Additionally, when choosing a monoclonal antibody therapy for treatment, it is important to take into consideration the predominant circulating strains of the local area. Table 2 highlights the activity of each available monoclonal antibody products against different COVID-19 variant strains. Although these monoclonal antibody products are currently indicated only for patients not hospitalized for COVID-19, their use in the inpatient setting has been evaluated with mixed results. A clinical trial yet to be peer reviewed suggests the use of casirivimab-imdevimab in seronegative patients hospitalized with COVID-19 may reduce 28-day mortality, and bamlanivimab failed in an earlier study of hospitalized patients.

Health care providers in the emergency department, urgent care, primary care, and testing sites are encouraged to support the administration of these monoclonal antibodies in appropriate patients to help reduce the progression of COVID-19 infection. At present, no other therapies exist that can prevent progression to severe disease that requires hospitalization. Clinician vigilance to refer eligible patients for monoclonal antibody therapy is key to improve outcomes and hospital capacity.

References are available at ContagionLive.com.
Reducing Peripheral Venous Catheter Infections

Lack of data may mean bloodstream infections caused by PVCs are an overlooked cause of morbidity in hospitalized patients.

BY RICHARD J. HANKINS, MD; AND LAURA SELBY, DO

(continued from cover page)

and inpatient care, with 30% to 80% of hospitalized patients requiring PVC insertion during their stay. In fact, an estimated 80% to 90% of all vascular catheters are PVCs, far exceeding central venous catheters (CVCs). Despite the large number of PVCs utilized yearly, data for infectious complication rates are less robust than with the less-prevalent central venous catheters. This can be at least partially attributed to the requirement of acute care hospitals to track and report central-line associated bloodstream infections (CLABSIs) but not peripheral venous catheter–bloodstream infections (PVC-BSIs).

This can be at least partially attributed to the requirement of acute care hospitals to track and report central-line associated bloodstream infections (CLABSIs) but not peripheral venous catheter–bloodstream infections (PVC-BSIs).

CENTRAL VENOUS CATHETER VS PERIPHERAL VENOUS CATHETER BLOODSTREAM INFECTIONS

BSIs from PVCs are reported at lower rates than for CVCs. However, the rate of PVC-BSI varies widely around the world. Results of studies of PVCs performed in the United Kingdom, US, and Australia have shown rates of 0.2 to 0.7 per 1000 catheter days. A prospective study in resource-limited areas of Southeast Asia found 2.65 PVC-BSI events per 1000 catheter days for patients in intensive care units. Although in resource-rich countries the overall risk of PVC-BSI is low, considering that up to 350 million PVCs could be placed per year in the United States, the potential for morbidity and mortality from PVC-BSI could easily rival that of CLABSI. If only half of purchased PVCs in the US are placed successfully, a conservative estimate, with an average dwell time of 3 days and a rate of 0.4 PVC-BSI events per 1000 catheters days, then 210,000 PVC-BSIs potentially could occur each year in the United States alone.

Compare this with the estimated 30,100 used in the US in 2018. Please note, this is an estimate based on limited data to illustrate the possible magnitude of PVC-BSI; the true number of PVC-BSIs is unknown.

Data on the causative organism of PVC-BSI are more limited than for CLABSI. In adult patients, gram-positive cocci are the primary cause of PVC-BSI (Table). However, gram-negative rod bacteremia occurred at nearly twice the rate, 33.0% vs 18.8%, compared with CLABSI. Results of a 2021 pediatric study identified gram-negative bacteria as more prevalent than gram-positive bacteremia, with 59.3% of PVC-BSIs being caused by gram-negative bacteria. This study included a large number of children with chronic illnesses and recent health care exposures, which may have contributed to the higher-than-expected gram-negative bacteremia. Regardless, results of studies in both children and adults demonstrate gram-negative bacteremia as a substantial cause of PVC-BSI. Patients with PVC-BSIs caused by Staphylococcus aureus are more likely to have metastatic seeding of the infection and higher mortality than PVC-BSIs caused by other pathogens.

PLACEMENT AND MANAGEMENT OF PERIPHERAL VASCULAR CATHETERS

As with all vascular catheters, one should consider the type of access required prior to placement, including the intended duration of catheterization, the patient’s history of device-related infections, and the risk of developing a catheter-related infection.
to the placement of the catheter. PVCs are appropriate for patients who have an anticipated vascular access need of less than 6 days and do not require medications that should be infused via central access. Midline catheters should be considered if access is known to be needed for more than 6 days, but central venous access is not required.\(^1\)

Reductions in CLABSI rates have been achieved through implementing care bundles designed to standardize practices and ensure infection prevention strategies are utilized during placement and maintenance of a CVC. Placement and maintenance bundles for PVCs are less well-studied, and lack of consistency across components and end points has made systematic review problematic.\(^1\) More research is needed to determine if bundles are effective at PVC-BSI prevention, and if so what elements of a bundle are needed to reduce complications.\(^1\)

A study published in July 2021 demonstrated that alcohol-based chlorhexidine for skin preparation prior to PVC placement decreased both BSI and catheter colonization compared with iodine-based skin antiseptic preparation.\(^1\) Guidelines recommend hand hygiene, alcohol-based chlorhexidine skin prep, disinfection of needless connectors, and implantation of a PVC insertion bundle; however, the guidelines acknowledge the lack of evidence for specific bundle components.\(^1\)

Patients who have difficult venous access sometimes have a central venous catheter or peripherally inserted central venous catheter placed due to inability to place a PVC.\(^1\) For patients with difficult venous access, multiple attempts to place a PVC can cause physical and emotional distress; for some patients this distress is enough to delay hospitalized care.\(^1\) Placement of PVCs under ultrasound guidance decreases need for CVCs in patients with difficult venous access.\(^1\)

**DWELL TIMES**

The dwell time has a complicated association with PVCs and PVC-BSIs. Results of studies have shown that longer indwell times are associated with both an increase in catheter colonization and increased rates of PVC-BSIs.\(^1\) However, current evidence suggests that removal of PVCs does not result in the same benefits seen in removal of CVCs. Routine removal and replacement of PVCs every 72 to 96 hours to prevent complications has similar rates of PVC-BSI when compared with clinically indicated removal.\(^1\) Clinically indicated removal means that a PVC would be removed if signs of infection, inflammation, blockage, or infiltration are present.\(^1\) PVCs should be inspected each shift to assess for complications and removed if complications are noted.\(^1\) Clinically indicated removal does not increase risk of PVC-BSI, but the overall exposure to PVC is a risk factor for PVC-BSI.\(^1\) When no longer clinically needed, PVCs should be removed, as unused catheters remain a risk for infection even when not in use.\(^1\)

**WHAT’S NEXT?**

PVC-BSIs are studied less than CVC associated infections, yet the number of PVCs placed yearly far exceeds those of CVCs. Based on available data, bloodstream infections due to PVCs outnumber those from CVCs. The medical community needs to be aware of the serious risks and complications from PVCs, and as such PVCs should be treated with similar respect afforded to CVCs. PVCs should be removed when no longer clinically necessary because the total number of catheter days increases the risk of PVC-BSIs. Similarly, they should not be inserted unless there is a clinical necessity. Based on recent literature, it would be reasonable to consider chlorhexidine and alcohol for skin preparation prior to PVC insertion, although further research will need to be done to evaluate if this is lowering only localized insertion site infections or PVC-BSIs as well. PVCs should be assessed daily and removed when they are no longer clinically indicated as routine replacement does not decrease rates of PVC-BSIs. Further research is desperately needed to identify if bundles are effective strategies to decrease PVC-BSI and, if so, which components are needed to reduce infection rates.\(^1\)

References are available at ContagionLive.com.
Influenza Virus Is Primed for Continual Emergence and Pandemic Potential

The broad host range and natural reassortment of the influenza virus has played an instrumental role in previous pandemics, and the virus is poised for future large-scale outbreaks.

BY RYAN P. MCNAMARA, PHD; AND RODNEY E. ROHDE, PHD, SV/SM/MB(ASCP) CM, FACSC

Influenza virus has a basic reproductive number (R0) usually ranging from 1.0 to 1.5. Pandemic influenza such as the 1918 and 2009 strains might have had a slightly higher reproduction rate of 1.3 to 2.7. The world has received a crash course in respiratory infectious diseases in the past 20 months. The emergence of SARS-CoV-2 coincided with the annual influenza season in the northern hemisphere. The 2 viruses share similarities in that they are transmitted primarily through inhalation, are capable of infecting a broad range of hosts, and can have similar clinical manifestations including fever, myalgia, and respiratory distress.

Globally, influenza accounts for tens of millions of infections and hundreds of thousands of deaths annually, particularly in the young, elderly, and immunocompromised/immunosuppressed populations. Influenza virus is a frequent cause of pneumonia in individuals with AIDS and is one of the leading causes of AIDS-related deaths each year. Multiple pandemic-scale events involving influenza have occurred since the beginning of the 20th century, most notably the 1918 and 2009 H1N1 pandemics. The infamous 1918 influenza pandemic is estimated to have infected more than 33% of individuals worldwide and claimed more lives than both world wars combined. The origins of the 1918 influenza strain remain murky to this day. Two characteristics of influenza viruses make them a particularly formidable and constant threat to public health: their broad host range and their ability to reassort their genomes. Influenza viruses are encoded by segmented RNA genomes that are packaged into the virus particle and transmitted. In the case of an influenza superinfection (an infection on top of an existing influenza infection), the virus can package segments from multiple infecting influenza viruses. Most of the time this results in a nonfunctional progeny virus. However, occasionally this gives rise to a novel influenza virus through reassortment. The 2009 H1N1 virus was a prime example of the emergence of a novel influenza virus via this mechanism, being a mixture of avian, human, and swine influenza viruses that were further reassorted in swine. The resulting H1N1, at the time referred to as the “swine flu,” went on to infect approximately 20% of the global population. Although clinical outcomes were far better compared with those of the 1918 influenza strain, the 2009 pandemic highlighted the ability of influenza viruses to possess pandemic potential in large part by virtue of their broad host range and ability to reassort in host species.

2021-2022 INFLUENZA OUTLOOK

Almost certainly, we can expect the upcoming influenza season to coincide with the ongoing COVID-19 pandemic. Routine annual influenza vaccination is recommended for all persons 6 months or older who have no contraindications, and immunization will be critical this season to help reduce similar symptoms between influenza and COVID-19. Likewise, influenza and SARS-CoV-2 immunizations will have a synergistic reduction on health care strain and help to alleviate bed shortages and staffing issues during the pandemic. This is especially important as other respiratory viruses, such as respiratory syncytial virus, are similarly increasing and causing additional strain on the health care system.

The Advisory Committee on Immunization Practices (ACIP) has provided updates on the use of seasonal influenza vaccines in the United States during the 2021-2022 influenza season. The committee made 6 primary updates to their report:
- All seasonal influenza vaccines available in the United States for the 2021-2022 season are expected to be quadrivalent;
- The composition of the 2021-2022 US influenza vaccines includes updates to the influenza A(H1N1)pdm09 and influenza A(H3N2) components.
US-licensed influenza vaccines will contain hemagglutinin derived from an influenza A/Victoria/2570/2019 (H1N1) pdm09–like virus or an influenza A/ Wisconsin/588/2019 (H1N1)pdm09–like virus; an influenza A/Cambodia/ e0826360/2020 (H3N2)-like virus; an influenza B/Washington/02/2019 (Victoria lineage)-like virus; and an influenza B/Phuket/3073/2013 (Yamagata lineage)-like virus;

- The approved age indication for the cell culture–based inactivated influenza vaccine has been expanded from ages 4 and older to ages 2 and older;
- Discussion of the administration of influenza vaccines with other vaccines includes considerations for the coadministration of influenza vaccines and COVID-19 vaccines;
- Guidance concerning the timing of influenza vaccination now states that vaccination soon after the vaccine becomes available can be considered for pregnant women in the third trimester; and
- Contraindications and precautions to the use of cell culture–based inactivated influenza vaccines (ccIIV4) and recombinant influenza vaccine (RIV4) have been modified, specifically concerning individuals with a history of severe allergic reactions (eg, anaphylaxis) to an influenza vaccine.

A history of a severe allergic reaction to a previous dose of any egg-based IV, ccIIV, or live attenuated influenza vaccine of any valency is a precaution to the use of RIV4. The use of ccIIV4 and RIV4 in such instances should occur in an inpatient or outpatient medical setting under the supervision of a provider who can recognize and manage a severe allergic reaction; providers also can consider consulting with an allergist to help identify the vaccine component responsible for the reaction.

**BEYOND THE 2021-2022 INFLUENZA SEASON**

Recent human spillover events of high-pathogenicity avian influenza virus (HPAI) strains have caused international alarm due to the high case-fatality rates and the source of a constant animal reservoir. Although these events have resulted in little, if any, subsequent human-to-human transfer, the continuous transmission of HPAI in nonhuman hosts allows the virus to accumulate a number of mutations through recombination and intrinsic replication errors. This “dead-end transmission” after spillover is reminiscent of those individuals who showed antibodies toward bat-hosted SARS-related coronaviruses in 2015 before the emergence of SARS-CoV-2. Although human-to-human transmission of SARS-related coronaviruses post spill-over was not observed, the continuous transmission of the virus in their bat-host reservoir allows SARS-related coronaviruses to persist in the wild. HPAI and other influenza variants function similarly. Previous investigations concluded that very few changes were required for the mammalian adaptation of HPAI for airborne transmission. Therefore the continuous hosting of influenza viruses in nonhuman reservoirs poses a major risk for the emergence of not only seasonal influenza but high-pathogenicity strains with pandemic potential.

In sum, influenza viruses, exhibiting a broad host range, pose a constant threat to public health. They are continuously propagated in multiple hosts, and their replication cycle allows for the reassortment of gene segments during superinfection. Combined with inherent replication error rates, the generation of novel variants and strains of the influenza virus can occur at high frequency. Influenza pandemics are not infrequent, and the close interaction between humans and wildlife hosts allows spillover events to occur. Most of these events do not result in forward transmission, but it is simply a matter of time until the next influenza pandemic. Until then, seasonal influenza, which claims tens of thousands of lives each year, will continue to be an annual public health menace. ▲

**References are available at ContagionLive.com.**

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Examining the Changing Treatment of Women Living With HIV in the US

As the number of non-AIDS comorbidities in individuals living with HIV increases, clinicians are moving away from optimizing individual chronic conditions and instead thinking more holistically.

BY JENNIFER COCOHOBA, PHARMD, MAS

Women comprised 19% of new HIV cases in 2019, and approximately 22% of individuals with HIV as of 2018 were women.1 Women face a number of unique issues related to HIV care. Sex disparities in treatment and adherence continue to exist, and investigators strive to better understand issues around antiretroviral pharmacokinetics, contraception, pregnancy, other AIDS-related conditions, and prevention for women with or at risk for acquiring HIV.

In the past several years, antiretroviral therapy (ART) has advanced in ways that make achieving viral suppression tangible for many. Individuals with HIV in the United States are living longer.2 As this cohort ages, increasing focus has been placed not only on controlling the virus, but also on understanding the development and prevalence of other common chronic diseases in the setting of HIV and the impact of these combined factors on an individual’s health.

Several recent studies have examined non-AIDS comorbidities in women with HIV to raise awareness of the opportunities to provide preventative screenings and improve overall care for this population.

HIV INCREASES THE RISK OF MULTIPLE COMORBIDITIES

Living with HIV appears to accelerate or intensify comorbidities. In the Women’s Interagency HIV Study (WIHS), 2,309 women with HIV who were virally suppressed on treatment were compared with 923 HIV-seronegative women.3 The long-standing WIHS cohort had lengthy follow-up, and on average the participants were observed for greater than 15 years. Women with HIV accumulated a higher number of non-AIDS comorbidities than HIV-seronegative women (3.6 vs 3.0, P < .0001). This trend was also observed in a retrospective study of administrative claims from the Optum database.

Women with HIV more frequently had multiple (> 2) comorbidities (59.4% vs 52.9%) and more than 5 nonantiretroviral medications (81.5% vs 74.9%) when compared with women without HIV across any age strata.4

These 2 recent studies, along with several other published studies, strongly suggest that having HIV imparts higher risk for multimorbidity.5-9 This increased burden of non-HIV related comorbidities can result in increased healthcare costs. The present study aimed to describe the profile, the prevalence and the incremental costs of non-HIV related comorbidities in PLHIV compared to non-HIV matched controls (1:2 ratio). Investigators also have attempted to identify specific comorbidities driving this increase.

In the WIHS study, psychiatric illness, dyslipidemia, non-AIDS cancers, kidney, liver, and bone disease were more prevalent in women with HIV compared with the HIV-seronegative control participants. The WIHS results did not show differences in hypertension, diabetes, and cardiovascular and lung disease by HIV status.5 In contrast, a study of a large US population database included 10,590 women with HIV on antiretroviral treatment who were active in the database from 2015 to 2020 and compared them with 14,546,020 women controls.

This study’s results found that cardiovascular disease (PR 2.05, 95% CI, 1.96-2.15), hypertension (PR 1.37, 95% CI, 1.35-1.40), lung disease (2.06, 95% CI, 2.01-2.11), and diabetes (PR 1.48, 95% CI, 1.43-1.53) were more prevalent in women with HIV after adjustment for age and race.10 The Optum administrative claims database also showed an increased prevalence of hypertension (44.6% vs 38.8%), cardiovascular disease (14.3% vs 12.6%), and diabetes (21% vs 19.5%) in women with HIV compared with those without.4 The contrasting findings between the database-driven studies and the WIHS study are likely due to differences in control groups; WIHS includes a cohort of women at risk for HIV whereas the latter studies used a more generalized population database.
ASSOCIATIONS BETWEEN SEX, HIV, AND COMORBIDITIES

Although many studies have documented an increased prevalence of comorbid conditions for individuals with HIV compared with those without, biological sex may add an additional layer of risk. The Multicenter AIDS Cohort Study (MACS/WHI) Combined Cohort Study (MWCCS) examined non-AIDS comorbidities among its participants. In the study there were significant differences between the male and female populations by race, income, and other characteristics; the MWCCS attempts to recruit a cohort that represents populations most affected with HIV in the United States. Overall, women (HIV-infected and noninfected) had an increased number of comorbidities compared with men (3.4 vs 3.2, \( P = .015 \)). In the group of individuals living with HIV, women had significantly more comorbidities than men across all age strata. Amongst HIV-seronegative individuals, this pattern of increased comorbidity burden by sex was not observed. When adjusted for self-reported race, tobacco, alcohol, or crack/cocaine use as well as socioeconomic status, HIV and age remained important modifiers of the relationship between sex and non-AIDS comorbidities (\( P \) for interaction term = .038).

Another study examined the relationships between sex, HIV, and diabetes using a large US electronic medical records database. The cohort included 39,485 individuals with HIV and 13,015,560 seronegative controls seen between 2015 and 2020. Diabetes was present in more women with HIV compared with those without HIV (22% vs 14%, \( P < .001 \)) whereas the opposite was true for men living with HIV (16% vs 17%, \( P < .002 \)). Women with HIV had consistently higher rates of diabetes across different age categories, whereas for men the prevalence differed across the age strata. In the regression analysis examining the relationship between type 2 diabetes and HIV, women had a significantly higher odds of diabetes (OR 1.31, 95% CI, 1.06-1.13) even after adjustment for age, race, obesity, hypertension, hyperlipidemia, and smoking.

Much research is still required to untangle the biological pathways through which sex influences the development of these comorbidities and subsequent outcomes. Differences in inflammatory biomarkers may provide some insight. A recent study conducted in the CFAR Network of Integrated Clinical Systems cohort evaluated participants who were suppressed on antiretroviral therapy for at least 1 year and had received a diagnosis of myocardial infarction (MI), ischemic stroke, or venous thromboembolism (VTE).

It compared them with a cohort of individuals who did not develop any of these events. The study examined 11 inflammatory markers and their association with vascular event risk, age, sex at birth, CD4+ nadir, smoking, injection drug use, atherosclerotic cardiovascular disease risk scores, and hepatitis C history. There were 159 cases of myocardial infarction or stroke and 80 cases of VTE among 979 eligible individuals. The investigators found a significant interaction between age and inflammation for women. Women had higher levels of C-reactive protein (CRP), low back pain, sCD14, soluble urokinase plasminogen activator receptor (suPAR), ICAM-1 and cytomeglovirus (CMV) immunoglobulin G (IgG) compared with men (1.4-fold to 2.5-fold increased interquartile range, \( P < .003 \)). For women, inflammatory biomarkers were more closely associated with myocardial infarction and stroke, whereas in men, the biomarkers were more strongly associated with VTE events. This study’s results suggest that although inflammation plays an important role in all types of cardiovascular and thromboembolic events, sex differences influence their occurrence.

Women with HIV more frequently had multiple comorbidities and more than 5 nonantiretroviral medications when compared with women without HIV across any age strata.

Multimorbidity and its consequences are influenced by a complex set of factors that include sex, HIV infection, and more. The ProjEcting Age, MultimoRbidity, and PoLypharmacy model is a simulation tool that utilizes data from the North American AIDS Cohort Collaboration on Research and Design to predict the burden of multiple morbidities in key HIV populations in the United States through 2030. This program predicts that the highest overall comorbidity burden will be seen in Black women with HIV who use injection drugs, and the steepest increase in comorbidities will be seen in Hispanic heterosexual women with HIV. The conditions that were most prevalent in the model included hypertension, diabetes, chronic kidney disease, anxiety, and depression. The ability to predict potential comorbidities that will affect women and other populations can be deeply informative for screening, prevention, resource allocation, and differentiated care models.

IMPLICATIONS FOR CARE

Awareness of the influence of HIV and sex on the development of non-AIDS comorbidities has several implications for the clinician. Prior studies have suggested disparities in the quality of preventative care provided for individuals with HIV. At minimum, this growing body of information regarding the associations between sex, HIV, and multimorbidity advocates for increased vigilance around screening for common chronic conditions in women and others with HIV. As specific comorbidities are identified by sex and age earlier, more targeted screenings may also play a role. The increasing presence of multiple non-AIDS comorbidities in women and others living with HIV challenges clinicians to steer away from the approach of optimizing individual chronic conditions but to think more holistically. It is difficult to untangle the biological, social, and environmental factors that are interconnected with HIV and sex, and clinicians must consider all of these as they manage HIV and other chronic conditions.

Managing comorbidities can be challenging due to lack of specific guidance for certain conditions in the setting of HIV as well as the difficulty of staying abreast of updates and changes. The Primary Care Guidance for Persons Living with HIV as published by the HIV Medicine Association HIV Medicine Association of the Infectious Diseases Society of America released in 2020 is a compact compendium of recommendations. Another helpful resource is the HIV & Aging website developed by the American Academy of HIV Medicine. It has a number of articles on managing chronic conditions. As women with HIV age, their care needs will continue to change across their lifespans. Further research around HIV, comorbid conditions, and sex will help to inform best care practices.

References are available at ContagionLive.com.
An Overview of Cefiderocol Resistance Among Clinical Pathogens

Here is a review of the mechanisms that lead to resistance, including risk factors.

BY SUNISH SHAH, PHARMD, BCIDP

(continued from cover page)

A comprehensive understanding of the agent’s novel mechanism of action and mechanisms of resistance. Cefiderocol is actively transported across the outer cell membrane of bacteria into the periplasmic space using novel siderophore iron transporters called TonB-dependent receptors.7 Cefiderocol then exerts a bactericidal action by inhibiting cell wall biosynthesis through penicillin-binding proteins.1 Indeed, this novel mechanism of action allows cefiderocol to have in vitro activity against Klebsiella pneumoniae carbapenumase (KPC), Guiana extended-spectrum (GES), Imipenemase (IMP), Verona Integron-encoded MBL (VIM), New Delhi metallo-β-lactamases (NDMs), L1, and Oxacillinases (OXA) carbapenemases.5

Furthermore, cefiderocol evades other mechanisms of carbapenem resistance, including decreased outer membrane permeability and increased expression of antibiotic efflux pumps.1 Mechanisms through which resistance to cefiderocol develops remain to be fully elucidated. In this short review, the latest data and understanding of mechanisms leading to resistance to cefiderocol by Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacterales are described.

DEFINING RESISTANCE TO CEFIDEROCOL

The absence of clinical data has resulted in varying interpretative criteria across institutes (Table 1).1,2 From a pharmacokinetic standpoint, the standard dosing regimen of cefiderocol 2g administered every 8 hours over a 3-hour infusion has been shown to achieve a 85% or greater probability of target attainment for 100% fT>MIC minimum inhibitory concentration (MIC) when applying MICs of 4μg/mL or less across all infection sites (eg, pneumonia, bloodstream, and urinary tract) and renal function groups.3 Although data remain limited, CREDIBLE-CR, a phase 3 randomized trial comparing cefiderocol with best available therapy for carbapenem-resistant pathogens, did not find clinical or microbiological cure to be associated with cefiderocol MIC values; however, most pathogens isolated from patients displayed MICs 4μg/mL or less.4

From an epidemiology standpoint, the ongoing SIDERO-WT surveillance study being conducted has found that among meropenem-nonsusceptible isolates, cefiderocol MICs were ≤4 mg/L against 99.6% of Enterobacterales, 99.7% of P aeruginosa, 96.1% of Acinetobacter species (sp), and 87.1% of Burkholderia cepacia complex sp.5,6 While resistance is infrequent at baseline, susceptibility testing prior to the initiation of treatment is recommended, and it is strongly recommended for isolates that are recovered after treatment with cefiderocol to identify MIC changes.

Iron transport receptor deletions

Unlike other β-lactam antimicrobials, cefiderocol is unique in that it is transported into the periplasmic space through siderophore iron transporters known as TonB-dependent receptors. This novel mechanism of action has led to investigation of novel mechanisms of resistance in gram-negative bacteria. PirA, PiuA, and PiuD are genes that encode for TonB-dependent receptors in P aeruginosa and A baumannii (Table 2).7,8 Mutations in these genes can lead to a loss of function for the TonB-dependent receptors that are required for cefiderocol import. Deletion of PirA and PiuD have been shown to increase the cefiderocol MIC against P aeruginosa by 2- and 32-fold, respectively.4 Although there are even fewer data regarding these resistance mechanisms from a clinical standpoint, mutations in PiuD and PiuR have been reported in a P aeruginosa isolate collected from a patient without cefiderocol exposure.7 TonB-dependent receptor deletions have also been described in Enterobacteriales. CirA and Fiu encode for 2 iron transporters exclusive to Escherichia coli, and deficiency of both genes has been shown to lead to a 16-fold increase in cefiderocol MICs.9

Enzymatic mutations

Associations between elevated cefiderocol MICs and β-lactamases have also been reported. Perhaps the most notorious of these β-lactamases to be associated with elevated cefiderocol MICs are NDMs. In SIDERO-WT, MIC values for cefiderocol were 4μg/mL or less against 97.7% of tested isolates; however, only 64.3% of NDM-positive isolates demonstrated a cefiderocol MIC 4μg/mL or less.5,6
Several mechanisms leading to resistance to cefiderocol have been observed, including extended resistant (PER) β-lactamases. Notably, the addition of avibactam to cefiderocol can be shown to restore the activity against PER-producing isolates.

In a post hoc analysis of MICs from CREDIBLE-CR, 12 isolates from 12 different patients had at least a 4-fold MIC increase from baseline following exposure. Importantly, only 3 of the 12 isolates demonstrated a cefiderocol MIC of more than 4 mg/L, which would be classified as resistant by all available criteria (Table 1). A similar rate was observed in the APEKS-NP trial, underscoring that the single most important risk factor for the development of resistance to cefiderocol is prior exposure.

As with all other antimicrobials, failure to exercise judicious antimicrobial stewardship may also jeopardize the efficacy of cefiderocol over the long term. As previously described, exposure of β-lactams that have potential to induce ampC β-lactamases in Enterobacterales may represent a risk factor for the development of resistance to cefiderocol. Furthermore, excessive use of ceftazidine/avibactam has been shown to select for metallo-β-lactamases and for NDMs, for which cefiderocol MICs are elevated.

Finally, the patient's travel history and geographical location may represent risk factors for resistance to cefiderocol. For instance, although bacteria have been rarely reported to harbor NDM worldwide, Egypt, India, Pakistan, Serbia, and the United Arab Emirates have a prevalence of NDM-positive strains among Enterobacteriaceae species of ≥5%. Similarly, PER β-lactamases are not unusual in Switzerland and Turkey, but are uncommon in the United States.

CONCLUSIONS
Cefiderocol is a novel antimicrobial with a unique mechanism of action. Risk factors leading to the development of resistance to cefiderocol are not clear, but they likely include geographic location and prior antimicrobial exposures. Mechanisms of resistance to cefiderocol include both β-lactamases and novel mechanisms through mutations in genes involved in the iron transport pathway. Real-world data remain limited, and thus the significance of higher baseline MICs or 4-fold shifts following cefiderocol exposure is unknown. Ultimately, further clinical data are needed to establish this antimicrobial's place in therapy and to understand mechanisms leading to resistance.

References are available at ContagionLive.com.
Strengths and Limitations of T2Candida Implementation From an Antimicrobial Stewardship Perspective

This novel, rapid diagnostic assay uses polymerase chain reaction and magnetic resonance to identify the 5 most common Candida species.

BY VICTORIA GRANT, PHARMD; JACINDA C. ABDUL-MUTAKABBIR, PHARMD, MPH, AAHPV; AND KAREN TAN, PHARMD, BCIDP

(continued from cover page)

40%. The estimated total economic burden of invasive candidiasis (IC) infections, including candidemia, in the United States is upward of $1.2 billion per year. Blood cultures (BCs) remain the gold standard for diagnosing IC but are positive in only 50% of cases. In cases in which BCs are positive, the time to positivity of Candida species can be significantly prolonged. Candida albicans, Candida tropicalis, and Candida parapsilosis tend to be detected within 24 to 36 hours, whereas cultures with Candida glabrata can take up to 80 hours to turn positive.

Low BC sensitivity, prolonged time to detection, and poor-performing risk scores contribute to delayed initiation of antifungal therapy when it is needed. Delayed initiation of antifungal therapy has been shown to be an independent predictor of mortality in patients with candidemia. Additionally, these same factors may lead to inappropriate use of antifungal therapy. Both scenarios present different but significant challenges to antimicrobial stewardship programs (ASPs) when assessing which patients should or should not receive antifungal treatment.

T2CANDIDA PANEL

The T2Candida Panel, designed to be used with the T2Dx Instrument, is a novel, rapid diagnostic assay that uses polymerase chain reaction and magnetic resonance to identify the 5 most common Candida species from whole blood samples: C albicans, C tropicalis, C parapsilosis, C glabrata, and C krusei. The test is performed independent of BC and results are available in approximately 3 to 5 hours. Results are grouped based on antifungal resistance patterns: C albicans/C tropicalis, C parapsilosis, and C glabrata/krusei. A result of “positive” or “target not detected” is assigned to each group.

The FDA approved the T2Candida Panel in 2014 based on the results of the DIRECT trial (NCT01525095), in which BC samples were tested after being inoculated with less than 1 to 100 colony-forming units (CFUs)/mL of the 5 Candida species included in the panel. Overall sensitivity and specificity were 91.1% and 99.4%, respectively. Positive predictive value (PPV) and negative predictive value (NPV) were reported as 72% to 84% and 99%, respectively. Lower limits of detection previously determined were redemonstrated in the DIRECT trial: 3 CFUs/mL for C albicans and C tropicalis, 2 CFUs/mL for C glabrata and C krusei, and 1 CFU/mL for C parapsilosis.

STRENGTHS AND LIMITATIONS

Since its approval and introduction to the market, T2Candida has been evaluated for its performance against clinical samples collected in real time from patients with proven or suspected candidemia. The sensitivity and specificity rates have ranged from 89% to 100% and 92% to 96%, respectively, whereas its PPV and NPV have ranged from 25% to 60% and 89% to 100%, respectively. Unfortunately, T2Candida has shown suboptimal performance when identifying deep-seated IC in patients without candidemia. Recent studies showed T2Candida was positive in only 27% to 33% of culture-proven IC cases in which BCs were negative.

When contemplating the implementation of the T2Candida Panel at an institution, ASPs must consider its strengths and limitations. Its undeniable strengths include its independence from BC positivity, low limits of detection, rapid turnaround times, excellent NPVs, and modest PPVs. These factors have contributed to positive outcomes from several, real-world studies, the majority of which evaluated patients with suspected or proven IC. T2Candida implementation has consistently shown statistically significant reductions in time to detection of candidemia and time to appropriate antifungal therapy. Similarly, significant reductions in total duration of therapy (DOT) have also been shown.

One study evaluated the financial effect of T2Candida use and saw a $280 cost savings per patient as a result of reductions in overall duration of antifungal therapy. Another significant strength is that, unlike many other rapid diagnostic tests, the T2Candida Panel used on the T2Dx Instrument is fully automated and does not require manual, time-consuming DNA extraction. This reduces the risk of human error/contamination and overall burden on the microbiology department. These outcomes are incredibly important for ASPs to recognize when considering implementing the T2Candida Panel as a tool for improved antifungal stewardship.

However, T2Candida has limitations that all clinicians should be aware of and consider when initially implementing the technology and subsequently interpreting results. Although early initiation of antifungal therapy has been shown to significantly reduce mortality, studies evaluating outcomes when using T2Candida have shown only non–statistically significant trends of reduced rates of death. Significant reductions in time to appropriate therapy associated with T2Candida use may not translate to significantly reduced mortality because of small sample sizes and the inability to reach power to identify significant differences. Similarly, no significant reductions in overall length of stay (LOS) or intensive care unit LOS have been shown. This negatively affects expected cost savings associated with T2Candida use.
T2Candida has not shown as significant an effect on rates of appropriate antifungal de-escalation as one may expect. Two publications showed that only 27% to 47% of patients had their empiric antifungal therapy discontinued following a negative T2Candida result. Despite consistently high NPVs and years of the T2Candida Panel being available commercially, providers may not feel comfortable discontinuing treatment based solely on a negative result, especially in patients with a high clinical suspicion of IC. One potential reason for this is T2Candida’s poor sensitivity for detecting deep-seated IC in patients without candidemia. If clinical suspicion for noncandidemic IC is high, it would be prudent to continue antifungal therapy despite a negative T2Candida result. Unfortunately, there is a widespread lack of knowledge of which populations may benefit most from T2Candida testing. This has led to significant variations in the type of patients represented in clinical studies and is likely responsible for the low PPVs that have been associated with T2Candida. Although the majority of patients tested in these studies had suspected or proven IC, the inclusion criteria differed widely, using various combinations of the patient’s clinical status and present risk factors to determine eligibility. Taking this into account, a positive T2Candida may represent a false-positive result in cases in which BCs are negative and there is a low clinical suspicion for deep-seated IC. Positive results must be interpreted carefully depending on the patient’s clinical picture.

Another potential limitation is the time and cost required to obtain and validate equipment, adequately train personnel, and integrate testing into workflow. Although this may not significantly affect hospitals with more available resources, it would likely be challenging for small, community institutions. Also, T2Candida has shown poor performance, reported as high rates of invalid results, when tested on previously frozen samples. This may be a challenge for institutions that want to offer T2Candida testing offsite, as samples must be refrigerated and tested within 72 hours to avoid the need for freezing.

Unfortunately, the T2Candida Panel can detect only 5 species of Candida. This should not be a significant limitation because these 5 species are responsible for 95% of IC infections in the United States. However, each institution should evaluate its own etiologic distributions prior to implementation. Also, like the majority of commercially available rapid diagnostic tests, T2Candida does not provide susceptibility data. Although Candida species tend to have stable resistance patterns and susceptibility can often be inferred based on the species identified, only positive BCs can be used to determine true susceptibilities. Lastly, T2Candida is validated for testing on only whole blood samples. Samples from alternative sources (i.e., peritoneal fluid) have been tested in small studies and this will likely continue to be an area of investigation in the future.

FUTURE DIRECTIONS
Hope exists that with continued use and research, current utilization can be optimized and discoveries of new uses can be made. Future studies should evaluate and identify the patient populations that will most benefit from testing. Until this population is defined, the medical community will continue to see low PPVs and have to consider the possibility of false-positive results in patients with negative BCs. Another area of research could be focused on the performance of the T2Candida Panel as a monitoring tool for the clearance of candidemia. Thus far, studies have identified that T2Candida results can remain positive long after BCs have cleared. The significance of this and whether antifungals should be continued until a negative result is obtained are unclear. Lastly, a new panel, the T2Cauris Panel, is currently being evaluated for the detection of Candida auris, Candida dubashuhaemulonii, and Candida haemulonii in skin and blood samples. As C. auris is a serious, global, public health threat, its rapid and accurate identification is imperative because identifying and isolating colonized and/or infected patients in a timely manner is key to slowing the spread.

CONCLUSIONS
ASP must carefully consider all strengths and limitations associated with T2Candida implementation and use. Despite its limitations, T2Candida use positively affects common antifungal stewardship initiatives and should be considered a breakthrough technology for the detection of candidemia.

References are available at ContagionLive.com.

**TABLE.** Strengths and Limitations of T2Candida

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent from BC collection</td>
<td>Not yet proven to significantly reduce mortality or LOS</td>
</tr>
<tr>
<td>Low limits of detection</td>
<td>Reduced performance when detecting deep-seated IC in patients without candidemia</td>
</tr>
<tr>
<td>Rapid turnaround time</td>
<td>Low PPVs, unclear target population</td>
</tr>
<tr>
<td>High sensitivity, specificity, and NPVs</td>
<td>Time and cost required to validate testing and train personnel, changes to departmental workflow</td>
</tr>
<tr>
<td>Fully automated, requiring little hands-on time</td>
<td>Reduced performance when used on previously frozen samples</td>
</tr>
<tr>
<td>Reduced time to detection, time to appropriate antifungal therapy, and overall DOT</td>
<td>Detects only 5 types of Candida</td>
</tr>
<tr>
<td>Potential cost savings</td>
<td>Does not provide susceptibility data</td>
</tr>
<tr>
<td>Can test up to 7 samples at once</td>
<td>Currently validated for use on only whole blood samples</td>
</tr>
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BC, blood culture; DOT, duration of therapy; IC, invasive candidiasis; LOS, length of stay; NPV, negative predictive value; PPV, positive predictive value.
Expert Perspectives on Advances in the Management of *Clostridioides difficile*: Bezlotoxumab and Unmet Needs

**By Gina Battaglia, PhD**

When used in conjunction with antibiotic therapy, bezlotoxumab (Zinplava) has shown promising efficacy in reducing recurrence of *Clostridioides difficile* infection (CDI) in patients who are at high risk for recurrence, but the high cost of the therapy limits widespread use in clinical practice, according to infectious disease experts who participated in a *Contagion*® Peer Exchange panel moderated by Peter L. Salgo, MD. Teena Chopra, MD, MPH, concluded the panel with an overview of the need for microbiome- and metabolome-sparing treatments for recurrent CDI.

**C DIFFICILE TREATMENT: BEZLOTOXUMAB**

Bezlotoxumab, an intravenously administered human monoclonal antibody that binds to *C difficile* toxin B, was approved as an adjunct to antibacterial drug treatment for patients at least 18 years of age who are at high risk for recurrent CDI. This approval was supported by data from the MODIFY I and II trials (NCT01241552 and NCT01513239, respectively), which showed that the rate of recurrent CDI was significantly lower with bezlotoxumab than it was with placebo (MODIFY I: 17% vs 28%; adjusted difference, –10.1 percentage points; 95% CI, –15.5 to –4.3; *P* < .001). MODIFY II: 15% vs 26%; adjusted difference, –10.7 percentage points; 95% CI, –16.4 to –5.1; *P* < .001).2 Bezlotoxumab plus actoxumab, a human monoclonal antibody targeting *C difficile* toxin A, was also associated with lower rates of recurrent CDI than placebo (MODIFY I: 16% vs 28%; adjusted difference, –11.6 percentage points; 95% CI, –17.4 to –5.9; *P* < .001). MODIFY II: 15% vs 26%; adjusted difference, –10.7 percentage points; 95% CI, –16.4 to –5.1; *P* < .001). But the addition of actoxumab did not improve efficacy over bezlotoxumab alone.2

“[Bezlotoxumab’s] sole purpose is to reduce the recurrence rate,” said Dale N. Gerding, MD. Gerding was the first author on a post hoc analysis of participants in the MODIFY I and II trials, which analyzed the efficacy of bezlotoxumab in patients with risk factors for recurrent CDI, including aged 65 years or older, history of CDI, compromised immunity, severe CDI, and ribotype 027/078/244.3

“The target [of this study] was to determine which patient is most likely to respond to the use of bezlotoxumab in terms of having a significant reduction in recurrence,” said Gerding.

“Newer therapies that are sparing the microbiome are definitely much better. We want to make sure that we have a lot of diversity in our gut microbiome, and this diversity decreases as we age.”

—TEENA CHOPRA, MD, MPH

Among the participants who received placebo and achieved an initial clinical cure, more than 30% of participants within each of the prespecified risk groups had recurrent CDI during the 12-week follow-up period, and the proportion of patients who had a recurrence increased with an increasing number of risk factors (from 20.9% among patients with no risk factors to 46.1% among patients with 3 or more risk factors).3 Bezlotoxumab was associated with lower rates of recurrent CDI than placebo for all of the prespecified groups, with a statistically significant difference in all except the ribotype 027/078/244 subgroup (65 years or older, 19.3% vs 39.4%; *P* < .001). History of CDI, 31.6% vs 49.5%; immunocompromised status, 19.0% vs 36.0%; severe CDI, 15.9% vs 31.5%; ribotype 027/078/244, 28.2% vs 41.1%).3 Furthermore, treatment with bezlotoxumab reduced rate of recurrent CDI among patients with at least 1 risk factor (relative reductions 45.3%, –34.5%, and –53.9% for patients with 1, 2, and 3 or more risk factors, respectively).3 Of the patients with no risk factors, the proportion with recurrent CDI was similar between the bezlotoxumab and placebo groups (18.8% and 20.9%, respectively).
The significant takeaway is that if patients did not have any of these risk factors...they did not appear to benefit from bezlotoxumab in terms of lowering [the recurrence rate] any further,” said Gerding. “We now know that if patients have any of these risk factors, and particularly if they have multiple risk factors, that [they] have a high risk for recurrence, and the likelihood is very high that they’re going to respond to bezlotoxumab.”

Joseph Reilly, PharmD, BCGP, added that reductions in recurrence for patients at high risk for recurrence are clinically significant, but cost continues to be a major barrier to widespread uptake. “This is another treatment option that seems to significantly decrease recurrences, which we should certainly be concerned about; it decreases the recurrences in patients who had CDI. Similar to fidaxomicin, the number needed to treat in MODIFY I and II was about 10... but if we target certain patients, like patients over the age of 65 years or those that had a prior history of CDI in that study, that number dropped to about 6. It’s an impactful treatment option. Cost seems to be a barrier for using this drug.”

Thomas Lodise, PharmD, PhD, added that whether bezlotoxumab should be used with fidaxomicin, another high-cost drug, remains an unanswered question because the combination may be cost prohibitive. Data from the MODIFY I and II trials showing that only 4% of participants received fidaxomicin strongly suggest that cost is a key barrier to access, according to Lodise. Lodise added that most of the data on fidaxomicin and bezlotoxumab are from patients who have had only a single recurrence, and whether these data can be extrapolated to patients with multiple recurrences is currently unclear, especially because such a small proportion of patients in the MODIFY trials used fidaxomicin with bezlotoxumab. “How do you support the argument for using 2 [premium]-priced agents [when] only 50 people received fidaxomicin in the MODIFY trials?” he said.

PREVENTING/TREATING C DIFFICILE UNMET NEEDS
At the conclusion of the panel, Teena Chopra, MD, MPH, said that the lack of effective treatment options for recurrent CDI remains a big gap in the research. “C difficile remains an urgent threat to public health in general, and we want newer treatments that are targeted toward the microbiome and are microbiome sparing,” she said. She also stressed the importance of colonization sparing in the microbiome when treating recurrent CDI and how the newer therapies such as fecal transplantation are generally better in that respect than conventional treatments. “Newer therapies that are sparing the microbiome are definitely much better,” she said. “We want to make sure that we have a lot of diversity in our gut microbiome, and this diversity decreases as we age.”

Chopra added that the diversity in the gut microbiome is low in patients with recurrent CDI and may reach “a point of no return” in which the microbiome is unable to overcome the colonization, so additional therapies are urgently needed for this subset of patients.

The metabolome is also thought to be affected by CDI, according to Chopra. One study of a mouse model of CDI showed that carbohydrates and amino acids, particularly proline and the branched-chain amino acids, decrease throughout colonization and infection, and C difficile gene expression was consistent with the utilization of these nutrients. Another study showed that had a significant effect on the metabolic environment in the guts of mice pretreated with cefoperazone or streptomycin, and metagenome-enabled metatranscriptomics showed that infected animals had reductions in transcripts for genes associated with carbon and energy acquisition (which suggests that the niches were occupied by C difficile), with the largest changes observed in the least abundant species. According to the study authors, the results suggest that C difficile promotes persistent infection by restructuring the nutrient-niche landscape.

Chopra concluded that the changes in the gut metabolome that occur with recurrent CDI are an area that needs further research. ▲

References are available at ContagionLive.com.
INCREASING FAMILY PHYSICIAN ENGAGEMENT WITH PREP THERAPY

BY KILLIAN MEARA

In Belgium, the provision of pre-exposure prophylaxis (PrEP) therapy is mostly centralized within specialized HIV clinics. To help scale up the delivery of PrEP and reach underserved populations, it is important to engage family physicians because of their broad range of person-centered health care.

Recently, investigators from the Institute of Tropical Medicine Antwerp, in collaboration with the University of Antwerp, set out to understand family physicians’ (FPs) perceptions of their role in providing PrEP therapy.

The team of investigators initiated online discussion groups of family physicians. In total, there were 81 participants between November 2020 and January 2021. The participants also completed an online questionnaire that assessed sociodemographics and experience with sexual health.

Data from the study were presented at the 11th International AIDS Society Conference on HIV Science. Findings showed that the majority of survey respondents had little PrEP-related knowledge and exposure through their practice. However, the investigators noted that they were interested in receiving more information on the therapy.

Although the physicians agreed that identifying and referring high-risk patients was important, they disagreed in their perceptions of how to operationalize that role. Additionally, most participants described a lack of clinical guidelines, absence of a formal referral mechanism, and perceived discomfort in proactively conducting sexual behavior risk assessments as main barriers to identify and refer clients for PrEP.

“Despite limited PrEP experience, Belgian FPs in our study clearly saw a role for them in linking clients to PrEP and in ensuring good-quality follow-up, particularly for clients not reached by specialized HIV clinics,” the authors wrote. “Providing additional training and creating FP-specialist collaborations were suggested to increase FPs’ engagement.”

How Does Adherence to Daily Dosing vs Event-Driven PrEP Regimens Compare?

BY JOHN PARKINSON

According to findings from a study looking at pre-exposure prophylaxis (PrEP) usage in men who have sex with men (MSM), event-driven usage increased and daily dosing decreased over a 1-year period.

Data from the study, Effectiveness and Medication Adherence of Daily and Event-Driven Pre-Exposure Prophylaxis Regimens among Chinese Men Who Have Sex With Men: a Real-world CROPPrEP Study, were presented at the 11th International AIDS Society Conference on HIV Science.

From December 2018 to October 2020, Chinese investigators offered PrEP to MSM with a self-chosen regimen of daily or event-driven tenofovir/emtricitabine (TDF/FTC). The study took place in 4 cities including Beijing, Shenyang, Chongqing, and Shenzhen.

Investigators followed up with those who used PrEP every 3 months up to 1 year. They reported PrEP adherence by measuring the proportion of covered sex acts by PrEP.

In the study, 520 MSM chose to use a daily dosing regimen and 503 decided upon an event-driven regimen. In addition, 507 other MSM were nonusers of PrEP. Eighty-eight percent of those using PrEP and 89% of those not using the therapy completed the 12-month follow-up.

Contrary to what some might expect in thinking that daily dosing would have greater adherence, the results showed that event-driven regimens increased whereas daily dosing regimens decreased.

“The proportion of covered sex acts by PrEP increased over time in event-driven PrEP users (from 57% to 78%), while the opposite trend was observed in the daily group (75% to 72%),” the investigators reported.

However, the 2 regimens remain important. “This real-world study showed that PrEP can effectively reduce HIV risk among MSM,” investigators wrote. “Compared with the traditional daily medication regimen, the event-driven regimen has increased trend of medication adherence and a better HIV protective effect.”
SCREENING FOR POTENTIAL PREP USERS AT RETAIL PHARMACIES

BY JOHN PARKINSON

Medical counseling remains paramount to offering education to the general public. Long considered one of the most trustworthy in their occupation, pharmacists have a unique opportunity to have health conversations with people and counsel them when appropriate.

The adoption of pre-exposure prophylaxis (PrEP) therapy is one area within HIV prevention that has been increasing overall, but still needs help in greater utilization amongst appropriate populations.

As of 2019, Kenya had 1.5 million people living with HIV, a 4.5% prevalence rate in adults aged 15 to 49, and 42,000 new infections, according to Avert. With that country’s high prevalence, yet people dealing with issues of stigma and long wait times in clinics, public health officials were looking for other potential solutions in the possibility of understanding HIV-associated behaviors and offering another option for PrEP counseling.

Investigators in Kenya set up a pilot program where they engaged customers at four retail pharmacies who were there seeking sexual and reproductive health (SRH) services, such as family planning. These customers were screened for PrEP eligibility, use the PrEP Rapid Assessment Screening Tool (RAST), which is used in public HIV care clinics in Kenya.

From November 2020 to February 2021, 227 customers completed RAST so as to determine PrEP eligibility.

“The majority (80%) of clients reported some behavior associated with HIV acquisition risk,” the investigators wrote. “Over half of clients (55%) reported inconsistent condom use, more than half (51%) reported not knowing the HIV status of their sexual partner(s), and almost a third (28%) reported multiple sex partners.”

With these findings, the investigators believed there was an opportunity for pharmacies to play a role with PrEP utilization.

“The prevalence of behaviors associated with HIV risk was high among clients accessing SRH services at retail pharmacies in Kenya,” investigators reported. “These findings suggest that the delivery of PrEP at retail pharmacies has great potential to expand the reach of PrEP to populations at HIV risk in Kenya and similar settings.”

PREP Use Low Among Individuals With Self-Reported HIV Risk Factors

BY KILLIAN MEARA

Pre-exposure prophylaxis (PrEP) use is part of a combined approach for the prevention of HIV in those who are at a high risk for infection. It is deemed a critical element of that approach. However, there is a significant lack of data that can be used to inform strategies for PrEP scale-up among transgendered individuals.

Recently, investigators from the Division of Epidemiologic Research at Kaiser Permanente Southern California conducted a study to further understand this area. Data were presented at the 11th International AIDS Society Conference on HIV Science.

Among the participants were 164 trans men, 151 trans women, and 81 gender nonbinary individuals. The majority were young, White, and had some college or higher education.

Findings from the study showed that 60% of the respondents were not in a committed relationship, and 98% had a drug benefit through a health plan.

Among the participants who reported behaviors associated with HIV risk and/or having had a sexually transmitted infection (STI) within the previous 6 months, only 8.8% reported using PrEP in that time span. Additionally, only 6.5% reported using PrEP at the time the survey was conducted.

Further, 74.8% had knowledge of PrEP, 77.5% agreed that those who use PrEP should use condoms, and 39% did not know whether PrEP helped to prevent STIs. The most commonly reported barriers to PrEP use was cost, adverse effects, having to take it every day, and not having enough information on its efficacy.

“PrEP use was very low among those with self-reported HIV risk factors,” the authors wrote. “Tailored PrEP education and patient-centered programs targeting barriers to PrEP use among high risk transgender and gender non-binary adults are urgently needed.”
A Case of Herpes Simplex Virus-2 Encephalitis in the Setting of Pembrolizumab Exposure

BY ERIC ALTNEU, MD, MS

FINAL DIAGNOSIS:
Herpes Simplex Virus-2 (HSV-2)

HISTORY OF PRESENT ILLNESS:
A 54-year-old man presented with stage IV non–small cell lung cancer (NSCLC), seizures, hypertension (HTN), and chronic obstructive pulmonary disease (COPD). The patient completed 4 cycles of pembrolizumab/pemetrexed/carboplatin and was on maintenance pembrolizumab/pemetrexed. On the day of admission, he was seen for a routine outpatient visit, with complaint of 2 weeks of unsteadiness and gait imbalance. Because of concern for metastasis to the brain, the patient was directly admitted to a community affiliate hospital. A stat MRI of the brain was performed. This imaging study demonstrated a solitary, large cerebellar mass with vasogenic edema and partial compression of the fourth ventricle. The patient was started on intravenous (IV) dexamethasone, and neurosurgery evaluated him for surgical intervention.

MEDICAL HISTORY
The patient had a history of NSCLC with known metastasis, COPD, and HTN.

KEY MEDICATION
Pembrolizumab

EPIDEMIOLOGICAL HISTORY
Noncontributory

PHYSICAL EXAMINATION:
General: The patient was somnolent and minimally arousable.
Head, eyes, ears, nose, and throat: His head showed evidence of a recent craniotomy. A nasogastric tube and nasal cannula were both in place.
Heart: His heartbeat was regular with regular rhythm. No murmurs, rubs, or gallops identified.
Lungs: clear to auscultation bilaterally, normal work of breathing
Extremities: No gross deformity of the extremities was noted.
Skin: No lesions were noted on the exposed skin.
Neurologic: His neurologic exam was notable for patient being minimally arousable to voice or noxious stimuli. He had occasional, incoherent vocalization.
The mechanism of HSV encephalitis is not fully understood, and whether it represents a new infection or reactivation is debated. The virus must breach the blood-brain barrier to cause central nervous system disease.

In our case, imaging of the brain did not show focal findings outside of the previous craniotomy, but the patient’s CSF cell counts demonstrated a lymphocyte predominance that helped focus our differential on possible viral etiologies. Given the patient’s immunosuppression, it was reasonable to send viral PCR studies. The literature supports early diagnosis and treatment as paramount to patient survival in viral encephalitis. In our case, initial clinical suspicion and treatment may have expedited improvement in mental status because of early use of acyclovir. Although a definitive link between pembrolizumab and HSV infection has not been established, it is important to keep this on the differential given the high risk of late recognition to patient morbidity and mortality.

References are available at ContagionLive.com.
A VICIOUS CYCLE WITH SIGNIFICANT BURDEN

WHAT COULD BE THE CONSEQUENCES OF RECURRENT C. DIFFICILE INFECTION?

Learn why it requires aggressive action

THE CDC ACKNOWLEDGES C. DIFFICILE INFECTION AS A MAJOR AND URGENT THREAT.1

IT RECURS IN UP TO 35% OF CASES WITHIN 8 WEEKS AFTER INITIAL DIAGNOSIS.2,3

THE CONSEQUENCES OF RECURRENTARE SIGNIFICANT, POTIENTALLY DEADLY.2

Now is the time to learn how Ferring is shedding light on the link between disease and disruptions in the gut microbiome, exploring the potential for repopulating its diversity and restoring hope to patients.