The emergence of coronavirus disease 2019 illustrates the need for vigilance for future pandemics.

RODNEY E. ROHDE, PhD, MS, SM(ASCP)CM, SVCM, MBCM, FACSc

EMERGING & RE-EMERGING INFECTIONS

Virus Spillover and Emerging Pathogens Pick Up Speed

Infectious diseases are emerging at an alarmingly rapid pace, faster than any other time in human history.

BY RODNEY E. ROHDE, PHD, MS, SM(ASCP)CM, SVCM, MB(M), FACSc; AND RYAN P. MCNAMARA, PHD

Zoonotic diseases such as Ebola virus, rabies, Zika virus, African swine fever (ASF), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged into the human experience through an intricate and complex biological process known as spillover. Spillover of novel pathogens typically occurs through the intersection of the agent (eg, viruses, bacteria, parasites) with livestock, vectors, wildlife, or even the natural environment. To make matters more complicated and concerning for public health and health care professionals, the spillover event is almost

(continued on page 12)

Shorter is better” has become the mantra for antimicrobial stewardship programs aiming to decrease unnecessary exposures for common infection types. In the case of β-lactam infusion times, however, longer is almost assuredly better. In a meta-analysis

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There are many core elements to successful antimicrobial stewardship, although one key element is prevention of infection occurrence or reoccurrence. When it comes to substance use disorders (SUDs),

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A Return to the Various Concerns in Infectious Disease

WITH SPRING blooms hope for recovery from coronavirus disease 2019 (COVID-19).

For all the reasons Editor-in-Chief Jason C. Gallagher, PharmD, details in his letter this issue, the need for curbing COVID-19 remains the greatest in the field of infectious disease.

But as we near 50 million fully vaccinated people and achieve the new administration’s goal of assured doses for every adult by May, there’s enough optimism that we could begin to divert some attention and care to other problems in this field.

What are the priorities of infectious disease, beyond COVID-19? Well, look no further than in this issue of Contagion® to find out.

Yes, you can read our breakdown of the first COVID-19 vaccine granted emergency authorization by the US Food and Drug Administration. But you can also read about other therapeutic innovations, including prolonged β-lactam infusions.

On the matters of HIV, we address the concerning prevalence of nonalcoholic fatty liver disease. We highlight a panel discussion on improving Clostridium difficile management.

Injection drug use–associated infections, a by-product of our nation’s continued drug addiction crisis, is described as a possible target for antimicrobial stewardship. Another piece addresses wound swab refinement for the mitigation of health care–associated infections.

And lastly, we take a comprehensive look into rapidly progressing virus spillover and emerging pathogens: What could soon take precedence over COVID-19?

There is no victory lap for our recent advances in pandemic response. But there is acquired time and resources to reconsider the burdens of infectious disease that were present before COVID-19 and may outlast it yet.

Mike Hennessy Sr
Chairman and founder

Let’s Say It Out Loud: Being Vaccinated Has Benefits

AS EXHAUSTING AS the pandemic has been, hope is amassing in the form of vaccinations. Millions of coronavirus disease 2019 (COVID-19) vaccine doses, as once promised, were not immediately available upon US Food and Drug Administration authorization, but much has improved since then. Manufacturing capacity has increased, distribution has improved, and vaccination infrastructure has scaled.

The (conservative) goal of achieving 100 million vaccinations in 100 days of the Biden administration was achieved quickly, and as of this writing, the US has vaccinated over 3 million people daily the past few days.

The rapid pace of vaccination has not yet been matched by decreases in infection rates. In fact, as I write this, the US is in danger of a fourth surge. Cases in regions including New York City, New Jersey, and Michigan have been increasing. Variants are spreading as well, and experts have been particularly concerned about the more contagious B.1.1.7 variant that led a surge in cases in the United Kingdom.

Concurrently, governors in some states have been loosening restrictions on public health measures including mask wearing and limits on indoor dining, gym capacity, movie theaters, and others. This reaction to the rapid decline of cases in late winter has created a concerning overlap with rapid variant increases and pandemic fatigue.

We find ourselves at the odd juxtaposition of hope and despair. Even with the concerning trends occurring, I think it is time to buttress the positive and be straightforward with people about what being vaccinated enables them to do.

Messages in the media of potential decreased effectiveness of vaccines against some variants have a negative impact on the perception of vaccine utility. I have only anecdotal experience to support this, but I hear both vaccine advocates and skeptics saying that they probably will not work anyway, whether they are on the side that wants to receive it or not. The message that vaccines are effective against the majority of variant strains, including the B.1.1.7 strain set to take over in the US, is being lost.

How can we improve this? Let’s tell people the truth about how vaccination can change their daily lives. We can do this starting with the most low-risk situations and work our way through others, allowing people to make their own decisions based on their risk tolerance. People who are vaccinated can safely mingle indoors and unmasked with other vaccinated people. Indoor dining and gym attendance are much safer for vaccinated people. Really, any event is safer for the vast majority of vaccinated people, and we should be honest about that.

Gray areas are coming into better focus, and I believe we should tell the public what we are learning and allow people to make assessments independently. Several studies have shown lower rates of asymptomatic infection in vaccinated individuals and populations, implying that they are unlikely to infect others. It seems that many public health officials are afraid that telling people this will discourage mask use and distancing, but I believe that people have the bandwidth to process that mask mandates are necessary since there is no way of knowing who is vaccinated and who is not.

Of course, some vaccinated people will develop COVID-19, and that fact needs to be broadcast as well. Instead of a series of black-and-white, this-or-that scenarios, the model of degrees of risk and protection that public health authorities espouse needs reinforcement.

The Centers for Disease Control and Prevention took a step forward in March with updated guidance for what vaccinated people can do safely. It is important that this continues to be updated as new evidence emerges and not stay too conservative. Let’s tell people the truth about what vaccination represents. It is not just the path toward a safer society, it is the way to individual normalcy.

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

Gallagher is a clinical professor at Temple University School of Pharmacy and clinical pharmacy specialist in infectious diseases at Temple University Hospital, both in Philadelphia, Pennsylvania. He is also the director of the PGY2 residency in infectious diseases pharmacy at Temple.
Virus Spillover and Emerging Pathogens Pick Up Speed

Infectious diseases are emerging at an alarmingly rapid pace, faster than any other time in human history.

BY RODNEY E. ROHDE, PHD, MS, SM(ASCP)SM, SVCM, MBCM, FACSC; AND RYAN P. MCNAMARA, PHD

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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.

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Program Objectives

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V<sup>iridans group streptococci (VGS)</sup> comprise streptococci that are normal human colonizers. Rarely do these organisms cause infections in immunocompetent individuals, although they can be pathogenic in the right patient host. A recent article called VGS the leftover “grab bag” of organisms when β-hemolytic streptococci, enterococci, and pneumococci are excluded from streptococci.<sup>1</sup> The 6 major groups of VGS are Streptococcus mutans, S salivarius, S anginosus, S mitis, S sanguinis, and S bovis. Antimicrobial resistance can vary among VGS, with the S mitis group harboring the highest resistance rates.

β-lactams remain therapies of choice for VGS infections, although there are limited data supporting the therapy over another. Penicillin G (PCN G), ampicillin (AMP), and ceftriaxone (CRO) are frequently used in clinical practice. Wo et al attempted to differentiate clinical outcomes using CRO compared with PCN G (in which they also included AMP). This single-center, retrospective study included patients if they grew VGS from at least 1 blood culture, had documentation of bacteremia in the medical record, and received at least 4 weeks of therapy aimed at VGS. Patients who received an antibiotic for at least 50% of duration of therapy were included in that therapeutic arm. The primary composite end point was a composite outcome of hospital readmission due to VGS bacteremia or therapy adverse event (AE), Clostridioides difficile, treatment modification or discontinuation due to an AE, or development of extended-spectrum β-lactamase (ESBL) resistance. It is important to note that clinical cure was not outright evaluated, just safety end points.

Ninety-four patients were included: 64 in the CRO group and 30 in the PCN G group (26 PCN G, 4 AMP). Patients were mostly White and male with median ages of 69 (CRO) and 64 (PCN G) years. Patients in both groups were similar in terms of concomitant medical conditions and admission to intensive care units. Unsurprisingly, more patients (21.9%) in the CRO group had a history of a β-lactam allergy compared with the PCN G group (0%). S mitis was the most common organism, followed by S anginosus. Whereas endocarditis was the most common source of bacteremia, there were more patients in the PCN G group with an unidentified source (16% vs 3.1%). Additionally, more patients in the PCN G arm were not able to achieve source control. There were no differences in infectious diseases consult, time to documented clearance of blood cultures, or duration of therapy. More patients in the PCN G arm received concomitant therapy with gentamicin.

There was no difference in the primary end point: 14.1% of CRO versus 26.7% of PCN G group. Hospital readmission due to bacteremia or therapy was the leading cause of composite end point, occurring in 10.9% of CRO and 20% of PCN G patients. There were no differences among the other parts of the composite end points: emergence of ESBL, C difficile infection, or therapeutic modification. In a multivariate analysis, source control was found to be protective (odds ratio [OR], 0.116; 95% CI, 0.020-0.677), and receipt of gentamicin was found to be predictive of composite end point (OR, 6.553; 95% CI, 0.893-48.106).

As this was a retrospective study with limited patient numbers, there are noticeable limitations. However, it is the largest safety study comparing β-lactam therapies for this indication. Emergence of resistance or C difficile may not have allowed for enough follow-up time or for it to be adequately powered. Still, there are a number of benefits demonstrated by this study’s results.

An overarching tenet of antimicrobial stewardship is selecting the most-targeted, narrow therapy based on the organism isolated.<sup>2</sup> In the case of VGS, this includes PCN G or AMP. However, each of those medications requires frequent dosing intervals. This can be labor intensive for the patient and their caregiver(s) once they are discharged on outpatient parenteral antimicrobial therapy. Conversely, CRO, as a third-generation cephalosporin, has a broader spectrum of activity and may be associated with additional AEs, such as development of C difficile or ESBL. The trade-off, however, is that it is only dosed once per day and is much easier to administer outside the inpatient setting. Cost can also be a factor. All 3 antibiotics are available as generic products. However, due to complicated insurance coverage and manufacturing for the others, CRO may be the most cost-effective option. PCN G and, more recently, AMP can be given as continuous infusion, but to do so requires more sophisticated infusion devices, which may also incur a higher cost to the patient. An infectious diseases physician at my institution, Beth Israel Deaconess Medical Center in Boston, Massachusetts, is known for saying that the most expensive antibiotic is the one that does not work. An extension of that would also be one that the patient does not take. Wo and colleagues provided additional information that CRO, PCN G, and AMP appear to have similar safety composite end points in the treatment of VGS bacteremia. Therefore, when discharging patients, the choice of therapy can be based on which administration technique best suits the patient’s lifestyle and financial constraints.
Wound Swab Quality Control: Diagnostic Stewardship Augments Antimicrobial Stewardship Efforts

BY CHRISTINA YEN, MD

Innovative initiatives such as Choosing Wisely, which promotes avoiding unnecessary and low-value tests and procedures, recommend screening low-quality wound specimens given their negative financial and clinical impact on patient care. However, little investigation has been done into the impact of wound swab quality on prescribing practices. Superficial wound swabs are widely considered to have poor diagnostic yield, and their results may be difficult to interpret: Are the isolates representative of contamination, colonization, or true infection?

To discern the differences, methods such as the Q score are used to determine the quality of nonsterile respiratory samples taken for culture. The score grades a sample’s quality using the quantity of neutrophils and epithelial cells; lower scores represent lower quality samples. A study by Marchand-Sénécal et al sought to apply the Q score to nonsterile, superficial wound swabs and assess subsequent changes in lab resource utilization and antimicrobial prescribing.

The controlled before-after study was done at a 638-bed academic hospital and a 530-bed veterans’ long-term care home in Toronto, Ontario, Canada. Applying the Q score to the quality of superficial wound swabs, those with a score of less than 1 were rejected, with an addendum to the microbiology report stating that further processing would require a formal request by the ordering clinician. Superficial, nonduplicate wound swabs of the highest quality submitted for adult patients at the acute care or long-term care settings were included from the preintervention (March 5-September 16, 2018) and postintervention (September 17, 2018-September 16, 2019) periods. If multiple specimens of equal quality were submitted, the specimen with the largest number of different isolates was included.

All low-quality specimens were part of the intervention group; high-quality swabs were part of the control group. Wound swabs from patients in outpatient clinics, operative samples, biopsies, the burn unit, or emergency department who were not admitted were excluded. The primary outcome of interest was the proportion of patients receiving antibiotics within 5 days after specimen collection. The secondary outcomes were inpatient antibiotic days of therapy (DOT) and the proportion of patients whose empiric antibiotics started on the day of swab attainment were discontinued by hospital day 5.

Of the 656 swabs included in the study, 58% (382/656) were of low quality, with 140 received in the preintervention period and 242 post intervention. Another 68% (165/242) of the postintervention, low-quality swabs were not processed. Post intervention, there were fewer antibiotic prescriptions for low-quality swabs compared with those with high-quality swab groups (4.5% vs 9.4%; 95% CI, 1.00-4.72; P = .05). Comparing pre- and postintervention low-quality swab groups, there was also an observed decrease in new prescriptions (P = .04). However, there was no change in the secondary outcomes of antimicrobial discontinuation and average DOT. Only 2 low-quality swabs were followed by physician calls for processing. Finally, more than 14,000 workload units were saved with this intervention, meaning work saved in technician time, reagents used, and cost.

This study acknowledges how the clinical microbiology lab enhances antimicrobial use interventions. Although it was a single-center study and 1 of 3 that attempted to utilize the Q score on samples, the idea of applying diagnostic stewardship methodologies to wound swabs with observed changes in antimicrobial initiation is encouraging. It would be interesting to know if the 2 locations had changes to their review practices that were simply augmented by rather than wholly attributable to this intervention. Regardless, Marchand-Sénécal et al have contributed a novel implementation of diagnostic stewardship that warrants further investigation into ways to enhance antimicrobial stewardship efforts nationally and globally.

References are available at ContagionLive.com.

Highlighted Study
A systematic review of reports comprising almost 1000 children affected with multisystem inflammatory syndrome (MIS-C) subsequent to severe acute respiratory syndrome coronavirus 2 infection found that aggressive treatment has kept the fatality rate low.

“The initial descriptions exposed important clinical heterogeneity, partially overlapping with features of Kawasaki disease or toxic shock syndrome, but nevertheless distinct from these known inflammatory conditions,” said Levi Hoste, MD, an investigator at Ghent University Hospital in Belgium.

Hoste and his colleagues found that scattered case reporting had provided insufficient insight into clinical, epidemiological, immunological, and prognostic characteristics of this novel pediatric phenotype associated with coronavirus disease 2019 (COVID-19). They decided to undertake what they describe as the most extensive systematic review of published reports on the syndrome. From an initial 918 publications in their literature search, they identified 68 studies published after May 9, 2020, which comprised 953 individual patient cases (median age 8 years).

Comorbidities were rare, except for obesity (25.3%). The principle presentations of MIS-C were fever (99.4%), gastrointestinal manifestations (85.6%), cardiovacular manifestations (79.3%), and increased inflammatory biomarkers. Although MIS-C is not associated with the pulmonary manifestations typical of COVID-19, the reviewers also found respiratory symptoms in 50.3% of the children.

Although the condition is relatively rare, it can be severe; more than half of patients (56.3%) presented with shock, and many (73.3%) required intensive care treatment, including extracorporeal membrane oxygenation (3.8%). Prompt, intensive treatment has succeeded in keeping the morality rate to a relatively low 1.9%.

Therapeutic interventions included intravenous immunoglobulins (75.9%). Multiple doses were administered to 73 of the 662 patients (11%). Acetylsalicylic acid was received by 52.3%; high, anti-inflammatory dosages of 80 to 100 mg/kg/day were received by 39 of 171 (22.8%) patients. Heparin was administered in 46% of cases.

Biopharmaceuticals included interleukin (IL) 1 receptor antagonist anakinra (7.6%), IL-6 inhibitors tocilizumab and siltuximab (6.7%), and TNF α inhibitor infliximab (2.3%). Remdesivir, which is approved by the US Food and Drug Administration for COVID-19 in hospitalized adult and pediatric patients, was rarely prescribed for MIS-C (2.3%). Inotropic drugs were prescribed to 55.3%. Mechanical and noninvasive ventilation were initiated in 23.6% and 25.8% of patients, respectively.

“It remains challenging to recognize this heterogeneous disease in daily clinical practice,” Hoste observed. “Prompt recognition is pivotal to ensure a good individual prognosis.”

In recently updated interim guidance on MIS-C, the American Academy of Pediatrics (AAP) recommended that any child with suspected MIS-C should also be evaluated for infectious and noninfectious etiologies. In that guidance, which is also referred to in a Partner Update from the Centers for Disease Control and Prevention (CDC), the AAP stressed that any fever accompanied by severe symptoms or coincident with exposure to an individual with COVID-19 should raise suspicions.

The AAP indicated that a child sick enough to warrant hospital admission with suspected MIS-C should be cared for in a facility with tertiary pediatric/cardiac intensive care units. Diagnostic testing is likely to include chest radiography, electrocardiogram, and troponin. If these or physical examinations are abnormal, subsequent diagnostic testing for myocardial injury would include echocardiogram and/or cardiac MRI by pediatric cardiology.

The CDC urges health care providers to report suspected cases to their local, state, or territorial department. After-hours phone numbers for health departments are available at the Council of State and Territorial Epidemiologists website.
**Novel Treatment Shows Promise for Flu and COVID-19**

**BY KILLIAN MEARA**

Results of a recent study published in *Nature Biotechnology* found that a new treatment appears to halt the replication of coronavirus disease 2019 (COVID-19) and influenza viruses and could be delivered using a nebulizer, making it simple for use at home. The study was conducted by investigators at the Georgia Institute of Technology and Emory University in Atlanta.

“One of the first things that society and the CDC [Centers for Disease Control and Prevention] is going to get when a pandemic emerges is the genetic sequence. It’s one of the first tools that the CDC and the surveillance teams are going to use to identify what kind of virus this is and to begin tracking it,” study investigator Daryl Vanover, PhD, a research scientist at Emory University, said. “Once the CDC publishes those sequences, that’s all we need. We can immediately screen across the regions that we’re interested in to target it and knock down the virus.”

The investigators collaborated with the CDC and employed CRISPR-Cas9 technology, which targets and edits portions of genetic code to specifically target RNA molecules.

For the study, investigators used messenger RNA technology, coding it for a specific protein known as Cas13a. The protein destroys parts of genetic code that allows a virus to replicate within lung cells. Investigators used a guide strand to tell the protein where to attach on the viral RNA sequence and begin to destroy it.

Study results showed that the Cas13a protein could work directly in the lung tissue and was effective in stopping the replication of severe acute respiratory syndrome coronavirus 2. It was also discovered that the approach could potentially work against 99% of influenza strains that have been in circulation for a decade.

“In flu, we’re attacking the polymerase genes. Those are the enzymes that allow the virus to make more RNA and to replicate,” corresponding author Philip J. Santangelo, PhD, said. “We went after those because they’re far better conserved. We let the biology dictate what our targets would be.”

The findings suggest that the novel approach could be adaptable as new virus strains emerge, due to its flexibility. This could result in candidates for trials in just a short few weeks.

“This project really gave us the opportunity to push our limits in the lab in terms of techniques, in terms of new strategy,” Chiara Zurla, PhD, the team’s project manager and a coauthor on the paper, said. “Especially with the pandemic, we feel an obligation to do as much as we can as well as we can. This first paper is a great example, but many will follow; we’ve done a lot of work, and we have a lot of promising results.”

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**Minorities, Older Individuals Are Underrepresented in Vaccine Clinical Trials**

**BY JONNA LORENZ**

Black, American Indian, Hispanic, and older adults have been underrepresented in vaccine clinical trials during the past decade, according to results of a study published in *JAMA Network Open*.

The cross-sectional study included 230 clinical trials based in the United States and registered on ClinicalTrials.com between July 1, 2011, and June 30, 2020. The trials involved 219,555 participants.

“I believe there are 3 big takeaways from our research,” first author Laura Flores, a PhD candidate at the University of Nebraska Medical Center in Omaha, told *Contagion*. “Our study highlighted a decade’s worth of disparities—with Hispanic or Latino, Black or African American, American Indian/Alaska Native, and older populations often left out of vaccine clinical trial research. Additionally, the lack of race and ethnicity reporting in *ClinicalTrials.gov* was a startling finding. With missing ethnicity data in [more than] 60% of trials and missing race data in 40% of trials, it is difficult to assess the true representation among clinical trials participants.

“Female adults were overrepresented overall and within all phases of vaccine clinical trial research over the past decade.”

Age and sex of participants were reported for every trial (100%), race was reported for 134 trials (58.3%), and ethnicity was reported for 79 trials (34.3%).

“I believe the lack of data reporting was a big shock to the entire team,” Flores said. “We can’t begin to solve inequalities in clinical trial research without the whole picture.”

Compared with US census data, White Americans were overrepresented in vaccine clinical trials, accounting for 77.9% of adult participants, whereas those underrepresented included Black or African American individuals at 10.6%, American Indian or Alaska Native individuals at 0.4%, and Hispanic or Latino individuals at 11.6%. Asian individuals were equally represented in the census data at 5.7%.

Adult trials compared with the census data included more women (56%). Those 65 years and older were underrepresented (12.1%). Pediatric trials also showed an underrepresentation among Black participants (10.1%) and Hispanic participants (22.5%).

“Our study highlighted some good news in that we are close to reflecting the racial makeup of the US population in vaccine clinical trials,” Flores said. “With race, the gaps we identified are much smaller than in other research areas, [such as] oncology clinical trials, and this signals we might be on the right track. That being said, we believe it is important to note that small inequities are still important inequities. We are doing a genuine disservice to these populations by not reaching out, not keeping records, and not including them in trials that might benefit them.”

The National Institutes of Health (NIH) Revitalization Act of 1993 established guidelines for including women and minorities in clinical trials. In 2017, the NIH amended the policies for reporting data, and the US Food and Drug Administration (FDA) issued a consumer update stressing the importance of diversity in clinical trials.

Lack of data on race and ethnicity deprives studies of important context for understanding health disparities such as socioeconomic barriers, implicit bias, and increased burden of comorbidities.

Flores said she hopes the study results lead to better demographic reporting by investigators. “Enrolling the right populations and, in particular, the most [affected] populations in clinical trials is not a luxury but a necessity,” study author Carlos del Rio, MD, of Emory University School of Medicine in Atlanta, Georgia, told *Contagion*. “I am hopeful that the National Academy of Sciences, Engineering, and Medicine committee will come up with good recommendations that will help improve the representation of diverse populations in clinical trials and research.”

Author Michele Andrasik, PhD, EdM, of Fred Hutchinson Cancer Research Center in Seattle, Washington, emphasized the importance of building trustworthy relationships with communities to ensure good public health for all. “We need concerted efforts to ensure the inclusion of diverse participants in clinical trials,” Andrasik told *Contagion*. “This will require going beyond guidelines and potentially implementing sample requirements going forward. The same is true for the collection of race and ethnicity data. The large incidence of missing data is unacceptable.”

The coronavirus disease 2019 pandemic has brought additional challenges to clinical trials. Last year, the FDA issued guidelines for conducting clinical trials during the pandemic; acknowledging challenges brought by quarantines, site closures, travel limitations, and interruptions to the supply chain; and urging measures such as safety monitoring, shifting to telemedicine platforms, and including an explanation for any missing data due to disruptions.
BNT162b2: The First COVID-19 Vaccine

An assessment of data for the first prophylaxis authorized for preventing the disease in the US

BY JAMIE WAGNER, PHARM.D., BCPS; AND RYAN IMEL, PHARM.D., BCPS

Just a little more than a year after the United States reported its first case of coronavirus disease 2019 (COVID-19), there have been more than 29 million cases and more than 540,000 deaths in the US, according to the Centers for Disease Control and Prevention.1

Lockdowns, travel restrictions, masking, and social distancing were not enough to contain the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its strain on the health care system. The focus of the outbreak has turned from containment to prevention through vaccination.

Traditionally, vaccines contain weakened or inactivated microorganisms, fragments of microorganisms, or genetic material from microorganisms that the immune system uses to produce a protein that elicits an immune response, thus producing antibodies.2

The Pfizer-BioNTech COVID-19 vaccine, BNT162b2, utilizes messenger ribonucleic acid (mRNA) of the spike protein for SARS-CoV-2.3,4 The mRNA is contained within lipid nanoparticles, which allow the mRNA to enter cells.5,6 Once inside the cell, the mRNA is released and transcribed into the SARS-CoV-2 spike protein.7 This protein migrates to the cell surface, triggering a T-cell–mediated immune response against the spike protein.8 Immune activity against the spike protein hinders SARS-CoV-2’s ability to attach to host cells. Because the mRNA does not remain viable in the cell for very long, it cannot become a permanent part of the host cell.8

Normally, vaccines undergo years of rigorous research and testing. In extenuating circumstances, such as the current COVID-19 pandemic, companies may apply for an Emergency Use Authorization (EUA) to expedite vaccine availability prior to full US Food and Drug Administration (FDA) approval. The process of issuing an EUA involves 6 key steps (Figure 18,9), which require the FDA to determine that the benefits of the product outweigh its risks and that it is appropriately efficacious.8 The World Health Organization (WHO) also has an emergency use listing (EUL) that allows countries to expedite their own approval process for the new agent, as well as allowing UNICEF and the Pan American Health Organization to obtain the agent for distribution to countries in need.10

Before approval, Pfizer-BioNTech was required to provide at least 2 months of follow-up data post second-dose administration to gauge the vaccine’s safety and efficacy. This allowed sufficient time for immune-mediated allergic reactions and other adverse events (AEs) to manifest, as well as sufficient time to detect waning protection generated by IgM and IgG antibodies against the virus.11 The FDA issued an EUA for the BNT162b2 vaccine on December 11, 2020, and the WHO issued an EUL on December 31, 2020.

A phase 1 trial of BNT162b2 at a dose of 30 mcg, delivered in a 2-dose series separated by 21 days, determined the dosage had an acceptable amount of reactogenicity per AEs and sufficient antibody titers (ie, immunogenicity) against SARS-CoV-2.12 This vaccine then was tested in a phase 3 trial that randomized participants 1:1 to receive either BNT162b2 or placebo.11 Participants were included if they were at least 16 years of age and were either healthy or had stable chronic medical conditions, including HIV, hepatitis B, and hepatitis C. Individuals were excluded if they were pregnant or breastfeeding, had a medical history of COVID-19, were immunocompromised, or were actively receiving immunosuppressive therapy. The primary safety end points were solicited and unsolicited AEs within 7 days of each dose through 6 months post dose (nonserious AEs, 1 month post second dose; serious AEs, 6 months post second dose). The primary efficacy end points were efficacy against confirmed COVID-19 with the onset at...
TABLE 1. Baseline Characteristics of Participants in Main Safety Population

<table>
<thead>
<tr>
<th>Characteristic, N (%)</th>
<th>BNT162b2 (N = 18,860)</th>
<th>Placebo (N = 18,846)</th>
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<td><strong>Sex</strong></td>
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<td></td>
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</tr>
<tr>
<td>Female</td>
<td>9221 (48.9)</td>
<td>9410 (49.9)</td>
<td>18,631 (49.4)</td>
</tr>
<tr>
<td>Male</td>
<td>9639 (51.1)</td>
<td>9436 (50.1)</td>
<td>19,075 (50.6)</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-55 years</td>
<td>10,889 (57.7)</td>
<td>10,896 (57.8)</td>
<td>21,785 (57.8)</td>
</tr>
<tr>
<td>&gt; 55 years</td>
<td>7971 (42.3)</td>
<td>7950 (42.2)</td>
<td>15,921 (42.2)</td>
</tr>
<tr>
<td><strong>Body mass index ≥ 30 kg/m²</strong></td>
<td>6556 (34.8)</td>
<td>6662 (35.3)</td>
<td>13,218 (35.1)</td>
</tr>
</tbody>
</table>

TABLE 2. Primary Safety End Points for BNT162b2 at Least 7 Days Post Dose

<table>
<thead>
<tr>
<th>Characteristic, (%)</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local reactogenicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>16-55 years</td>
<td>71%</td>
<td>66%</td>
</tr>
<tr>
<td>&gt; 55 years</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Redness</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>16-55 years</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>&gt; 55 years</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Systemic reactogenicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>16-55 years</td>
<td>1%</td>
<td>11%</td>
</tr>
<tr>
<td>&gt; 55 years</td>
<td>47%</td>
<td>59%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34%</td>
<td>51%</td>
</tr>
<tr>
<td>16-55 years</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>&gt; 55 years</td>
<td>25%</td>
<td>39%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>21%</td>
<td>37%</td>
</tr>
<tr>
<td>16-55 years</td>
<td>14%</td>
<td>29%</td>
</tr>
</tbody>
</table>

least 7 days post second dose and efficacy in participants with and without evidence of prior infection. Secondary efficacy end points included efficacy against severe COVID-19 infection.

A total of 37,706 participants were enrolled, with 18,860 receiving at least 1 dose of the BNT162b2 vaccine (Figure 2). Baseline characteristics were similar between groups, with 42.2% of the population older than 55 years (Table 1). Localized reactogenicity was evaluated in 8183 participants within 7 days after the injection. Systemic reactogenicity was evaluated in the entire cohort and most often began within 1 to 2 days post vaccination and resolved within 24 hours of symptom onset, with more common and severe reactions occurring after the second vaccine dose. Fatigue, headache, and muscle pain were the most commonly reported AEs, with fever occurring more frequently after the second dose (Table 2). Notably, lymphadenopathy occurred in 64 (0.3%) participants in the vaccine group compared with 6 (<0.1%) participants in the placebo group. Additionally, there were 4 reports of Bell palsy occurring within the vaccine group; however, this incidence rate is consistent with the rate in the nontrial population. No COVID-19–related deaths occurred in either group.

The efficacy rate between the first and second doses was 52%, which then climbed to 91% within the first 7 days post second dose. Ultimately, a 95% efficacy rate was achieved post second dose for participants who had no evidence of existing or prior COVID-19 infection. A 94.6% efficacy rate was achieved post second dose for participants with and without evidence of prior COVID-19 infection, and an 88.9% efficacy rate was achieved post first dose for preventing severe COVID-19 infection.

Additional research of efficacy is ongoing against newly discovered viral variants, including the UK variant (B.1.1.7), the South Africa variant (B.1.351), and the Brazil variant (P.1). These variants are able to transmit more readily and may be able to better evade the immune system (Table 3). Laboratory testing suggests BNT162b2 produces a sufficient immune response to B.1.1.7 and B.1.351; however, activity against B.1.351 was lower in comparison with other SARS-CoV-2 variants. In a phase 1/2 trial in Germany (NCT04380701), BNT162b2 efficiently neutralized 19 pseudoviruses, indicating that the vaccine could remain efficacious against a variety of mutations. Unfortunately, investigators currently do not have enough data to know when changes to the BNT162b2 vaccine need to occur.

However, as of February 14, BNT162b2 has been authorized or approved for emergency use for individuals 16 years and older in 57 countries. This vaccine continues to be studied in different populations limited or excluded in the original trial, and investigators are following up on participants enrolled in the original trial. Additionally, Pfizer and BioNTech are working on developing a third “booster” vaccine to be given 6 months to a year after the second dose. They also are working on a process that will allow faster development (eg, 6 weeks) of vaccine derivatives to better combat the current and future variants. References are available at ContagionLive.com.
Respiratory tract infections remain a frequent cause of antimicrobial use in the hospital setting. The Centers for Disease Control and Prevention (CDC) noted in its report 2017: Antibiotic Use in the United States that there are 47 million unnecessary antibiotic prescriptions written each year by US providers, and most of these are for respiratory tract infections, including suspected pneumonia. The CDC estimated that at least 50% of antibiotic prescriptions for acute respiratory conditions were unnecessary.

From the commonly used respiratory viral panel to the coronavirus disease 2019 (COVID-19) polymerase chain reaction (PCR) testing, molecular diagnostic tests for the identification of frequent pathogens causing pneumonia have gained considerable attention. Early identification of pathogens in respiratory viral infections can lead to improved antimicrobial stewardship efforts to ensure that pathogens are appropriately treated, antibiotics are narrowed as appropriate, and better outcomes are achieved.

The PCR-based respiratory viral panel is frequently used to diagnose pneumonia. However, using molecular detection techniques for bacterial pathogens is not as...
widespread. Similar to using blood or sputum cultures, selective use of these techniques may lead to more targeted antimicrobial therapy to ensure that target pathogens are being treated while using as narrow a spectrum of antibiotic as possible.

However, in facilities where bacterial pneumonia molecular diagnostics are not available, there are other methods that can be used for nosocomial pneumonia, such as the methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screen and standard sputum culture. The MRSA nasal screen has been shown to correlate with the need for ongoing anti-MRSA therapy for nosocomial or ventilator-associated pneumonia (VAP) and is readily available.\(^4\)\(^5\) Despite this availability, there often is still prolonged vancomycin use in patients with VAP.\(^6\) If an already available method is not being frequently used, is there a reason to think that more advanced techniques will lead to appropriate narrowing of the antimicrobial spectrum in patients with pneumonia?

Another consideration is cost. Standard, commercially available molecular diagnostic panels for respiratory viral pathogens can carry significant expense (up to $170 per test, according to 1 estimate).\(^7\)

Utility of molecular diagnostic tests also depends upon the clinical setting. For example, in the outpatient setup, it is not likely that PCR-based bacterial pneumonia panels will be frequently indicated, given the minimal overall severity of most patients and logistical issues with testing in these settings. Meanwhile, these tests can be a game changer in an inpatient setting, particularly in intensive care units where early selection of appropriate antibacterial therapies can save lives. Similarly, in the emergency department setting, such testing may more likely be technically possible because of the hospital-based laboratory facilities. Patients may be selected based upon risk factors and severity of illness to determine the need for PCR-based testing, and the quick test result may help in deciding triage and level of care. Molecular diagnostics for bacterial pneumonia, in the appropriate setting, may lead to improved antibiotic use and patient outcomes. However, testing alone will not accomplish this. There needs to be a combination of testing the appropriate patients and using the results to adjust antibiotic regimens accordingly.

**CHANGING OUTCOMES**

This leads to diagnostic testing stewardship. The concept is based on choosing a diagnostic test wisely, based on pretest probability in a relevant clinical scenario. Although it may be easy to order molecular testing on all patients with community-acquired pneumonia (CAP), it is unlikely that overall treatment will change in patients with a straightforward presentation, such as an aspiration event. However, testing would be much more likely to change outcomes in patients with VAP or nosocomial pneumonia, given the wide spectrum of pathogens that may be in play. As these patients tend to receive the broadest spectrum antibiotics for the longest duration, appropriate diagnostic stewardship may optimize their clinical outcomes. It may be reasonable to limit molecular testing of pneumonia to patients who are not improving, have a history of resistant organisms, or have nosocomial or ventilator-associated infections. It is important to highlight that the 2019 American Thoracic Society/Infectious Diseases Society of America CAP guidelines recommend obtaining sputum culture in patients with severe pulmonary disease as well as in all admitted patients being empirically treated for MRSA or *Pseudomonas aeruginosa*.\(^8\) Unfortunately, there is often a delay in obtaining sputum samples for culture until after antibiotics have been taken, which decreases the yield of this testing. In cases such as this, molecular diagnostic techniques may be beneficial, allowing detection of pathogens that will no longer grow in culture due to previous antibiotic exposure.

As antimicrobial stewardship service is now required for all hospital settings per the Centers for Medicare & Medicaid Services and The Joint Commission, evaluating both conventional culture and molecular testing results and communicating with the bedside providers can be part of the standard practice. In a retrospective review, Weiss et al elaborated that utilization of the multiplex respiratory panel with a clinically actionable turnaround time was associated with reduced hospital admissions and lesser antibiotic initiation in patients without abnormal radiographic findings.\(^9\) It is reasonable to expect that collaboration between the bedside providers and antimicrobial stewardship teams will lead to better patient outcomes and should decrease both overall expense and unnecessary diagnostic testing.

As there was initially much objection when certain antibiotic restrictions were first instituted, there may be similar objections to the restriction of certain diagnostic testing. Ongoing educational efforts and demonstrably better outcomes, however, will likely lead to acceptance over time. It is strongly recommended that institutions begin the process of establishing guidelines for the use of novel molecular diagnostic tests for bacterial pathogens (diagnostic stewardship), expand the influence of antimicrobial stewardship teams, and thus optimize patient care and clinical outcomes.\(^\uparrow\)

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**References**

References are available at ContagionLive.com.
Virus Spillover and Emerging Pathogens Pick Up Speed

Infectious diseases are emerging at an alarmingly rapid pace, faster than any other time in human history.

BY RODNEY E. ROHDE, PHD, MS, SM(ASCP)SM, SVCM, MB(ASCP)CMS, SVCM, MBCM, FACSc; AND RYAN P. MCNAMARA, PHD

The characterization and prediction of spillover intersections are of global importance, and it is critical to develop an understanding of how, when, and where spillover events occur. The coronavirus disease 2019 (COVID-19) pandemic has highlighted this issue; it is imperative to be better prepared for future pandemics.

CAN WE PREDICT THE NEXT PANDEMIC SPILLOVER EVENT?

The jump of animal and environmental pathogens into human populations or other hosts is an ongoing biological “long game” that dates back thousands of years. From the current version of SARS-CoV-2, Ebola virus, measles virus, and HIV to historical epidemics such as plagues (eg, smallpox, cholera, and bubonic plague), pathogens have consistently found a way to move into the human population. In contrast to newer threats, rabies is one of the oldest described infectious diseases, likely with an ancient pedigree that predates most historical accounts. Regardless of the pathogen, this ongoing and longstanding “dance” between pathogens and susceptible hosts is a natural process, with the outcome of pathogen emergence in human populations likely comprising only a small percentage of spillover events between all animals.

With so many variables, such as complex pathogen life cycles, modes of transmission, and random susceptible hosts’ interaction, an initial spillover event resulting in ongoing transmission into a new host is relatively rare and usually an imperfect process. Most mammalian viruses lack the ability to infect humans. Moreover, should a zoonotic virus spill over into a human host, subsequent human-to-human transmission is often not possible or unsustainable. However, with enough opportunities, pathogens can adapt themselves to broaden their host range or evolve to sustain transmission in a more suitable host. Experts in pathogen spillovers believe that the rate of novel infectious disease emergence has increased in recent history. The dichotomy between host-range transmissibility bottlenecks and the increased rate of naturally occurring spillovers makes predicting what pathogen could trigger the next pandemic extremely difficult.

Discovering an exact emerging pathogen within the global ocean of emerging and reemerging agents is a tall task, even for those equipped with advanced molecular diagnostics and epidemiologic technologies. That being said, there is a working knowledge of spillover events and how zoonotic and human intersections throughout the world can increase risk.

THE BASICS OF THE VIRUS SPILLOVER EVENT

Most spillover events are dead ends, meaning that the infectious agent could infect a novel host but is not capable of sustaining a transmission cycle within that new host. This happens frequently, particularly in areas where human and zoonotic populations overlap. Avian influenza is an excellent example of this. High pathogenicity avian influenza (HPAI) strains such as H5N1 and H7N9 have repeatedly spilled over into human hosts. Luckily, to date, there has not been a subsequent sustained human-to-human transmission in the spillover events from the current strains of HPAI; when human-to-human transmission has occurred, it has been limited.[1]

Unfortunately, viruses have an extensive history of learning to adapt to transmission within a new host. Occasionally a virus will acquire enough of the right mutations to infect a novel host and allow for subsequent and sustainable transmission. HIV is an excellent example of this. The evolutionary ancestor of HIV is simian immunodeficiency virus (SIV), which has circulated in nonhuman primates for tens of thousands of years. Multiple independent spillover events of SIV occurred, but the virus was not fit to maintain transmission in a human host. That changed in the early 20th century when handling of bushmeat from an infected primate and blood-to-blood contact with the handler were believed to have occurred. This resulted in the initial spillover of a variant of SIV that could sustain itself in a novel host, humans, which led to the HIV pandemic.[6]
Reemerging Deliberately emerging

Hantavirus pulmonary borne viruses.8 significant driver for exposure to rodent- and the proximity of homes to fields is a can vary. Hunting is a notable source of rhabdoviruses).1 Spillover pathways also rodents (especially for arena- and bunya - viruses), primates (retroviruses), and bats document history of previous spillover events (eg, HPAI and Yersinia); and reemerging infectious diseases with an incidence of disease that significantly declined in the past but have since reappeared (eg, measles).9

As the recent COVID-19 pandemic and prior emergence of pathogens have shown, there will be a “next” pandemic (or at least epidemic) pathogen. Investigators feel strongly there will be a SARS-CoV-3 pathogen.1 Additionally, variants of SARS-CoV-2 have quickly spread, demonstrating that novel phenotypes from a singular virus can take hold when multicontinental transmission rates are high.10 There are clues in recent history to what some of the more likely emergent pathogens will be. For example, 1 instance of a tropical disease that has spread recently into new areas due, at least in part, to changing climate is the chikungunya virus. As with dengue virus, it is transmitted by the Aedes mosquito, including the Aedes albopictus “tiger mosquito.” Chikungunya virus was previously confined to tropical regions around the Indian Ocean. However, in the past decade, the virus has been reported in countries in Europe, Asia, Africa, and the Americas, achieving sustained transmission. Another example is the Zika virus, which burst onto the international scene through its association with a birth defect known as microcephaly. The Ebola virus epidemic that emerged in 2014 in West Africa illustrates how a virus that previously affected only small groups of individuals, perhaps a few hundred, can sweep rapidly through an area to affect tens of thousands and become extremely difficult to contain. In February, health authorities in Guinea declared an outbreak of Ebola in the rural community of Gouéké in Nzérékoré prefecture. The Ebola virus epidemic that emerged in 2014 in West Africa illustrates how a virus that previously affected only small groups of individuals, perhaps a few hundred, can sweep rapidly through an area to affect tens of thousands and become extremely difficult to contain. In February, health authorities in Guinea declared an outbreak of Ebola in the rural community of Gouéké in Nzérékoré prefecture. Authorities in Guinea declared an outbreak of Ebola in the rural community of Gouéké in Nzérékoré prefecture after 3 cases of Ebola were confirmed—2 by local authorities in Guinea and 1 in a Liberian aid worker. The outbreak of Ebola virus disease in Guinea and Sierra Leone was first identified in December 2013. As of 2017, more than 20000 cases of Ebola virus disease had been reported, with more than 8000 deaths. As of 2017, more than 20000 cases of Ebola virus disease had been reported, with more than 8000 deaths. It has been a challenging and deadly outbreak, with many deaths occurring in the first few weeks of infection. The outbreak has been particularly devastating in rural areas, where health care facilities are scarce and the disease spreads rapidly through close contact. The outbreak has also been complicated by the presence of multiple cases in the same household, which can lead to rapid transmission. As the outbreak continues, it is clear that Ebola virus disease is a formidable threat to human health, and efforts to control the outbreak must be intensified. In addition to improved case management and contact tracing, efforts must be made to improve the availability of Ebola virus disease vaccines and therapeutics. The development of new vaccines and therapeutics is critical to controlling the outbreak and preventing future outbreaks. As the outbreak continues, it is clear that Ebola virus disease is a formidable threat to human health, and efforts to control the outbreak must be intensified. In addition to improved case management and contact tracing, efforts must be made to improve the availability of Ebola virus disease vaccines and therapeutics. The development of new vaccines and therapeutics is critical to controlling the outbreak and preventing future outbreaks. As the outbreak continues, it is clear that Ebola virus disease is a formidable threat to human health, and efforts to control the outbreak must be intensified. In addition to improved case management and contact tracing, efforts must be made to improve the availability of Ebola virus disease vaccines and therapeutics. The development of new vaccines and therapeutics is critical to controlling the outbreak and preventing future outbreaks. As the outbreak continues, it is clear that Ebola virus disease is a formidable threat to human health, and efforts to control the outbreak must be intensified. In addition to improved case management and contact tracing, efforts must be made to improve the availability of Ebola virus disease vaccines and therapeutics. The development of new vaccines and therapeutics is critical to controlling the outbreak and preventing future outbreaks.
NAFLD Is Increasingly Affecting Patients With HIV

The prevalence of this disease in this patient population is much higher than in the general public.

BY ZAHRA QAMAR, MD; STEVEN F. SOLGA, MD; AND LISA A. SPACEK, MD, PHD, FIDSA

(continued from cover page) is defined by the presence of 5% or greater hepatic steatosis in patients without risk factors of heavy alcohol consumption, viral hepatitis, treatment with steatogenic medications, or genetic causes of hepatic fat deposition.¹ NASH is a histological diagnosis characterized by inflammation, ballooning of hepatocytes, and fibrosis or nonalcoholic fatty liver that is not associated with hepatocellular damage. Worldwide, the prevalence of NAFLD in the general population is rising and estimated to be 25%.² This mirrors the rising prevalence of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome. The disease is most prevalent in the Middle East and South America, whereas it is lowest in Africa. Patients with NAFLD experience increased morbidity and mortality, which are most commonly attributed to cardiovascular disease when compared with matched controls.³ In the US, NAFLD is the third most common cause of hepatocellular carcinoma, with up to 13% of cases occurring in absence of cirrhosis.⁴ With longer life expectancy and declining AIDS-associated mortality, non-AIDS-related comorbidities have emerged as diagnostic and treatment problems in persons with HIV (PWH). Chronic liver disease is the second most common cause of non-AIDS-related mortality in PWH.⁵ Results of a US study of 47,062 PWH from 2006 to 2016 showed that 22% had some form of liver disease. The increased prevalence of liver disease is multifactorial and attributable to NAFLD, alcohol use, and viral hepatitis.⁶ In a meta-analysis of PWH, the prevalence of NAFLD, biopsy-proven NASH, and fibrosis were 35%, 42%, and 22% respectively, which is significantly higher than that of the general population.⁷ PATHOGENESIS AND RISK FACTORS SPECIFIC TO HIV INFECTION There are multiple complex mechanisms by which HIV infection increases the risk of NAFLD. These are incompletely understood and include comorbid risk factors, direct viral effects, and adverse effects of antiretroviral therapy (ART).

Components of metabolic syndrome are more common among PWH. T2DM is 4 times more prevalent in PWH, and dyslipidemia and hypertension are also more common.¹¹ Results of a US

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outpatient study revealed that nearly half of patients were obese at the time of starting ART, and in the next 2 years, 20% moved up to a higher body mass index (BMI) category.14 Achhra et al showed that weight gain in the first year after initiation of ART was associated with increased risk of cardiovascular disease and diabetes.15 NAFLD, which is called lean NAFLD when it affects patients with a BMI of less than 25 kg/m², occurs in 1 in 4 lean PWH. Lean patients with NAFLD had more metabolic derangements, such as higher triglyceride and ALT levels and lower HDL levels, than lean patients without NAFLD. They had longer duration of HIV infection and higher CD4 lymphocyte counts, and they were more likely to maintain viral suppression. This clinical phenotype may be related to genetic factors, change in gut microbiota, dysfunctional adipose tissue, and improved ability to adapt to an excess intake of calories. However, the exact mechanism is not completely understood.16

Direct viral effects also may contribute to NAFLD. Depletion of CD4+ lymphocytes in the gut causes disruption of the gut epithelial barrier, facilitating microbrial translocation into the portal and systemic translocation. This promotes liver fibrosis by activation of hepatic Kupffer cells and induction of proinflammatory cytokines, including tumor necrosis factor, IL-1 receptor antagonist, IL-6, and IL-18. HIV-induced mitochondrial dysfunction results in production of reactive oxygen species, which causes oxidative stress that is known to increase fat accumulation in hepatocytes.17

Finally, certain ARTs may contribute to the pathogenesis of NAFLD. Older nucleoside reverse transcriptase inhibitors, (eg, stavudine, didanosine, and didanosine) inhibit mitochondrial RNA and have been associated with liver fibrosis. Although these drugs are no longer recommended, associated adverse effects may be irreversible.7,20 Protease inhibitors increase central adiposity, decrease hepatic clear ance of very-low-density lipoproteins, increase hepatic triglyceride production, and potentially contribute to NAFLD.7,12 ART in the current era, particularly integrase strand transfer inhibitors, is associated with weight gain with metabolic consequences that are not yet known.13

**DIAGNOSIS**

The American Association for the Study of Liver Diseases does not recommend screening high-risk groups for NAFLD. However, the European AIDS Clinical Society recommends screening all PWH with metabolic syndrome for NAFLD by ultrasound, evaluation of liver enzymes, and serum fibrosis biomarkers.22,24

The severity of NAFLD is assessed by stratifying the degree of steatosis. Simple hepatic steatosis is generally benign, whereas NASH can progress to cirrhosis, liver failure, and liver cancer. Vodkin et al compared 66 biopsy-proven cases of NAFLD in patients who were infected with HIV versus those who were HIV negative. They found that those with HIV-associated NAFLD were more likely to have definite steatohepatitis (36.4% vs 62.7%; P = 0.027) and had higher scores for noninvasive markers of advanced disease.25 Noninvasive tests have varying degrees of performance in assessing NAFLD in people living with HIV (PLWH).22 Of the imaging modalities, MRI and transient elastography have the best-performing characteristics. APRI score (AST:platelet count) and FIB-4 (fibrosis-4) score can be considered when evaluating patients who are HIV positive with NAFLD.26 Although liver biopsy is the gold standard for diagnosing and staging NAFLD, it is invasive, prone to sampling errors, and at risk for complications.

**MANAGEMENT**

Managing NAFLD consists of treating liver disease as well as its associated metabolic comorbidities such as obesity, hyperlipidemia, and diabetes. First-line therapy in NAFLD/NASH consists of lifestyle changes focusing on physical activity and diet. Weight loss of 10% is associated with resolution of steatosis and improvement of fibrosis in most individuals.27 Liver-specific dietary recommendations, such as diet composition, are generally lacking or controversial. Patients with NAFLD must avoid routine or heavy alcohol consumption, and many practitioners recommend complete abstinence, especially for patients with advanced NAFLD.

Bariatric surgery improves comorbid diseases and improves long-term outcomes in obese individuals. A systematic review of studies focusing on pre- and postoperative liver enzymes and histology revealed that bariatric surgery is associated with significant reduction in liver enzymes and histological features of NAFLD, including steatosis, fibrosis, and inflammation. However, further studies are needed before recommending bariatric surgery as a treatment for NAFLD.28

Although there are currently no FDA-approved treatments for NAFLD, multiple agents are under investigation. Pioglitazone has been shown to improve liver histology in patients with and without T2DM and biopsy-proven NASH.29 This effect was also seen among patients with HIV/hepatitis C (HCV) coinfection.30 In individuals with and without HIV, vitamin E use improves steatosis and steatohepatitis but does not improve hepatic fibrosis.31,32

Tasamorelin is an FDA-approved growth hormone (GH)-releasing hormone analogue that restores endogenous pulsatile GH secretion and reduces visceral fat in individuals in PWH. A randomized-controlled trial (RCT) of PWH showed that tasamorelin significantly reduced hepatic fat fraction and prevented the progression of fibrosis but did not improve existing fibrosis.33

Obeticholic acid, a farnesoid X receptor agonist, plays a central role in the regulation of bile acids and metabolism. Interrim analysis of an RCT revealed that it improved fibrosis and markers of NASH disease activity.34 However, due to safety concerns, it is currently not approved for treatment of NASH.

Maraviroc, a chemokine receptor 5 antagonist, may reduce the incidence of NAFLD as an add-on therapy for individuals with NAFLD and well-controlled HIV infection.35 Cenicriviroc, a chemokine 2 and 5 receptor inhibitor, may also prove to be an effective treatment for NASH.36

Other investigational drugs undergoing evaluation include elafibranor, a peroxisome proliferator-activator, and resmetirom, a thyroid hormone receptor β-agonist.37,38

**CONCLUSION**

Addressing NAFLD is an important issue for PWH. Because these individuals are living longer, they are at increased risk of developing chronic diseases such as obesity, T2DM, and NAFLD. PWH with features of metabolic syndrome should be evaluated for NAFLD. As both NAFLD and HIV may lead to increased risk of cardiovascular disease, managing dyslipidemia, hypertension, T2DM, and obesity may improve patients’ longevity and quality of life.39

References are available at ContagionLive.com.
of 1876 patients, prolonged infusions (≥ 3-hour infusion time) of antipseudomonal β-lactams were associated with lower all-cause mortality among patients with sepsis compared with shorter bolus infusions (≤ 1-hour infusion time; risk ratio, 0.70; 95% CI, 0.56-0.87).2 Indeed, prolonged or continuous β-lactam infusions achieve higher rates of pharmacokinetic-pharmacodynamic (PK-PD) target attainment, which results in a greater probability of clinical cure from severe infection.3 The contemporary PK-PD target for β-lactams to optimize efficacy is to maintain free (unbound) plasma drug concentrations above the minimum inhibitory concentration (MIC) against the causative pathogen for 100% of the dosing interval (fT > MIC).3-5 Recent studies have further corroborated the importance of prolonged infusions for ceftolozane-tazobactam and ceftazidime-avibactam to improve clinical outcomes among patients infected with carbapenem-resistant Pseudomonas aeruginosa and Enterobacterales (CRE), respectively.6,7 Taken together, prolonged infusion β-lactam therapy improves clinical outcomes and lowers mortality. Whether this approach will curb the risk for the emergence of resistance is less well defined. It is an active research priority in studies assessing the clinical impact of β-lactam therapeutic drug monitoring (TDM).

HOSPITAL ANTIBIOTICS

β-lactam resistance against P aeruginosa is a focal point of hospital antibiograms due to the direct association with high rates of treatment failure, recurrent infections, and empiric treatment selection. Each day of antipseudomonal β-lactam therapy carries a 4% increased risk for subsequent resistance.8 In clinical trials of hospital- and ventilator-associated pneumonia (VAP) due to P aeruginosa, 10% to 50% of patients treated with β-lactams developed resistance.9,10 Hopes for improved durability of newer agents such as ceftolozane-tazobactam have been dashed by recent reports documenting treatment-emergent resistance within the same range.6,11 Thus, a more aggressive β-lactam PK-PD target of 100% fT greater than 4x MIC has been proposed by consensus guidelines to both optimize efficacy and suppress the emergence of resistance.12 The recommendation accounts for several factors, including variability in MIC determination, inaccuracies of β-lactam plasma concentration measurements, exposures at the site of infection, and the relative safety of β-lactams. At the same time, it is important to highlight that clinical data linking prolonged infusions to suppression of resistance are lacking and preclinical experimental models offer mixed results.

Felton et al compared the effectiveness of bolus versus prolonged infusions of piperacillin-tazobactam to suppress resistance against P aeruginosa PAO1 in a hollow-fiber infection model (HFIM).13 At low inocula (10^4 cfu/mL), trough piperacillin/MIC ratios of 3.4 for bolus infusions and 10.4 for prolonged infusions were required to suppress resistance; expansion of resistant subpopulations, however, occurred at a similar rate with either infusion strategy. At higher inocula (10^7 cfu/mL), amplification of resistant subpopulations occurred with all doses (up to 17g/day piperacillin) administered as either a bolus or prolonged infusion. Extending these studies, Tam et al used classification and regression tree analysis to determine that a ceftazidime, cefepime, or meropenem trough/MIC ratio of 3.8 was required to suppress resistance against a baseline inocula of 10^6 cfu/mL P aeruginosa in an HFIM.14
The in vitro data demonstrate that β-lactam trough concentrations of at least 3x MIC are required to suppress resistance, but resistance may not be reliably suppressed at higher bacterial inocula. These data most directly apply to patients with VAP or other high-inocula infection types where bacterial densities often exceed the natural inverse of the β-lactam mutational frequency, suggesting that resistant subpopulations are present at baseline and selected for over time. Accordingly, suppression of β-lactam resistance during or following treatment with prolonged infusions should be viewed through the lens of the initial bacterial burden, infecting pathogen, patient characteristics, duration of treatment, and antibiotic exposures at the site of infection.

SUPPRESSION OF RESISTANCE

To illustrate the importance of these factors on suppression of resistance, Yusuf et al showed that receiving meropenem for greater than 8 days was independently associated with the emergence of meropenem-resistant P aeruginosa infections after adjustment for age, gender, severity of illness, and length of stay. Interestingly, rates of resistance were nearly identical for patients receiving prolonged (45.5%; n = 46) or bolus (45.5%; n = 11) meropenem infusions. Similarly, Dhaese et al found no difference in the risk for resistance among patients receiving continuous versus bolus infusions of piperacillin-tazobactam or meropenem after multivariate adjustment. Although only 11.7% (24/205) of patients developed resistance in this retrospective cohort study, 34% (14/41) of patients infected with P aeruginosa developed resistance, which was the only factor independently predictive of emergent resistance. TDM and molecular analysis of resistant isolates were not performed in either study. In contrast, real-time TDM was performed in a recent study by Cojutti et al. They used continuous infusions of meropenem to target a meropenem to MIC ratio of 4:8 among patients with febrile neutropenia. Twenty percent of patients in this study had documented gram-negative infections (n = 15; 4 with P aeruginosa), and no patients developed CRE colonization within 3 months of treatment. TDM-guided β-lactam therapy provides important supportive data to institute prolonged infusions and optimize exposures necessary to suppress resistance vary across patient populations. In a prospective, observational study of critically ill patients in the Netherlands, only 37% achieved a PK-PD target of 100% T > MIC greater than 4x MIC. Factors associated with lower rates of target attainment included an eGFR of 90 mL/min/1.73m² or greater and higher BMI. To demonstrate the utility of TDM-guided therapy, Al-Shaer et al reported outcomes of 206 patients who had β-lactam levels measured as standard of care. Overall, 8% (17/206) of patients developed resistance, but more importantly, attainment of β-lactam exposures 100% T > 4x MIC was independently associated with suppression of new resistance (P = .0043).

Identifying and characterizing the emergence of β-lactam resistance in clinical trials is a major challenge due to short observation periods, sparse microbiologic sampling, and a reliance upon categorical MIC interpretations. In randomized and observational studies assessing the impact of β-lactam prolonged infusion, microbiologic eradication is often assumed and not measured. Confounding interpretation of these data, resistance is typically defined by a single representative isolate that may not be related to the isolate identified at baseline. Population estimates derived from clinical breakpoints also have been used. Neither approach, however, interrogates within patient evolution of resistant or heteroresistant bacterial populations that are common for P aeruginosa and other multidrug-resistant gram-negative pathogens. On the whole, the impact of β-lactam prolonged infusion on suppression of resistance has not been appropriately delineated, and mixed clinical results are not surprising. Moving forward, additional real-world data are needed to inform β-lactam dosing strategies within well-defined patient populations and specific infection types. Current studies can be advanced by capturing outcomes over time that include both clinical efficacy and microbiologic end points derived from studying bacterial populations rather than single isolates or clones. Until such time, prolonged infusions of β-lactams undeniably improve patient outcomes and should be implemented whenever possible. The full benefits of this approach, however, are still to be determined.

In randomized and observational studies assessing the impact of β-lactam prolonged infusions, microbiologic eradication is often assumed and not measured.

References are available at ContagionLive.com.
Antimicrobial Stewardship Can Help Prevent Injection Drug Use–Related Infections

Escalating usage and more drug choices are putting more people at risk.

BY ALYSSA M. PECKHAM, PHARMD, BCPP; AND MICHAEL G. CHAN, PHARMD, BCCCP, CACP

particularly those involving injection drug use (IDU), the risk of infection is significantly increased, which warrants intervention with preventive measures. The most successful prevention strategy is to stop IDU altogether. It may sound simple, but it may not be a realistic goal for some and, for others, may be very challenging and take time. With this in mind, how can preventive education be adapted to include those who continue to engage in IDU? The answer is harm reduction.

IDU has increased as the opioid crisis continues to ravage the United States. With the landscape of the opioid crisis changing from predominantly prescription opioids in the 1990s to heroin in 2010, and now to fentanyl and other synthetic opioids since 2013, the route by which opioids are used has changed from oral or intranasal to predominantly IDU. Fentanyl has a faster onset and a shorter half-life than heroin, which has led to an increase in the amount of injections per day. An added layer of complexity is the emerging stimulant crisis, where there has been an uptick in those engaging in cocaine or methamphetamine IDU. This is particularly worrisome from an infection standpoint because stimulants, especially cocaine, are more damaging to veins and local tissue surrounding injection sites.

Furthermore, likely stemming from decades of stigma and misconceptions about drug use, there remains a paucity of syringe service programs. According to the Policy Surveillance Program, as of August 2019, there were still 7 states where local law did not allow syringe services programs. However, in states where local law does allow for such programs, significant restrictions prevent full expansion, such as requiring 1-to-1 exchanges or involvement of law enforcement, and deter some individuals. Similarly, federal law makes it illegal to operate a safe consumption site, so those that are in operation are clandestine, leading to lack of funding and program support.

There has been an increase in blood-borne infections such as hepatitis C virus (HCV) and HIV, in addition to other complications such as skin and soft tissue infections (abscesses, cellulitis) and more serious infections, including endocarditis, osteomyelitis, and sepsis/bacteremia. Although the diagnosis and treatment of these infections are well documented in the literature, implementing harm reduction interventions in clinical practice settings is not as widely documented, but it is imperative given the lack of access elsewhere.

Harm reduction involves evidence-based public health strategies designed to reduce the negative consequences of drug use for the individual and surrounding community. It is important to note that although harm reduction does not promote drug use or ignore the associated dangers, it does accept that drug use is part of our world and that steps should be taken to minimize harmful effects rather than disregard them. There are various IDU-related harm reduction strategies that can be implemented to reduce infections, including safer injection supplies and technique, SUD treatment, and prophylactic medications. As such, antimicrobial stewardship programs (ASPs) are uniquely positioned to support these interventions.
Identifying an individual’s injection practice and supplies is the first step to a fruitful harm reduction discussion, as this allows for targeted interventions. Common supplies that may increase risk of infection if not sterile include syringe, cooker, dissolver, acidifier, and filter. Sterile syringes should be used for each injection rather than reusing or sharing. Syringes lose their integrity after just 1 use, which continues to worsen with each reuse, and they may become microscopically jagged or bent, which can damage veins. Additionally, reintroduction of a syringe that harbors bacteria may result in skin or blood infections. Sharing syringes may expose the individual to transmittable diseases such as HCV and HIV. Cookers, which are used to hold the drug during the dissolving, acidifying (if applicable), and drawing-up process, should also be unique to the individual and sterile because viruses such as HCV can survive at room temperature for weeks. When dissolving substances, using sterile water or boiled water that has been cooled decreases bacterial infections. If an acidifier is used to dissolve substances, vitamin C is preferred over lemon juice or vinegar, which may introduce bacterial sources and are direct irritants. Filters, sometimes referred to as cotton pellets, should never be reused because the damp environment facilitates bacterial growth. Lastly, hands should be washed before injecting, the injection site should be swabbed with alcohol prior to injection, and a dry swab should be placed over the injection site with light pressure to allow for platelet aggregation.

In states where local laws do allow for syringe services programs, significant restrictions prevent full expansion, such as requiring 1-to-1 exchanges or involvement of law enforcement, and deter some individuals.

SUD treatment, particularly for medications for opioid use disorder (MOUD) such as methadone, buprenorphine, and extended-release naltrexone, has been associated with lower risk of transmitting HCV and HIV and improved viral suppression for those with active infection. Methadone, a full agonist opioid taken orally, can be started quickly during hospitalization, but it must be dispensed from a licensed opioid treatment program upon discharge. Buprenorphine, a partial agonist opioid, can be started quickly via microdosing or after onset of opioid withdrawal symptoms via traditional induction. It must be prescribed by a licensed provider upon discharge, with potential to change to extended-release injection in as soon as 7 days, or fewer in certain circumstances. Extended-release naltrexone typically cannot be started until an individual has been without opioid exposure for 7 to 10 days.

Discussing infection-prevention measures is an opportunity to discuss other safety measures, such as overdose prevention. In addition to reducing risk of IDU-related infection, MOUD has been associated with significantly reduced risk of opioid craving, use, and overdose. Overdose recognition and response training, alongside provision of naloxone, are essential to rapidly reverse an opioid overdose. Naloxone should not be limited to those with OUD, as there has been an increase in accidental opioid overdoses due to substances laced with fentanyl. Lastly, other measures to reduce overdose risk include maintaining the same supply source, using a small test amount of the substance first (particularly after a period of abstinence) to gauge effects, and avoiding high-risk combinations that further increase risk of respiratory depression, such as opioids and benzodiazepines.

For a more comprehensive overview of other IDU-related harm-reduction strategies, National Harm Reduction Coalition offers a publicly available safety manual detailing many safer injection techniques and supplies and is written for those who engage in IDU. The College of Psychiatric and Neurologic Pharmacists offers a harm-reduction tool kit specifically written for pharmacists.

ASPs are often involved in treatment of various IDU-related infections, which allows ASPs to identify individuals who may benefit from harm reduction with the prospect of delivering this education at bedside or during the office visit. Harm reduction aimed at preventing IDU-related infections should include, at a minimum, SUD treatment options, education regarding safer injection supplies and technique, and prophylaxis medication options. Ideally, these encounters also will cover other harm-reduction measures such as overdose prevention strategies and provision of naloxone.

References are available at ContagionLive.com.
Lostridioides difficile infection (CDI), particularly in the recurrent setting, is associated with substantial disease and economic burdens for patients and health care systems. Using patient care strategies that minimize infection risk is vital, according to experts who participated in a recent Contagion® Peer Exchange panel moderated by Peter L. Salgo, MD.

RISK FACTORS AND MANIFESTATION

According to Paul Feuerstadt, MD, the impact of CDI is “huge.” An estimated 462,100 cases of CDI occurred in the United States in 2017,¹ and the economic cost of CDI was estimated to be $5.4 billion overall ([$4.7 billion in health care settings]) in 2014, according to a decision-analytic model.² Recurrence is common and can be debilitating for patients, according to Teena Chopra, MD, MPH.

“I’ve had patients who’ve had recurrent disease, and they’ve [lost] jobs because of the nuisance it causes with the diarrhea they experience,” she said.

Feuerstadt added that although much of the focus is on the vegetative stage, during which the spores germinate to produce toxins that cause symptoms, the pathogen is harder and more easily spread in the spore phase, because the spores are resistant to gastric acid and alcohol-based hand sanitizers.

“When we swallow the spore phase, it can get through our gastric acid, it gets to our small bowel,” Feuerstadt said. “In the small bowel, there’s a convergence to the vegetative phase where the vegetative phase multiplies, divides, and multiplies some more.”

Feuerstadt added that CDI risk factors include age greater than 65 years; female gender; immunocompromised state such as chronic kidney disease, HIV infection, or inflammatory bowel disease; recent

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use of antimicrobials, proton pump inhibitors, or histamine blockers; and residence in a skilled nursing facility or prolonged hospital stay. Chopra added that highly virulent toxigenic strains, such as the North American strain that caused outbreaks in the United States and Canada, are also of concern when considering transmission in the hospital or community setting.

**STRAINS OF C DIFFICILE**

More than 800 strains of *C difficile* have been identified, although toxin-producing strains are the only ones associated with illness. Colonization by toxigenic strains leads to production of toxin A and toxin B in the gut, which leads to the diarrhea associated with CDI. Mortality is relatively higher and may exceed 5% with ribotypes 027 and 078, which have been epidemic since 2000, according to Dale N. Gerding, MD. He attributed the high mortality rate in part to the fact that the strain tends to infect older and immunocompromised patients, with the highest rates of mortality reported in patients in their 80s and 90s.

Thomas Lodise, PharmD, PhD, said that the mortality rate increases substantially in patients older than 65 years, with an estimated rate of 10%. Chopra noted that CDI has been labeled as an urgent threat by the Centers for Disease Control and Prevention (CDC) because of the high rate of associated morbidity and mortality. She added that, although the rate of hospital-acquired infections has plateaued in recent years, the increase in community-acquired infection indicates the need for improvement in community stewardship programs.

**MANAGING COMMUNITY-ONSET INFECTION**

*C difficile* spores are ubiquitous in the environment and even are present at low levels in meat, root vegetables, and lettuce, but health care environments are more contaminated with the spores, Gerding said. A news release from the CDC stated that 82% of patients with community-associated CDI had been in an outpatient setting (eg, doctor’s or dentist’s office, chronic dialysis unit, or ambulatory surgery unit) in the 12 weeks prior to receiving a diagnosis of CDI. Gerding attributed this risk to the high rate of patients being prescribed antibiotics as well as the high level of contamination of *C difficile* spores in these environments.

Joseph Reilly, PharmD, BCGP, added that the durability of *C difficile* spores also contributes to their ability to spread infection.

“Those spores can live for a significant period of time on many surfaces, even when exposed to sunlight,” he said. “You’ll see some data that say, ‘Alcohol and certain products can kill the spores,’ but they really have to be used properly, [to have] the liquid [sit] on a surface for a significant period of time, to have effect. The fact that the spores can be taken home with you on your lab coat and [remain] in your house and on surfaces for 6 months, a year, or longer certainly puts [individuals] at risk.”

**RECURRENT INFECTIONS**

Recurrence of symptomatic CDI is relatively common, difficult to treat effectively, and a cause of significant morbidity and economic costs. Recurrence occurs in 20% to 30% of cases, with higher rates reported with each subsequent episode.

“If we saw 100 patients with [CDI] and we treated them all...25 patients would come back with their first recurrence,” Reilly said. “If we treated those 25 successfully, 40% of those patients would come back with their second recurrence. And if we treated those patients successfully, 60% would come back for their third recurrence. So, for every 100 patients we treat, you wind up [with much more than 100 visits], which is the nature of the beast.”

Lodise added that the level of risk varies among antibiotics and increases with longer duration spent in a health care setting. He said that fluoroquinolones and third-generation cephalosporins are among the most commonly used antibiotics and have a higher risk for selecting for CDI compared with other drugs. “One thing I would say with antibiotics is that every day matters,” he said. “Even 1 dose of an antibiotic can put a patient at a greater risk for [CDI] relative to no antibiotics. That risk increases substantially after 3 days of antibiotics.”

He added that for patients who are older and have a high risk of mortality, morbidity, or recurrences, keeping them on an antibiotic without an indication is “often the worst thing you can do” because the risk of CDI is elevated for at least 3 months after taking antibiotics. Through his stewardship efforts, Lodise communicates how important it is to get patients off antibiotics, particularly broad-spectrum antibiotics.

According to Feuerstadt, the burden of disease with recurrent CDI is significant. Physical manifestations include abdominal cramps, diarrhea, dehydration, and syncope related to the frequent loose stools. There also are psychological, adaptation, relational, and productivity effects. He added that these effects are observed in patients with active disease as well as those with a distant history of infection.

“One of the concepts that is very important for patients to acknowledge is that this is real and that what they’re going through is not just them,” Feuerstadt said. “[Patients] feel stressed about this. They have posttraumatic stress disorder; they feel anxiety or depression. Sometimes they feel [as though] they can’t be the person they were before. Educating ourselves as clinicians about this disease, both the physical manifestations and the emotional manifestations, will make all of us better clinicians and better equipped to approach these individuals and help them get better physically and emotionally.”

References are available at ContagionLive.com.
Single Dose of mRNA Vaccine May Cover Individuals Previously Infected With COVID-19

BY KILLIAN MEARA

There’s been much discussion about whether individuals who previously had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) require both doses of the mRNA vaccines. Understanding this issue is a public health priority, as more doses could be given to others if some individuals require only a single dose.

Investigators from the NYU Infectious Diseases With Public Health Importance (IDPHI) Study Team sought to measure the immune responses before and after mRNA vaccine in individuals with or without histories of coronavirus disease 2019 (COVID-19) infection. The data were presented during the Conference on Retroviruses and Opportunistic Infections (CROI) 2021 virtual sessions in March.

The investigators collected specimens from participants before and 6 to 14 days after both vaccination doses. Humoral assays included an S1-specific immunoglobulin (Ig) enzyme-linked immunosorbent assay, as well as a live-virus microneutralization assay vs the original SARS-CoV-2 USA-WA1/2020 strain. The enzyme-linked immunospot (ELISpot) assays and 36-color spectral analysis flow cytometry assessed B- and T-cell responses.

The study included 33 participants; 32 received the Pfizer-BioNTech vaccine and 1 received the Moderna vaccine. Fourteen of the participants had a history of COVID-19, and 19 were SARS-CoV-2 naive.

Findings from the study showed that S1-specific IgG ASCs were present at baseline in SARS-CoV-2–experienced participants, they peaked at 6 to 14 days after dose 1, and no boost was observed after dose 2. In naïve participants, S1-specific IgG ASCs were not present at baseline, low at day 6 to 14, higher at day 21, and boosted by the second dose. Other findings showed that by 6 to 14 days after dose 2, both experienced and naïve participants had similar S1-specific IgG titers.

“Patients with a history of SARS-CoV-2 infection who received a single dose of mRNA vaccine produced binding and neutralizing antibody titers at 6 to 14 days that were similar to or higher than titers in SARS-CoV-2 naïve patients who had received 2 doses,” the authors wrote. “Their titers were not boosted by a second dose. These findings support a hypothesis that SARS-CoV-2–experienced patients may require only a single dose of mRNA vaccine.”

Using the MINMON Approach as a Safe and Simple Treatment for HCV

BY KILLIAN MEARA

The hepatitis C virus (HCV) is one of the most common blood-borne infections in the world. The infection, which attacks the liver and causes inflammation, is a serious burden on health care globally, with individuals who contract the virus often developing chronic illness. There is currently no vaccine for the disease.

Approximately 71 million individuals worldwide have HCV. To achieve the broad goal of eliminating the virus by 2030, 80% of those with HCV will need to be treated. This requires simplifying the treatment delivery and associated laboratory monitoring without compromising efficacy or safety.

Investigators from the Johns Hopkins University School of Medicine in Baltimore, Maryland, have focused on a way to do this. Their data were presented during the Conference on Retroviruses and Opportunistic Infections (CROI) 2021 virtual sessions in March.

The ACTG A5360 study (NCT03512210), a single-arm, open-label trial, evaluated the safety and efficacy of a minimal monitoring (MINMON) approach to HCV therapy in treatment-naïve individuals with no evidence of decompensated cirrhosis. Included in the trial were 400 participants from 38 sites in 5 countries across 4 continents. The participants received a single-tablet, fixed-dose regimen of sofosbuvir/velpatasvir daily for 12 weeks.

Of the 399 who initiated treatment, the median age was 47 years, with 35% of participants identifying as cisgender women, 22 participants identifying across the transgender spectrum, and 166 participants identifying as White. The MINMON approach included no genotyping, tablets dispensed at entry, no on-treatment visits/labs, and 2 remote contacts at weeks 4 (adherence assessment) and 22 (scheduling sustained virology response [SVR] visit).

Findings from the study showed that the remote contact was successful at week 4 for 99% of the participants and successful at week 22 for 84% of the participants. Additionally, 95% of the participants achieved SVR.

“In a diverse, global patient population, the MINMON approach to HCV treatment delivery was safe and achieved SVR comparable to current standards,” the authors wrote. “Wider adoption of this approach, coupled with innovative case-finding strategies, may facilitate HCV elimination while minimizing in-person appointments and resource use.”
Women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are less likely to be admitted to the hospital than men, and when they are admitted, they present with lower mean parameters of respiratory and inflammatory burden driven by coronavirus disease 2019 (COVID-19), according to new research.

In data presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2021 virtual sessions in March, investigators from Johns Hopkins University reported discernable differences in severe COVID-19 infection among men and women and at varied ages.

The findings could indicate the means by which clinicians may be able to monitor suspected SARS-CoV-2 and an individual’s risk of severe disease progression.

As author Eileen P. Scully, MD, PhD, said in her presentation, early pandemic data suggested a bias in male mortality risk. As of February 2021, men have made up less than half (49%) of all SARS-CoV-2 diagnoses but 57% of all deaths, based on data from 132 countries.

Whether this is due fully or partially to factors such as sex-differentiated care-seeking tendencies, health status, illness presentation, comorbidities, or treatment responses is still not understood.

“The mechanisms for this effect have not yet been defined and may potentially offer therapeutic targets for intervention,” Scully said.

Scully and colleagues assessed data from the Johns Hopkins Medicine (JHM) 5-hospital system for SARS-CoV-2 test positivity and admission rates from March to October 2020. They used the JHM COVID-19 registry, JH-CROWN, to extract detailed patient-level data, which were analyzed for male-female differences through descriptive statistics.

Of the observed 213,175 tests, 57% were conducted in women; they reported a SARS-CoV-2 positivity rate (8.2%) similar to that of men (8.9%). However, men were more likely to become hospitalized after SARS-CoV-2 confirmation (33% vs 28%).

Among the 2608 hospitalized patients with SARS-CoV-2, more men reported fever and women more frequently reported headaches, loss of smell, and vomiting ($P < .05$).

Regarding respiratory metrics, women had more favorable profiles, on average, with lower respiratory rates than men ($P < .001$).

Women reported lower interleukin 6 levels, ferritin, higher absolute lymphocyte count, and lower neutrophil to lymphocyte ratios at admission and in peak lab values.

Comorbidity burden, per Charlson scores, was similar across genders but specifically different: Women had greater rates of obesity and asthma ($P < .001$). Heart disease ($P = .06$), complicated hypertension ($P < .01$), chronic kidney disease, smoking, and alcohol use ($P < .001$) were all greater among men.

Medication prescribed to combat SARS-CoV-2 was similarly frequent among men and women, though tocilizumab was prescribed more frequently to men.

Overall, men had a greater incidence of severe disease and death outcomes across all observed age groups (36%) than women (36%; $P < .001$). The gender outcome difference was most significant among patients in the aged 18 to 49 years group, where it was more than 2-fold for men (25% vs 11%; $P < .001$).

Despite the greater rates of obesity and asthma among patients hospitalized with COVID-19, women were less frequently hospitalized due to the illness than men, had less frequent severe outcomes, and presented with less severe respiratory and inflammatory parameters.

Women had a lower severity of respiratory parameters and lower inflammatory markers on presentation and had a lower frequency of severe outcomes from SARS-CoV-2 infection. Sex and age interactions with severe disease highlight critical risk features unique to men and women.

“Taken together, these data suggest that sex differences in the inflammatory response to SARS-CoV-2 infection and subsequent clinical presentations are the mediators of the differences we see in outcomes of males and females and suggest that we should focus attention on the immune response after we encounter this virus,” Scully said. ▲
A Case of Hemophagocytic Lymphohistiocytosis Secondary to Cytomegalovirus Infection

There have been sporadic cases of hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection (CMV) suggesting that CMV may cause clinically significant disease beyond mononucleosis in immunocompetent individuals.

BY STEPHEN PAGKALINAWAN, MD

Final Diagnosis:
Hemophagocytic lymphohistiocytosis secondary to cytomegalovirus infection in an immunocompetent individual

History of the Present Illness
A 56-year-old woman initially presented in November 2020 with a 2-week history of almost daily subjective fever with chills. She had daily fevers as high as 39.7 °C, along with nausea and emesis. Her initial work-up was extensive, but no source of infection was found. Extensive imaging studies were obtained, including transthoracic echocardiogram, CT scan of the head, and CT scan of the chest/abdomen/pelvis with contrast. All were unremarkable for source of infection, and no hepatosplenomegaly or lymphadenopathy was noted. The patient’s comprehensive metabolic panel demonstrated elevations in alanine aminotransferase and aspartate aminotransferase, as well as elevated Epstein-Barr virus (EBV) and cytomegalovirus (CMV) serum levels. However, her viremia was thought to represent reactivation caused by another acute illness and to not be primarily responsible for her fever, given her immunocompetence and unremarkable imaging. The patient was started on an empiric 2-week course of doxycycline.

A bone marrow biopsy revealed rare hemophagocytic cells, which raised the possibility that hemophagocytic lymphohistiocytosis (HLH) could be the source of her fevers. In addition to her bone marrow findings with hemophagocytosis, the patient met criteria for HLH with 4 other clinical findings: fever, hypertriglyceridemia, elevated ferritin, and an elevated soluble CD25 antigen (interleukin-2 receptor) result of 2818. She was started on a 7-week steroid taper for HLH, and she received 7 days of dexamethasone 15 mg daily. She was discharged at the end of November 2020 after 18 days of hospitalization.

Unfortunately, the patient was readmitted in December 2020 for worsening lower extremity edema, dyspnea, and nausea. In the work-up for her new nausea, she received a diagnosis of Helicobacter pylori via stool antigen and was started on triple therapy. She was otherwise afebrile, and she was continued on her dexamethasone taper. A renal biopsy revealed collapsing focal segmental glomerulosclerosis, so diuresis was recommended to help with her lower extremity edema and dyspnea. Her creatinine improved over the course of this second hospitalization.

The patient appeared to be stable and improving until hospital day 9, when her fever reached 38 °C, which coincided with the tapering of her dexamethasone dose from 8 mg daily to 4 mg daily. She began to have daily fevers with temperature as high as 38.7 °C, as well as moderate diffuse abdominal pain. Additionally, the patient’s ferritin, triglycerides, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) increased, causing concern for recrudescence of HLH. It was

BY STEPHEN PAGKALINAWAN, MD

Stephen Pagkalinawan, MD, completed his undergraduate and medical education at Rutgers University and his internal medicine-pediatrics residency at Maine Medical Center in Portland. He is a first-year adult infectious disease fellow at Temple University Hospital in Philadelphia, Pennsylvania, and also has an interest in lesbian, gay, bisexual, transgender, queer health.

STEPHEN PAGKALINAWAN, MD
noted that her EBV viremia had resolved, but her CMV viral load was still elevated at 7750 IU/mL (down from 15,567 in November). On hospital day 18, an infectious disease specialist was consulted due to concern that the patient’s CMV viremia could be the primary trigger for her HLH (Table).

### PAST MEDICAL HISTORY
The patient presented with type 2 diabetes mellitus, hypertension, hyperlipidemia, and irritable bowel syndrome.

### KEY MEDICATIONS
The patient was taking amlodipine, carvedilol, simvastatin, dicyclomine, and trimethobenzamide.

### EPIDEMIOLOGICAL HISTORY
The patient has never smoked. She drinks 1 glass of wine per week and never uses recreational drugs. She is sexually active and in a monogamous relationship with a man for the last 5 years. She lives with her children and pet cat. She works as a certified nursing assistant. She briefly traveled to Miami 1 month prior to her initial admission but denies any recent international travel.

### PHYSICAL EXAMINATION
At examination, her vitals included the following: Temperature, 100.2 °F; Pulse rate, 100/min; blood pressure, 118/84 mm Hg; and oxygen saturation was 96%. Exam was otherwise unremarkable.

### TREATMENT AND FOLLOW-UP
The infectious disease specialist ultimately recommended treating the patient’s CMV viremia due to concern for worsening HLH as the steroid dose was decreased. With her EBV viremia resolved, CMV was the only other potential HLH trigger that could be identified. Ganciclovir was renally dosed at 2.5 mg/kg daily. CMV levels were checked weekly with a plan to transition to a 3-month course of oral maintenance dosing once the patient had 3 consecutive CMV levels that were undetectable. By hospital day 29, repeat soluble CD25 returned at 1174 and the patient’s other laboratory values had improved, causing her to no longer meet criteria for HLH. Steroid taper also was completed. The patient’s CMV level became undetectable on hospital day 38.

### DISCUSSION
Human cytomegalovirus (or human herpesvirus 5) is a DNA virus from the Herpesviridae family. CMV is the largest and most complex herpesvirus, with a genome approximately 50% larger than that of HSV. CMV is commonly acquired during childhood and persists in epithelial cells in multiple organ types, and more notably CD34+ myeloid mononuclear stem cells within bone marrow. The mechanism of CMV persistence is not well understood, but is generally attributed to an interplay of low-level chronic infection and a viral latency state brought on by viral gene self-regulation. Prevalence studies suggest that more than 50% of the United States population is infected. CMV infection typically results in mild disease in immunocompetent individuals, causing 10% to 20% of cases of heterophile-negative infectious mononucleosis in adults. Patients who are pregnant or immunocompromised have more clinically significant CMV disease, which may lead to birth defects and opportunistic infections, respectively. However, within the last 20 years, there have been sporadic cases of HLH associated with CMV infection, suggesting that CMV may cause clinically significant disease beyond mononucleosis in immunocompetent individuals.

HLH is a rare but life-threatening multisystem syndrome resulting from a hyperactive immune system. It is thought to be caused by reduced negative feedback of macrophages, natural killer cells, and CD8+ lymphocytes, resulting in a hyperinflammatory state. HLH can be familial and associated with gene mutations, or it can be triggered by infection, as with this patient. It is seen more frequently in children, but HLH affects individuals of all ages. It has an incidence of 1.2 cases per million individuals worldwide each year, but its presenting symptoms are nonspecific, thus, underdiagnosis could be affecting its true incidence.

EBV is a major HLH trigger, but this patient’s EBV viremia had resolved by the time the patient began experiencing fevers during her second admission. CMV is an established trigger of HLH in immunocompetent children, but it is a rare trigger in immunocompetent adults. As of February 2020, there have been only 6 cases described in the literature of HLH secondary to cytomegalovirus infection in an immunocompetent adult. We hypothesize that given CMV’s proclivity to remain latent in CD34+ myeloid mononuclear stem cells, CMV could potentially have undiscovered downstream effects leading to HLH as monocytes differentiate into macrophages.

There are some aspects of this case that may prevent placing greater importance of CMV infection in immunocompetent individuals. Although CMV viremia levels were comparable across the case reports that are referenced, there was no effort to detect active CMV infection in lymph tissue. Another issue resulted from this patient’s ongoing gastritis, which could have increased her inflammatory makers and led to her meeting diagnostic criteria for HLH. Lastly, this patient was cotreated with both steroids and ganciclovir concurrently, and although steroids are a mainstay of treatment for both HLH, it is difficult to say definitively if the ganciclovir helped to resolve her HLH or if she needed a longer steroid course. Further investigation may warrant case-control trials with intention-to-treat analysis regarding benefit of CMV treatment in immunocompetent patients with HLH.

### TABLE. Patient Vitals During Hospital Stay

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range</th>
<th>HD 2</th>
<th>HD 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Latest reference:</td>
<td>825 (H)</td>
<td>553 (H)</td>
</tr>
<tr>
<td>Ferritin, serum (serial)</td>
<td>Latest reference:</td>
<td>1069 (H)</td>
<td>1773 (H)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Latest reference:</td>
<td>6.7 (H)</td>
<td>22.7 (H)</td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td>Latest reference:</td>
<td>52 (H)</td>
<td>116 (H)</td>
</tr>
</tbody>
</table>

*Latest units: copies/mL

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range</th>
<th>Nov 2020</th>
<th>Dec 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus DNA,</td>
<td>Latest units:</td>
<td>9300</td>
<td>&lt; 1000 copies/mL, detected</td>
</tr>
<tr>
<td>quantitative, PCR</td>
<td>Latest units: copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus DNA,</td>
<td>Latest units: IU/mL</td>
<td>15,567</td>
<td>7.75E + 3 (3.89)</td>
</tr>
<tr>
<td>quantitative, PCR</td>
<td>(Log10 IU/mL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H, high; HD, hospital day; PCR, polymerase chain reaction.
What is the power of the microbiome?

...and how can it be unlocked to treat disease?

Ferring is committed to exploring the crucial link between the gut microbiome and the threat of recurrent *Clostridioides difficile* infections. With the 2018 acquisition of Rebiotix and several other alliances, Ferring is rapidly advancing its microbiome research, developing novel therapies to address significant unmet needs in deadly and debilitating diseases, and helping people live better lives.