EMERGING & RE-EMERGING INFECTIONS

COVID-19 and Understanding Immunity

Fundamental aspects of immunity to SARS-CoV-2 remain elusive. Here is an examination of some potential clues to protection.

By Angela Rasmussen, PhD

The current coronavirus 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has been an unprecedented exercise in real-time data gathering and analysis. Since the first patients presented for treatment in China, scientists and physicians have scrambled to keep up in terms of understanding this virus’ many nuances. We have searched every scrap of data as they have been collected for meaning, trying to explain how this novel virus managed to profoundly disrupt our lives in every way and trying to understand the biological basis by which we can return to some semblance of normalcy.

For this reason, extraordinary attention has been paid to the growing body of data about immunity, since the most successful way of vanquishing major viral pathogens throughout history has been to choke them out of existence by depriving them of susceptible hosts. The concept of “herd immunity” rests on the principle that viruses, which are obligate parasites and require a host to reproduce themselves, cannot continue to spread in a population in which the majority of individuals are immune to them. While this (continued on page 12)
Managing an Outbreak by Treating Another

ANOTHER INFLUENZA (FLU) season has begun in the United States. But the focus put into these coming months of anticipated peak flu severity is amplified by our still-present concerns of coronavirus disease 2019 (COVID-19). How could dual infections interact? What is the damage done for not more greatly reducing COVID-19 spread in prior months? Are hospitals equipped for surges akin to what they saw in April? Conversely, we may actually have less to worry about. Southern hemisphere countries including Australia, Argentina, and Brazil reported significant drops in flu cases in recent months. Social distancing practices set for COVID-19, experts suggest, also hindered flu spread. Respect for one infection risk mitigated another—and a result, removed the worst-case scenario.

Yes, the associations between COVID-19 and flu have been discussed ad nauseam since the very beginning of this pandemic—and in many ways, to a fault. Dissenters to preventive practices have drawn uneven lines to either’s symptoms and mortality rates. Media has frequently likened to this current crisis to the 1918 flu pandemic, if not to just compare absolute tolls.

If we were to derive a practical use from this constant comparison, it may be that efforts to prevent, reduce, or isolate an infectious disease provides takeaways—or even byproduct benefit—to another. Infectious disease research, guidance, and discussion is never isolated.

Our issue this month highlights the manifold effects of individual breakthroughs in care: from the role of human papilloma-virus (HPV) and varicella-zoster virus (VCV) vaccination in immunocompromised patients, to the practicality of managing multidrug-resistant bacteria with the Pneumonia Panel. This issue also features perspective from Angela Rasmussen, PhD, on the current understanding of SARS-CoV-2 immunity.

To stay abreast of all COVID-19-related news and clinical updates, our parent company, MJH Life Sciences*, has launched the COVID-19 Coalition, a group of 10 nationally recognized thought leaders who will work to generate the most accurate, up-to-the-minute information on the pandemic’s ever-evolving impact on health care professionals and the patients they treat. Keep up with the latest events at mjhlifesciences.com/covid19-coalition.

Mike Hennessy Sr
Chairman and founder

COVID-19 Vaccination: Prepare to Engage

ONE DAY, I WILL once again have a column that is not about coronavirus disease 2019 (COVID-19). But as 2020 trudges onward, I find it difficult to focus on anything else. However, this month I am turning towards a hopeful area of COVID-19 therapeutics: vaccines.

With all the controversy surrounding statements and mis-statements about herd immunity, achieving immunity by vaccinating a sufficient portion of the population really is the way to move past COVID-19. Insufficient control of SARS-CoV-2 transmission has increased the urgency of our need for vaccination as the way forward and a COVID-19 US death toll passing 200,000 accentuates the dangers of this novel disease. Simply put, we need vaccines.

There is good news here. The early sequencing of the virus and response from both the pharmaceutical industry and government has been, to use an overused in 2020 term, unprecedented. Operation Warp Speed (OWS) may be poorly named, but it has furthered the development of an impressive number of vaccine candidates in ways that would not occur if companies were left to make decisions based exclusively on their own profit-versus-risk calculations. This initiative has funded the research of many vaccine candidates, but as importantly, the agreement to purchase doses “at-risk” allows companies to begin production early before the efficacy and safety of the candidate vaccines is proven.

The risk is financial, and it is likely that not all of the vaccine candidates survive the research process, but I think it is a price worth paying to save lives. It is even financially justifiable since the pandemic has taken an enormous toll on the economy. OWS has also put money into the development and purchase of some logistical aspects of vaccine production, storage, and delivery. I am sure that not all of the aspects it is developing will come to fruition or be optimal, but on the whole, I think it is a good program.

In the meanwhile, there is work to be done. The Centers for Disease Control and Prevention is working on the logistics of vaccine distribution, which will be challenging if the mRNA vaccines require ultra-low cold chain freezers, as is likely. This is likely to limit these vaccines to closed settings where high-risk persons and essential employees work. However, we also need to begin to work on public education about what is going on with vaccine development. Results from surveys have shown that the confidence of the public in a COVID-19 vaccine is low, and it is perceived as a political tool that is being rushed forward regardless of safety and efficacy, not because of it. While there is no doubt that it is a political issue, it is also true that what OWS should achieve is a compaction of the development process into overlapping steps, not a skip-ahead that absconds assessments of utility.

I have been a harsh critic of the US response to the COVID-19 pandemic in many ways. Vaccine development is the area in which I feel we have done best. However, trust is a component of vaccination also and we have work to do to restore it. If COVID-19 vaccines live up to the clinical promise that they have shown in early trials, it will be up to infectious diseases clinicians to start spreading the word. Our friends and family need our judgment.

Be well and thank you for reading Contagion®.

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

CHAIRMAN’S LETTER

EDITOR-IN-CHIEF’S LETTER
EMERGING & RE-EMERGING INFECTIONS

COVID-19 and Understanding Immunity

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Don’t miss the premier international infectious diseases meeting of the year.

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When Shorter May Not Be Better: *Pseudomonas* Infection in Hematopoietic Stem Cell Transplant Recipients

BY SARA W. DONG, MD

Recent literature suggests shorter duration of antibiotics and stepdown to highly bioavailable oral agents may be appropriate for gram-negative infections, in particular bacteremia. It is not clear, however, which patients may be poor candidates for shorter durations. There is general acceptance that *Pseudomonas* infections may require more aggressive therapy; but prior studies have focused primarily on uncomplicated Enterobacterales infections. A multicenter observational study by Fabre et al. looked more closely at uncomplicated *Pseudomonas* bacteremia to determine whether short and prolonged antibiotic therapy was associated with similar outcomes. Authors noted that patients with short duration (median, 9 days) had similar odds of recurrent infection or death as with longer courses (median, 16 days). However, HSCT recipients were still limited to 9% (n = 6) and 15% (n = 27) in the short and prolonged course cohorts, respectively.1

In *Open Forum Infectious Diseases*, Olearo et al from the Swiss Transplant Cohort Study further examined outcomes of shorter antibiotic courses for *Pseudomonas* infections. This retrospective cohort study evaluated the incidence and timing of recurrent *Pseudomonas aeruginosa* (PsA) bloodstream infection (BSI) and/or lower respiratory tract infection (LRTI) in allogeneic HSCT recipients over an 8-year period.2 There was an overall 4.2% incidence rate (n = 55) of primary PsA infections in the 1314 allo-HSCT patients. Of these 55 patients, 22 (40%) had PsA BSI, 24 (44%) had PsA LRTI, and the remaining 9 (16%) had concomitant BSI/LRTI. The median treatment duration for primary PsA infection was 15.5 days.

The primary outcome was recurrent *Pseudomonas* infection within 90 days of treatment completion. Twelve patients were excluded from this analysis due to death during treatment of primary infection or within 7 days of treatment completion. Further patient characteristics are noted in Table. Of the remaining 43 patients analyzed, 15 (35%) had recurrent *Pseudomonas* infection at a median of 28 days after treatment. Most of these (9/15; 60%) had recurrence within 30 days, and recurrent infection was observed equally among patients with primary BSI, LRTI, or concomitant infection. Recurrence was more likely to occur in patients who received shorter treatment courses (median, 13 days vs 21 days). Recurrent infection was noted in 69% of patients who received fewer than 14 days of antibiotics and in 50% who received fewer than 21 days. Assessed by primary infection type, recurrent infections were more likely to occur in those with LRTI with treatment courses fewer than 14 days. The only significant factor predictive against recurrent *Pseudomonas* infection in univariate analysis was longer duration (≥14 days) of treatment of primary infection (OR for 14-21 days, 0.11; OR for ≥22 days, 0.11: P = .02).3

These results align with a prior study suggesting an increased risk of recurrence among HSCT patients with *Pseudomonas* bacteremia and/or pneumonia who received fewer than 14 days of initial antibiotic treatment compared with at least 14 days (32% vs 10%, respectively; P = .06).3 A prior systematic review of hospital-acquired pneumonia also noted that shorter courses were associated with recurrent infection in a subgroup of ventilator-associated pneumonia (VAP) due to *Pseudomonas* and *Acinetobacter*.4 Subsequent meta-analyses were conflicting, with no difference noted in recurrence or mortality in subpopulations with VAP due to gram-negative infections. While the current Infectious Diseases Society of America clinical practice guidelines recommend a 7-day course of antibiotics for all pneumonias, both community- and hospital-acquired, certain infections in certain situations may nonetheless warrant longer duration.2 The study by Olearo et al provides further evidence supporting the idea that longer courses may be required in allogeneic HSCT recipients with *Pseudomonas* infections, and this may be true in other immunocompromised hosts as well. Further research is needed to investigate the optimal prolonged duration, but the results of this study should give pause in generalizing the use of 7-day antibiotic courses for BSI and pneumonia in those with prior HSCT or another immunocompromising condition. 

References are available at ContagionLive.com.

**Highlighted Study:**

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**TABLE.** Characteristics of 43 Allogeneic HSCT Recipients With *Pseudomonas aeruginosa* Recurrent Infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients; N = 43</th>
<th>Patients with recurrent PSA infection; n = 15</th>
<th>Patients without recurrent PSA infection; n = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of PSA infection (years)</td>
<td>55.7 (12.4, 24-70)</td>
<td>52.3 (15.9, 24-69)</td>
<td>57.5 (9.9, 32-70)</td>
</tr>
<tr>
<td>Time of primary PSA infection diagnosis post HSCT (days); median</td>
<td>280.0</td>
<td>335.0</td>
<td>258.5</td>
</tr>
<tr>
<td>Primary PSA infection site</td>
<td>BSI 18 (41.9)</td>
<td>5 (33.3)</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td></td>
<td>LRTI 19 (44.2)</td>
<td>8 (53.4)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td></td>
<td>BSI+LRTI 6 (13.9)</td>
<td>2 (13.3)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Primary PSA infection severity</td>
<td>Admission to intensive care unit 7 (17.9)</td>
<td>3 (23.1)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Intubation 4 (10.2)</td>
<td>1 (7.7)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td></td>
<td>BSI duration &gt;2 days 6 (27.3)</td>
<td>2 (28.6)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Treatment duration (days); median (IQR)</td>
<td>16 (13-29)</td>
<td>13 (11-16)</td>
<td>21 (14-31)</td>
</tr>
<tr>
<td></td>
<td>Treatment duration ≥10 days 39 (90.7)</td>
<td>13 (86.7)</td>
<td>26 (92.9)</td>
</tr>
<tr>
<td></td>
<td>Treatment duration ≥14 days 30 (69.8)</td>
<td>6 (40.0)</td>
<td>24 (85.7)</td>
</tr>
<tr>
<td></td>
<td>Treatment duration ≥21 days 17 (39.5)</td>
<td>2 (13.3)</td>
<td>15 (53.6)</td>
</tr>
</tbody>
</table>
Regulatory requirements have underscored the role of antimicrobial stewardship programs (ASPs), leading to their increased presence in hospitals. Although ASPs have demonstrated the ability to improve antimicrobial use and patient outcomes, concerns have been described regarding task-shifting away from infectious diseases consultation (IDC) because it purportedly antagonizes colleagues in other specialties; an overall reduction in IDCs has occurred as a result. In contrast, published data suggest that ASPs can actually increase the number of IDCs, since ASPs typically delineate roles separate from those of IDCs. IDC services are patient-focused and include direct communication with patients and making patient-specific plans, whereas ASPs are typically focused on activities that are more administrative in nature, such as developing institutional guidelines, updating antibiograms, and evaluating antimicrobial metrics. However, in hospitals with robust ASPs there may be overlapping patient care activities, because members of the ASP often perform prospective audits and provide patient-specific recommendations. So what is the impact of IDC in the presence of a well-established ASP?

Bork and colleagues sought to evaluate antibiotic use among patients with and without IDC in a hospital with robust ASP services. This was a cross-sectional retrospective analysis of inpatients at the University of Maryland Medical Center (UMMC), a large tertiary care center with a comprehensive IDC program consisting of 6 inpatient adult IDC services and primary ID service. Institutional policies promote pervasive influence by IDC, as IDC is required within 24 hours of ordering a restricted antimicrobial and is also required upon starting any antimicrobial for the treatment of infection among patients in the oncology ward, medical intensive care unit (ICU), or trauma services.

UMMC also has an established ASP with 2 ID physicians and 3 ID pharmacists. Prospective audit and feedback are the mainstay of the ASP, which is performed on all active antimicrobial orders started for treatment within 3 to 5 days of starting therapy for patients without IDC, and within 4-6 days for patients being seen by the IDC service. Antimicrobial appropriateness, along with the indication and any interventions, are documented in the electronic medical record for each antimicrobial reviewed.

The study included all antimicrobial prescriptions active for more than 2 days that were reviewed by the ASP over an 18-month time period. The primary outcome was antimicrobial appropriateness defined as (1) having an indication for antimicrobial treatment, and (2) using an antimicrobial consistent with institutional guidelines or using an antimicrobial that was otherwise justified by ASP review. Appropriate antimicrobial therapies were further categorized as either “guideline-concordant” or “guideline-discordant but justified.” The investigators performed several statistical analyses to mitigate limitations of the retrospective analysis, including multivariable logistic regression, stratification by primary service, and propensity score matching.

A total of 10,507 (6615 unique patient encounters) antimicrobial prescriptions met inclusion criteria. IDC was present in most (72%) of the antibiotics reviewed. Antimicrobial prescriptions with IDC were more likely to be a restricted antimicrobial and written for patients in the ICU. Patients with IDC were also more likely to have positive cultures and be colonized with organisms that were multidrug resistant.

Appropriate therapy was greater among antimicrobials with IDC compared with those without IDC (94% vs 84%; P < .0001). Unsurprisingly, “guideline-discordant but justified” antimicrobials occurred more frequently with IDC than without IDC (9% vs 5%; P < .0001). After propensity score matching, the sample size decreased to 3566 with relatively improved distribution of baseline characteristics. In the propensity score matched sample, IDC was positively associated with antimicrobial appropriateness (OR, 2.5; 95% CI, 2.1-3.0) and the difference in appropriate therapy remained (93% with IDC vs 85% without IDC; P < .0001). When stratified by primary service, IDC improved antimicrobial appropriateness among both the medical and surgical specialties, with the greatest benefit among surgical specialties. The authors conclude that IDC and ASPs may be synergistic.

Several considerations potentially limit the reproducibility of these results in other hospitals. The intensive and pervasive IDC and ASP services at the study site are one important reason. At UMMC, the ASP and IDC services appear well established and appropriately resourced, allowing the evaluation of a large proportion of patients receiving antibiotics. Institutions with an imbalance of resources for the ASP and/or IDC services may not observe such high rates of antimicrobial appropriateness and the results may skew in favor of the service, with its improved ability to provide direct patient care services to a greater proportion of patients. For example, in hospitals with ASPs that are unable to perform prospective audit and feedback on all antimicrobials, the baseline rate of appropriateness may be lower, potentially leading to a larger improvement with IDC. In this study, most patients were seen by IDC and all patients were prospectively evaluated by the ASP. Additionally, reviewer bias may have skewed the results, as only antimicrobials reviewed by the ASP were included in the analysis and appropriateness was determined by an unblinded ASP team member. Reviews were also performed later in the course of therapy for antimicrobials with IDC, which may have allotted more time for diagnostic tests and antimicrobial adjustments.

Overall, well-resourced centers with robust IDC services are best able to relate to these findings, which demonstrate the benefits of IDC even in the presence of a well-established ASP. Some centers, particularly those with other strong subspecialties, may have providers who are reluctant to consult ID. These findings underscore the benefits of bedside IDC services and add to the current body of published literature that supports the relationship between IDC and ASPs. ASPs can also use these data to quell fears of an ASP overtaking. Working together, IDC and ASPs can optimize antimicrobial use, particularly for more nuanced cases that fall outside of ASP guideline recommendations.

Published data suggest that ASPs typically delineate roles separate from those of IDCs. So what is the impact of IDC in the presence of a well-established ASP?

References are available at ContagionLive.com.

Highlighted Study:

IN THE LITERATURE

Benefits of ID Consultation and ASP Collaboration

BY CYNTHIA NGUYEN, PHARMD

Active member of the Society of Infectious Diseases Pharmacists
Managing New Practice Risks in the COVID-19 World

BY CHRIS MAZZOLINI

Medical practices across the country are reopening. But are they doing it safely? Although physicians are eager to return to normal, it’s vital that they have robust protocols and procedures ready to ensure patients and staff are safe. Medical Economics® sat down with Kerin Torpey Bashaw, vice president of patient safety and risk management with The Doctors Company, to discuss how physicians can prepare to reopen and manage their risk in this new normal of health care after coronavirus disease 2019 (COVID-19).

The following interview was edited for length and clarity.

Medical Economics® (ME): What criteria should physicians be using to make reopening decisions?

Bashaw: I think it’s really important for them to have a framework to use. So when we think about opening a practice, I would recommend 4 things.

The first thing is for them to look at their operations pre–COVID-19, because that’s what the staff is used to. That’s what the patients are used to. They also need to take a look at what’s happening from a federal perspective and from a state perspective. Local, it’s all about local public health, but the physicians should be getting their direction from the local public health authority; that’s where they’re going to get the most information that’s relevant to their practice. Then it’s really important for them to be checking, every single day, those websites with that information—so, having a framework, getting the information together and then making sure that the staff are up-to-date and know what’s going on. The staff and the patients, especially, are very frightened. Physicians are telling us that the patients are not coming in; hundreds of patients are not coming to their appointments. They’re fearful. Getting communication out, making sure that the patients know that you’re following infection control principles. And the rules have all changed. Before you even reopen your office, provide standard training regarding infection control and use of PPE (personal protective equipment) donning and doffing. If you are on the primary care medicine side, you’re probably used to wearing gloves, but you’re not used to wearing a mask. If you have a procedure or you’re doing wound care or something that has to be done in the office, you’re going to want to gown up, and you need to put that on correctly. For example, most practices are not used to using an N95 mask.

Communication cannot be stressed enough. Your staff members are afraid. They have been through a lot.

I highly recommend a leadership evidence-based practice: the daily huddle. At the beginning of your day, every day, you’re going to check the CDC website, you’re going to talk about the plan for the day, you’re going to look at the patient list and see who’s there and what their issue is. And you can explain what your process is; make sure that everyone on the team knows what the plans for the day are for the patients. And then do check-ins during the day. The staff will do many things that they have never done. Tackling COVID-19 is about standardization. It’s about standardizing your practices, so you can improve them and then tweak them every single day.

A huddle at the beginning of the day is going to be key, but you also need a debriefing at the end of the day. What went well? What didn’t go well?

I have a story, if you want me to share it. We had a practice call. The practice had done extensive work: They had their protocols in place; everybody was trained; they had their PPE. They did all their work offline with regard to educating the patients. The patients didn’t come into the waiting room. They didn’t allow family or staff to come in the patient rooms. In this instance, the provider went to give a deep injection and pulled the mask down to have a conversation with the patient and then left it down partway while giving the injection. And the family of this elderly person went ballistic, because that is not the standard of care. There are so many things that are changing, and I little slip is a break in the standard of care, which can be very problematic. Despite the extensive work that happened with this practice, I little slip—it can cause immense problems.

ME: What have you found to be some of the best practices in terms of communicating a standardized message?

Bashaw: People want to know that you’re doing the right thing. We have had a couple of stories about patients walking in videotaping or wanting to videotape the whole visit because they want to make sure that people are doing what they are supposed to be doing. It’s a good idea to call your risk manager so you can have a conversation and understand what the patients want.

We had a practice call in because they had a problem. They said they had hundreds of patients cancel and not show up for appointments that were either scheduled or that are for follow-up, and there can be some liability in that. So the practice standard was, “Hey, you know what? We’re going to call a patient who misses an appointment, and in 3 months we’re going to send a letter and document that we asked the patient to come in.” You can do that via your website or the patient portal, however you want to do it. But I can’t overemphasize the need to document all your attempts to communicate with your patients. And if you do communicate, you need to put that information in the chart, so it shows your due diligence by reaching out and communicating and making sure that the patients understand the implications.

ME: Is there anything else that you think is important for physicians to consider as they reopen their practice?

Bashaw: Physicians go into medicine because they want to practice good medicine. No physician goes in with the intent to harm. And so I think I would be remiss if I didn’t use this opportunity for those who aren’t physicians. Right now, our physicians and nurses are heroes, and they are putting their lives on the line to help their patients because they care about their patients. I can’t say it enough: I think we need to support providers and offer them protections. These are crisis times, and practices are doing the best they can. Malpractice is about not meeting the standard of care, and the standard of care is changing daily. But when you’re trying to do the best that you can in a complex and ever-changing environment, I think we owe it to our physicians and nurses to offer them protections.

This story was originally published in our sister publication, Medical Economics®.

To read more, visit contagionlive.com/link/2543.
When Is a Negative COVID-19 Test Truly Negative?

BY LAURIE SALOMAN, MS

A

mid the concern about the availability of testing for the novel coronavirus disease 2019 (COVID-19), and the focus on the sometimes lengthy delays in getting results, clinicians and patients should be aware that a subset of tests—no matter how abundant testing is in any particular locale and how quickly results are returned—will generate results that are false.

While both false negatives and false positives are undesirable, false negatives run the risk of increasing community transmission should individuals erroneously believe they're not infectious and fail to take necessary precautions. This can occur whether people have no symptoms or have symptoms but assume they're due to something other than COVID-19.

Given the skyrocketing numbers of infection in the US, it would be reassuring to know the true sensitivity—or ability to catch true positives—of the slew of tests currently being used. "The figure that a lot of people have been using is 70%, but it's really fuzzy and hard to hang your hat on it," Steven Woloshin, MD, MS, a general internist and co-director of the Center for Medicine and Media at The Dartmouth Institute for Health Policy & Clinical Practice in Lebanon, New Hampshire, told Contagion®. "The problem is nobody really knows."

Ideally, any new test given emergency authorization by the US Food and Drug Administration (FDA) can be evaluated against a clinical gold standard that would definitively establish whether a person has COVID-19. However, Woloshin explained, such a standard does not currently exist. "[P]reviously authorized PCR [polymerase chain reaction] tests are used as the gold standard when FDA considers authorizing new tests," he said. "That is, the assessment consists of seeing the level of agreement when the old test is positive or negative. This approach overestimates sensitivity because the old test might be [a] false negative."

According to Woloshin, several recent studies have highlighted a significant rate of false negatives, particularly if the test is administered soon after exposure to the virus. In these cases, tests may not capture viral material because there is not yet enough virus in the person to be picked up. It's also possible that poor testing technique can miss any virus that is there.

What should clinicians do when a patient tests negative but there is a question as to whether that result is accurate? One solution is multiple applications of even a low-sensitivity test, Woloshin said, the idea being that with more tests comes the likelihood that the virus will be detected. Before recommending repeat tests, clinicians may want to take into account whether the patient has symptoms and whether the patient is in an area that has experienced a lot of infection. A patient with symptoms in a hot spot who tests negative might be reasonably assumed to have the virus, while an asymptomatic patient in an area of low transmission who tests negative probably can take comfort in that negative result.

Woloshin pointed out that it can be difficult to assess a location's true COVID-19 prevalence without doing random testing within the community, as many people will never seek out a test unless they experience symptoms. Positivity rates at testing centers can give ballpark estimates of viral prevalence, he said.

One potential game changer in the effort to stop transmission would be the availability of inexpensive rapid tests, less sensitive ones that individuals could administer at home, ideally daily.

Researchers at Massachusetts Institute of Technology, Harvard University, and the Howard Hughes Medical Institute are developing 1 such test that hopefully will allow consumers to do a simple nasal swab or saliva test and get results in an hour, and other laboratories reportedly are working on similar platforms. Although it's unquestionably important for people who have COVID-19 to know their positive status as soon as possible, given that some people are much more efficient at spreading the virus than others, Woloshin would like to see testing go even further. "The holy grail would be a test that tells you if you're infectious," he said. ▲

Linking IBD With Antibiotic Use in Adults

BY JARED KALTWASSER

H

igh exposure to systemic antibiotic therapy appears to increase a person's risk of inflammatory bowel disease (IBD), according to a new population-level analysis.

The study was published in The Lancet: Gastroenterology & Hepatology.

The question of whether antibiotic exposure leads to IBD has been debated for many years. In children, significant studies have demonstrated that early exposure to antibiotics can lead to a higher risk of childhood IBD. However, the existing literature with regard to adults is limited.

An international team of investigators sought to remedy that problem by examining antibiotic use and IBD across a large population. The team identified people living in Sweden who were at least 16 years of age and had been diagnosed with IBD, ulcerative colitis, or Crohn disease. They used IBD data from an existing study and cross-referenced it with the Swedish National Patient Register and Sweden's Prescribed Drug Register. Patients’ cumulative antibiotic dispensations were tabulated up until 1 year before the time of matching, and the authors identified up to 5 matched control patients for each patient in the IBD cohort. Unaffected siblings were also included in the study as a secondary control group.

In total, the group identified 23,982 patients with some form of IBD, along with 117,827 controls and 28,732 siblings. The patients were diagnosed between 2007 and 2016.

"After adjusting for several risk factors, aOR (adjusted odds ratio) in patients who had used antibiotics versus those who had never used antibiotics was 1.88 (95% CI 1.79–1.98) for diagnosis of incident IBD, 1.74 (1.64–1.85) for ulcerative colitis, and 2.27 (2.06–2.49) for Crohn disease," wrote corresponding author Jonas F. Ludvigsson, MD, PhD, of the Karolinska Institute, in Sweden.

The authors noted increases in risk depending on how many times a patient had been prescribed antibiotics. Broad-spectrum antibiotics also appeared to heighten risk.

Ludvigsson and colleagues said the study underscores the problematic nature of antibiotics.

The mechanism by which this increased IBD risk occurs could be due to several interconnected factors. Ludvigsson and colleagues said. Among them: changes in metabolic functions, vitamin and nutrient production, and energy extraction.

"Most importantly, gut microbial perturbations promote the onset of intestinal barrier dysfunction, altered immune response, defective autophagy, and permissive pathogenic blooms, that are typically viewed as inciting events as early as several years before the development of IBD," they wrote.

Ludvigsson and colleagues said their findings will need to be confirmed in subsequent studies. However, given the existing evidence of antibiotics playing a role in childhood IBD, the authors said their study adds to the case that antibiotic stewardship and prescriber restraint are critically important. ▲
What’s New in 2020 From the CLSI Subcommittee on Antimicrobial Susceptibility Testing

A review of the biggest developments and regulatory decisions discussed at the midyear meeting.

BY MORGAN L. BIXBY, BS; KAYLYN N. BILLMEYER, BS; AND ELIZABETH B. HIRSCH, PHARMD

The Clinical and Laboratory Standards Institute (CLSI) Subcommittee on Antimicrobial Susceptibility Testing (AST) held the first of 2 scheduled 2020 meetings in January. Due to the coronavirus 2019 pandemic, its midyear meeting was held virtually during several dates in August and September. Although the subcommittee approved several new and revised breakpoints in January 2020, they are subject to change prior to official approval of the meeting minutes at the subsequent meeting(s).

NOTEWORTHY NEW BREAKPOINTS

Imipenem–relebactam for Proteaceae spp, Providencia spp, Morganella spp, and Serratia spp

Imipenem is a carbapenem with broad-spectrum activity against gram-negative, gram-positive, and anaerobic bacteria, including those expressing extended-spectrum β-lactamases. This β-lactam agent has been in use for decades and exerts its bactericidal activity by inhibiting penicillin-binding proteins (PBPs) responsible for cell-wall synthesis. Relebactam is a novel, slowly dissociating Ambler class A and class C β-lactamase inhibitor with no intrinsic antibacterial activity; however, when it is given in combination with imipenem, it enhances activity of the carbapenem among susceptible aerobes and prevents its degradation by certain β-lactamases. The combination of imipenem and relebactam (I-R) has demonstrated in vitro activity against Pseudomonas aeruginosa and Enterobacterales isolates with difficult-to-treat resistance phenotypes. While I-R maintains activity against Klebsiella pneumoniae carbapenemase–producing Enterobacterales, I-R lacks activity against class B metallo-β-lactamases such as VIM, IMP, and NDM. I-R was approved by the US Food and Drug Administration (FDA) in 2019 for treatment of complicated urinary tract infections (cUTI), intraabdominal infections, hospital-acquired bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP). The FDA-approved dosing is 1.25 grams (imipenem 500 mg, cilastatin 500 mg, relebactam 250 mg) intravenously (IV) every 6 hours, administered over 30 minutes.

Upon approval, I-R had FDA-approved breakpoints for disk diffusion (DD) and broth microdilution (BMD) for Enterobacterales, P aeruginosa, and anaerobes (Table 1). The AST subcommittee reviewed studies from epidemiological cutoff values, disk correlation, pharmacokinetic/pharmacodynamic (PK/PD) analyses, clinical studies, and outcomes by minimal inhibitory concentration (MIC) for indicated pathogens to validate the proposed CLSI breakpoints for publication in the M100 document. Data that were presented verified these proposed breakpoints for I-R; they demonstrated clinical efficacy and favorable outcomes across indications.

The AST subcommittee deemed that there is potential for further investigation into clinically appropriate dosing, because the PK/PD data that were presented suggested the use of higher doses for isolates with higher MIC values. There was also evidence of higher MICs at lower pH values, suggesting instability of imipenem in acidic conditions.

Considering all data presented, the AST subcommittee approved the proposed FDA breakpoints for Enterobacterales and P aeruginosa with a comment that they do not apply to Proteaeae. It also accepted the proposed FDA breakpoints for anaerobes. For all species, the committee noted that isolates that are susceptible to imipenem alone do not need to be tested in combination with relebactam. A final motion was...
passed to investigate breakpoints for other organisms within the spectrum of imipenem, specifically *Proteaceae* spp, *Providencia* spp, *Morganella* spp, and *Serratia* spp, to expand upon the current table.

**NOTEWORTHY REVISED BREAKPOINTS**

*Ceftolozane–tazobactam for Haemophilus influenzae*

Ceftolozane–tazobactam (C/T) is a cephalosporin and β-lactamase inhibitor combination drug for the treatment of gram-negative infections. Ceftolozane has bactericidal activity against both gram-negative and gram-positive organisms upon binding to and inactivating the cell wall of PBPs. When ceftolozane is combined with tazobactam, which irreversibly binds to β-lactamase enzymes produced by the organism, it is then able to treat β-lactamase–producing organisms. The combination has been FDA approved since 2014 for the treatment of cUTI and intraabdominal infections at a dose of 1.5 grams every 8 hours given IV over an hour-long period. In 2019, the FDA also approved C/T for the treatment of HABP and VABP at the higher dose of 3 grams every 8 hours given IV over an hour.

At the January 2020 meeting, the manufacturer requested the addition of HABP and VABP MIC breakpoints for *Haemophilus influenzae*. The FDA breakpoints for *H influenzae* that were previously approved for the cUTI and intraabdominal indications for susceptibility (*S* ≤ 0.5/4 mg/L) were voted to be modified to include HABP and VABP as modifications and added to the upcoming 31st edition of *M100: Performance Standards for Antimicrobial Susceptibility Testing*. In clinical trials for the HABP and VABP indications, the isolate distributions appeared similar to the large-scale surveillance isolates necessary to assess MIC breakpoints. Additionally, the available PK/PD data supported the FDA and European Committee for Antimicrobial Susceptibility breakpoints, and the Monte Carlo simulations showed the probable target attainment was more than 90%, which is the maximal killing effect, at the S = up to 0.5/4 mg/L breakpoint.

**Methicillin (oxacillin) for coagulase-negativa Staphylococcus spp**

The consensus is that the gold standard for identifying methicillin (oxacillin) resistance in coagulase-negative *Staphylococcus* spp is the presence of the mecA gene. Other methods for detecting resistance include oxacillin and cefoxitin BMD and DD, or penicillin-binding protein 2a (PBPA2a) tests. However, PBPA2a tests are not FDA approved. All 3 methods were investigated, along with mecA and mecC polymerase chain reaction (PCR), on isolates of *S capitis*, *S haemolyticus*, *S warneri*, *S hominis*, and *S epidermidis*, and 3 strains of *S aureus* were analyzed for quality control to determine which was the best for detecting resistance.

The results of PBPA2a testing conducted via lateral flow assays were extensively consistent with PCR results. Oxacillin and cefoxitin MIC and DD results prompted the committee to propose an increase in the oxacillin susceptibility breakpoint from at least 0.25 mg/L to at least 0.5 mg/L for all *Staphylococcus* except *S aureus* and *S lugdunensis*, and to remove the oxacillin DD breakpoint for *S epidermidis* for simplification of the table in the M100 document. The revised oxacillin breakpoints (Table 1) were passed, as was a motion to keep the comment that PBPA2a and mecA testing are the most definitive testing methods for methicillin resistance and may be used for isolates from serious infections with MICs of 0.5 to 2 mg/L. The breakpoints of oxacillin DD for *S epidermidis* were retained with a comment that cefoxitin disks are the preferred method.

**OTHER NEWS: FUTURE AMINOGLYCOSIDE BREAKPOINT EVALUATION**

Clinical data currently suggest safety concerns with the use of aminoglycosides that include nephrotoxicity, potentially leading to acute dose-dependent kidney failure, and ototoxicity, possibly leading to permanent complete or partial hearing loss. The United States Committee on Antimicrobial Susceptibility Testing (USCAST), established in 2015, released MIC breakpoints for 4 aminoglycoside antibiotics in 2020, all but 1 of which are lower than the current CLSI and FDA breakpoints: Enterobacterales, *Pseudomonas* spp, *Acinetobacter* spp, and *Staphylococci* (Table 2). Plazomicin, the newest aminoglycoside, approved by the FDA in 2018, was expected to be discussed at the midyear 2020 CLSI meeting, but this discussion has been rescheduled for the fall. Due to the concerns about other aminoglycoside class antibiotics, CLSI plans to review and possibly revise these breakpoints at a future meeting.

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

Novel β-Lactam Antibiotics Add Options for Multidrug-Resistant Gram-Negative Organisms

As the threat of infection with multidrug-resistant gram-negative organisms persists, new antimicrobials are a welcome addition to the armamentarium of infectious diseases clinicians.

BY ADRIENNE TERICO, PHARMD, BCPS, BCIDP

Terico is currently the clinical pharmacy specialist in infectious diseases at Pennsylvania Hospital in Philadelphia. Her interests include multidrug-resistant organisms and antimicrobial stewardship.

(continued from cover page)

As these pathogens continue to threaten the health of many, much focus has been on the development of new antimicrobials targeted against these organisms and their expressed resistance mechanisms. Imipenem-cilastatin-relebactam (IMI-REL) and cefiderocol are 2 intravenous novel beta-β-lactam–based therapies with broad-spectrum activity that target some of the most common modalities of resistance employed by MDR GNOs.

Relebactam is a non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor, with a structure similar to that of avibactam. When paired with imipenem, it provides additional activity against organisms that produce Ambler class A (eg, extended spectrum β-lactamases and Klebsiella pneumoniae carbapenemases) and class C (eg, AmpC) β-lactamases. This leads to enhanced activity against many species of Enterobacteriales as well as Pseudomonas aeruginosa.

The addition of relebactam to imipenem improves its activity against non-Proteaceae Enterobacteriales significantly, with 78.5% to 95% of imipenem-nonsusceptible organisms demonstrating in vitro susceptibility to IMI-REL.3,4 This improved activity is primarily due to inhibition of β-lactamases, especially Klebsiella pneumoniae carbapenemases. Against non-Proteaceae Enterobacteriales, IMI-REL has activity similar to that of ceftazidime-avibactam and meropenem-vaborbactam. Imipenem is intrinsically less active against Proteus mirabilis due to decreased binding of penicillin-binding proteins; therefore, the addition of relebactam has a negligible effect on its activity against this species.3,5

The major mechanism of P aeruginosa resistance against imipenem is a combination of downregulation of an outer membrane protein paired with AmpC production.1 Relebactam inhibition of AmpC resulted in improved in vitro susceptibility against approximately 78% of imipenem-nonsusceptible P aeruginosa isolates.6 Improved antipseudomonal activity is an advantage of IMI-REL when compared with meropenem-vaborbactam. This is due to differing mechanisms of resistance to the carbapenem backbone. Resistance to meropenem in P aeruginosa is the result of multidrug efflux pumps, namely the MexA-MexB-OprM system; therefore, the addition of the β-lactamase inhibitor vaborbactam does not improve the antipseudomonal activity of meropenem in the slightest.2 Other novel β-lactam/β-lactamase inhibitors with improved activity against carbapenem-resistant P aeruginosa include ceftolozane-tazobactam and ceftazidime-avibactam. Similar to IMI-REL, this is primarily due to inhibition of AmpC; ceftolozane-tazobactam is also less susceptible to efflux pumps.3,6 IMI-REL and the aforementioned agents do not have improved activity against other pathogenic nonfermenting GNOs, such as Acinetobacter baumannii or Stenotrophomonas maltophilia, as they frequently produce class B and D β-lactamases.2

IMI-REL received approval from the US Food and Drug Administration (FDA) for intraabdominal infections and complicated urinary tract infections (cUTI) on the basis of two phase 2 trials, which established the noninferiority of IMI-REL to imipenem alone. Most organisms in these studies were carbapenem-susceptible.3,10 RESTORE-IMI (NCT02452047)1 sought to study IMI-REL in a more applicable setting: the treatment of carbapenem-nonsusceptible infections. This study demonstrated an overall favorable response to IMI-REL that was comparable with imipenem plus colistin, with lower numerical 28-day mortality and less nephrotoxicity in patients who received IMI-REL. While this small study (n = 31) was not powered for statistical inference, it provided a basis for the utilization of IMI-REL to treat carbapenem-nonsusceptible GNOs.11 Results from RESTORE-IMI 2 led to an additional FDA indication for the treatment of hospital-acquired and ventilator-associated pneumonia. In this double-blind, phase 3, noninferiority trial, IMI-REL was noninferior to piperacillin-tazobactam with regard to 28-day mortality and response at end of follow-up.12 These studies provided an array of evidence to use IMI-REL confidently in clinical practice. A summary of the aforementioned studies is available in Table 1.

CEFIDEROCOL

Cefiderocol is a siderophore cephalosporin that utilizes a strategy to overcome resistance associated with passive
TABLE 1. Clinical Studies Evaluating Imipenem-Cilastatin-Relebactam

<table>
<thead>
<tr>
<th>STUDY</th>
<th>COMPARATOR</th>
<th>STUDY DESIGN</th>
<th>RESULTS</th>
<th>COMMENTS</th>
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<tr>
<td>Lucasti et al</td>
<td>Imipenem-cilastatin</td>
<td>Prospective, multicenter, double-blind, phase 2, dose-ranging study of adults with complicated intraabdominal infections randomly assigned (1:1:1) to receive imipenem-cilastatin 500 mg with 250 mg relebactam, 125 mg relebactam, or no relebactam</td>
<td>Favorable clinical response in microbiologically evaluable population (n = 255) was seen in 96.3% and 98.8% of IMI-REL–treated patients vs 95.2% imipenem (P &lt; 0.001 for noninferiority); similar rates of AE</td>
<td>Most isolates were carbapenem susceptible; patients with APACHE II scores &gt;30 excluded. Most common pathogens were E coli, K pneumoniae, P aeruginosa</td>
</tr>
<tr>
<td>Sims et al</td>
<td>Imipenem-cilastatin</td>
<td>Prospective, multicenter, double-blind, phase 2 dose-ranging study of adults with cUTI or acute pyelonephritis, randomly assigned (1:1:1) to receive imipenem-cilastatin 500 mg with 250 mg relebactam, 125 mg relebactam, or no relebactam</td>
<td>Favorable clinical response in microbiologically evaluable population (n = 213) was seen in 95.5% and 96.8% of IMI-REL–treated patients vs 98.7% imipenem (IMI-REL 250 vs imipenem –3.1 [95% CI, –11.2 to 3.2] and IMI-REL 125 vs imipenem –4.8 [95% CI, –14.7 to 4.7]); similar rates of AE</td>
<td>Most isolates were carbapenem susceptible. Most common pathogens were E coli, K pneumoniae, P aeruginosa</td>
</tr>
<tr>
<td>Motsch et al (RESTORE-IMI 1)</td>
<td>Colistin plus imipenem-cilastatin</td>
<td>Prospective, double-blind, phase 3 trial of hospitalized patients with pneumonia, intraabdominal infection, or cUTI caused by imipenem nonsusceptible pathogens. They were randomized 2:1 to receive IMI-rel or imipenem + colistin</td>
<td>Favorable overall response observed in 71% IMI-REL–treated and 70% imipenem + colistin–treated patients (90% CI, –27.5 to 21.4), day 28 favorable clinical response in 71% IMI-REL and 40% imipenem + colistin (90% CI, 1.3-51.5) and 28-day mortality 10% IMI-REL vs 30% (90% CI, –46.4 to 6.7); more AEs, especially nephrotoxicity, in colistin-treated group</td>
<td>Most common pathogens were P aeruginosa, Klebsiella spp, and other Enterobacterales Study not powered for statistical inference</td>
</tr>
<tr>
<td>Titov et al (RESTORE-IMI 2)</td>
<td>PIP-TAZ</td>
<td>Randomized, double-blind, multinational, phase III noninferiority trial in patients with hospital-acquired or ventilator-associated bacterial pneumonia</td>
<td>531 patients were included in the modified intention-to-treat analysis. IMI-REL was noninferior to PIP-TAZ with regard to 28-day mortality (15.9% vs 21.3%; 95% CI, –5.3% [-11.9 to 1.2]) and favorable response at end of follow-up (61% vs 55.8%; 95% CI, 5% [-3.2 to 13.2]). In patients with APACHE II scores ≤15, mortality was lower with IMI-REL than PIP-TAZ with a CI excluding 0. Overall AEs were similar between groups</td>
<td>66.1% of patients were treated in treatment of infections caused by MDR GNOs and 48.6% were ventilated. Most common organisms treated were K pneumoniae, P aeruginosa, A calcoaceticus-baumannii complex, and E coli</td>
</tr>
</tbody>
</table>

Diffusion across the cell membrane of GNOs. Although similar in structure to ceftazidime and cepefime, the addition of a catechol moiety on the side chain at position 3 permits cefiderocol to chelate iron, allowing for active transport across the cell membrane via iron transporter channels. In addition to avoiding resistance mechanisms associated with passive diffusion, cefiderocol is stable against hydrolysis by β-lactamases in all 4 Ambler classes, including metallo-β-lactamases, and it is minimally affected by multidrug efflux pumps.

As one might imagine, bypassing 3 major mechanisms of resistance leads to significantly improved in vitro activity against many GNOs, fermenters and nonfermenters alike. A series of surveillance studies under the SIDEROC-WT program evaluated 28,629 GNO clinical isolates from North America and Europe over a period of 3 years and demonstrated that more than 99% of isolates had low cefiderocol minimum inhibitory concentration (MIC) values. The multinational SIDEROC-CR 2014/2016 program specifically collected carbapenem-resistant isolates, for which cefiderocol suppressed the growth of 96.2% at the MIC breakpoint of 4 or less. Against carbapenem-resistant Enterobacteriales (n = 1022), including 23% ceftazidime-avibactam–resistant isolates, cefiderocol suppressed the growth of 97% of strains. For MDR A baumannii (n = 368), P aeruginosa (n = 262), and S maltophilia (n = 217), cefiderocol suppressed the growth of 90.9%, 99.2%, and 100%, respectively. This included 71.4% ceftolozane-tazobactam–resistant P aeruginosa. Its gram-positive and anaerobic activity is essentially negligible, which is a disadvantage when compared with the more recently available β-lactam/β-lactamase inhibitors described above.

While its in vitro activity is captivating, the indication cefiderocol received initial FDA approval was lackluster. Its approval for cUTI in adults with limited or no treatment options was based on a phase 2 study that established noninferiority of cefiderocol compared with imipenem/cilastatin. The CREDIBLE-CR study evaluated the use of cefiderocol compared with best available therapy (BAT) for infections caused by carbapenem-resistant organisms and was included as part of the application for approval prior to its peer review and publication. Although it was not powered to assess differences in mortality, an obvious imbalance was seen in patients receiving cefiderocol for pneumonia, bloodstream infections (BSI), or sepsis—a majority of which were caused by A baumannii in critically ill patients. The concern surrounding this result is reflected as a warning for increase in all-cause mortality in the prescribing information. Results were available as prepublication for the APEKS-NP study (NCT03032380), which evaluated patients with nosocomial pneumonia caused by carbapenem susceptible organisms. Cefiderocol met noninferiority compared with high-dose extended-infusion meropenem for the primary outcome of all-cause mortality at day 14, with similar results at day 28. This study led the FDA to expand the labeled indication of cefiderocol to include hospital-acquired and ventilator-associated bacterial pneumonia. While the APEKS-NP study did not show any mortality concerns, it also did not reflect real-world use of this agent for carbapenem-resistant organisms. A summary of clinical data is presented in Table 2 (online). The GAMECHANGER study (NCT03869437) is enrolling patients to receive cefiderocol or BAT for gram-negative BSIs and will hopefully provide insight on its utility for treatment of infections caused by MDR GNOs.

IMI-REL and cefiderocol are broad-spectrum agents that fill a void in the armamentarium against MDR GNOs. Although broad-spectrum, each has its own niche in vitro to combat specific resistance mechanisms expressed by these organisms, for which their use should be reserved. While data have been made available demonstrating success of IMI-REL against BAT for MDR GNOs, such data for cefiderocol are incomplete. However, in the grand scheme of gram-negative infections, those caused by extensively MDR organisms are few and far between and extremely difficult to study with sufficient power analyses in clinical practice. Hopefully, full publication of CREDIBLE-CR, APEKS-NP, and the GAMECHANGER studies will help define the clinical utility of cefiderocol. This agent will likely be reserved for the treatment of infections where other options are limited to none, as highlighted in a number of case reports of successful treatment thus far.

References are available at ContagionLive.com.
COVID-19 and Understanding Immunity

Fundamental aspects of immunity to SARS-CoV-2 remain elusive. Here is an examination of some potential clues to protection.

By Angela Rasmussen, PhD

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can be achieved by immunity acquired by natural infection, as may be the case with Zika virus[^1], the cost in lives is often too high and natural infections may not induce lifelong immunity. Therefore, the development of vaccines and mass vaccination programs are the gold standard for inducing herd immunity in the global population. Developing safe and effective vaccines, however, depends on an understanding of functional immune protection, which has led scientists to the most important questions of this pandemic: How does immunity to SARS-CoV-2 work? And how can we use that information to end the current public health crisis?

At first, immunity seems like a deceptively simple concept: In response to infection, the immune system springs into action to clear the infection. What’s more, the immune system stays on alert, protecting against future exposures. In reality, it’s much more complex than that, which is why fundamental aspects of immunity to SARS-CoV-2 remain elusive. Immune function cannot be measured simply by quantifying immunoglobulin G (IgG) titers or gauging the presence of antigen-specific T cells, and immune responses gone awry contribute significantly to disease severity. Understanding the immune responses to SARS-CoV-2 infection is essential to understanding how they contribute to protection or pathogenicity. However, a consistent theme of the public discussions about immunity to SARS-CoV-2 has been whether the virus is somehow different than other viruses. Reports of reinfection and recrudescence, as well as observations about antibody responses, have fueled speculation about whether immunity works in the same way for SARS-CoV-2 as for other respiratory viruses and influenza. Fortunately, although the data are still limited, the emerging picture so far is that SARS-CoV-2 is consistent with what we know about immunity to other viruses that infect the human respiratory tract: It does induce immunity in most people, as measured by antibody and T-cell responses.
Antibodies are often the first immune parameter measured in response to a novel emerging virus, as serum antibodies are easy to detect with a conventional blood draw. Therefore, numerous serology studies have been conducted in convalescent COVID-19 patients. The results of multiple studies have demonstrated that convalescent patients do mount antibody responses, including responses showing robust neutralizing IgG titers that occur very rapidly following diagnosis. Although study results have shown that overall neutralizing titers may be low, most patients produced some IgG targeting the SARS-CoV-2 spike protein receptor-binding domain with potent neutralizing capacity. Results of numerous studies also show that antibody titers correlate with disease severity and with sex (with men at greater risk of severe COVID-19 and death than women). While there is no direct evidence that antibody titers correlate with protection from infection in human COVID-19 patients, some evidence from rhesus macaque challenge studies suggests that antibodies do protect against reinfection upon a second challenge in convalescent animals. Similarly, a number of vaccine candidates that also induced high neutralizing antibody titers protected against severe disease and infection in macaque challenge studies. An outbreak on a fishing vessel served as a natural experiment, in which high titers of neutralizing antibodies were found in crew members who did not become infected. This suggests that neutralizing antibodies play an important role in both protecting against reinfection and attenuating disease severity in those who become infected.

There is some evidence that these responses wane over time in terms of the titer of detectable neutralizing antibodies in the blood, although the implications of this are not clear. Normally, after an initial spike in IgG during and immediately after the initial infection, antibody titers decrease to a baseline level unless there are subsequent exposures. The observed decreases in antibody titer after several months are consistent with this paradigm, and they do not indicate a corresponding loss of immune memory or functional immunity.

Whether or not functional immune protection decreases over a longer period of time is unknown, although studies with SARS-CoV suggest that it might. The Virome of Manhattan study results demonstrated that humans can become reinfected with other common cold coronaviruses within months, although those coronaviruses cause milder disease and are not directly comparable with more pathogenic coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2. However, as SARS-CoV has not reemerged, it is impossible to determine whether the reduction in detectable antibody titers resulted in a complete loss of immune protection; it is possible that other branches of the adaptive immune system also may offer protection.

Antibody titers have been shown to correlate with T-cell function, and SARS-CoV-2–specific T cells have been observed in numerous studies. In particular, follicular CD4 T cells, which coordinate adaptive immune responses, are particularly important for both CD8 T-cell function and B-cell responses. Thus, T-cell responses to SARS-CoV-2 are likely critical for mounting protective immune responses against SARS-CoV-2 and for maintaining immunological memory responses after the primary infection has been cleared. Additionally, SARS-CoV-2–specific T cells have been identified in subjects with no history of SARS-CoV-2 infection suggesting the presence of cross-reactive T cells primed by prior exposure to common cold coronaviruses, although their functional significance in protective immunity is not clear. They may attenuate disease or enhance B-cell responses to an initial exposure to SARS-CoV-2, or they may not play a significant role at all in immune protection. The results of at least 1 vaccine study have suggested that antibody neutralization is the single most significant correlate of protection, so the importance of preexisting cross-reactive T-cell immunity in pathogenesis remains unknown. T-cell polarization is likely important for the balance between protection and pathogenesis, although this is not well studied in SARS-CoV-2 natural infection. T helper cell type 1 (Th1) responses are usually associated with antiviral responses, such as CD8-mediated cytolytic responses and neutralizing antibody production, and Th1 responses have been observed in vaccine challenge studies demonstrating protective efficacy against COVID-19. On the other hand, Th2 responses are associated with acute respiratory distress syndrome and airway hyperactivity and could contribute to increased COVID-19 severity, although the relationship between Th2 polarization and COVID-19 severity is unknown.

Whether or not functional immune protection decreases over a longer period of time is unknown, although studies suggest it might.
Examining the Preexposure Prophylaxis (PrEP) Pipeline

Here is a look at some investigational therapies for HIV prevention.

BY MIKAYLA S. JOHNSON, PHARMD; RENATA O. SMITH, PHARMD, AAHIVP & AND MELISSA E. BADOWSKI, PHARMD, MPH, BCIDP, BCPS, AAHIVP &

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Although tenofovir disoproxil fumarate/emtricitabine is currently approved for all adults in the prevention of sexually acquired HIV, tenofovir alafenamide/emtricitabine is approved only for prevention in men who have sex with men and in transgender women.2 We report primary results from a blinded phase 3 study evaluating the efficacy and safety of pre-exposure prophylaxis. Most importantly, efficacy of these oral products relies on strict adherence, which poses a challenge for many at-risk populations.1,4 To address this disparity, several investigational products are under development that incorporate a diverse armamentarium of options, analogous to contraceptives including but not limited to on-demand PrEP, non-oral formulations, and longer-acting agents.

INJECTABLE PREP

Cabotegravir is an investigational integrase strand transfer inhibitor with potent antiviral activity.6 In combination with rilpivirine, its efficacy in the management of HIV has been documented.7 However, despite being well tolerated and acceptable as a long-acting injectable formulation, rilpivirine for PrEP has not moved forward into phase 3 studies because of storage and transportation limitations, and a low barrier to resistance.9,9 Conversely, cabotegravir is under investigation for long-acting PrEP.10 Interim analysis from HPTN 083 showed that cabotegravir 600-mg injection given every 8 weeks was statistically superior to daily tenofovir disoproxil fumarate/emtricitabine, with a 66% relative risk reduction in HIV acquisition.11 Both agents were well tolerated, and safe though injection-related adverse events were more common with cabotegravir and resistance testing data is in progress. But, the long pharmacokinetic (PK) tail of cabotegravir might complicate the management of drug adverse events in clinical practice. Secondary analysis from the HPTN 077 trial revealed that cabotegravir may remain detectable after discontinuation for nearly 3 years in men, 4 years in women, and longer exposures were detected in higher body-mass index individuals; irrespective of sex.12 Nonetheless, if approved, cabotegravir could address adherence issues. Yet, optimizing an implementation strategy for gluteal injection administration to suit patient needs will be critical component associated with this formulation of PrEP.

VAGINAL PREP

Dapivirine is an investigational nonnucleoside reverse transcriptase inhibitor (NNRTI) that has been studied in various formulations for the prevention of HIV.13,14 In 2 phase 3 trials (the Ring Study, NCT02028338, and ASPIRE, NCT01617096), the monthly intravaginal ring was effective and no difference in safety concerns between the dapivirine and the placebo arm.13,14 Effectiveness and tolerability of the vaginal ring containing 25 mg dapivirine was further demonstrated in an extension study, DREAM, which estimated a 63% reduction in HIV-1 risk.15,16 Minimal safety concerns related to dapivirine occurred in participants (7% experienced vulvovaginitis and 2% experienced severe adverse effects). However, the study lacked a contemporaneous placebo group and findings exposed a lower risk reduction in adolescent women due to poor adherence.

Currently, the monthly ring is under regulatory review by the European Medicines Agency; a 90-day vaginal ring containing 100 mg or 200 mg of dapivirine is also under investigation. The International Partnership for Microbicides (IPM) is planning to submit applications to the South African Health Products Regulatory Authority later this year, which may make the dapivirine ring available sometime in 2021 in Africa; the IPM also plans to submit an application to the US Food and Drug Administration (FDA) later this year.19 A 3-month ring with 200 mg of dapivirine and 320 mg of levonorgestrel is also being investigated to simultaneously offer PrEP and contraception.20,21

MONTHLY CAPSULATED PREP

Islatravir is a first-in-class long-acting nucleoside reverse transcriptase translocation inhibitor that is under investigation for use in prevention and treatment of HIV.22 Islatravir’s unique mechanism of action and
pharmacokinetic profile provides flexibility in therapy formulations. In preclinical studies, islatravir dosed orally once weekly for PrEP protected against simian–human immunodeficiency virus infection. A phase 2a trial, MK-8591-016, is currently enrolling to investigate the safety and PK of 60-mg and 120-mg islatravir doses administered orally in capsule form once monthly.

**PREP IMPLANTS**

Studies have also demonstrated the safety and feasibility of islatravir triphosphate implant. Modeling predicted that the levels of intracellular islatravir triphosphate were consistent with the potential for once-yearly implantable administration. Other antiretrovirals with encouraging preclinical results for subdermal implantable PrEP include tenofovir alafenamide and cabotegravir.

**MULTIPURPOSE TECHNOLOGIES FOR PREP AND MICROBICIDES**

Numerous technologies are in development to address multiple health concerns like HIV prevention and contraception in a single agent and are referred to as multipurpose prevention technology (MPT) products. The Population Council is working on coformulating a dual-purpose pill composed of the active pharmaceutical ingredients (APIs) in tenofovir disoproxil fumarate/emtricitabine and the combined APIs in the oral contraceptives levonorgestrel and ethinyl estradiol.

Many organizations are developing several other innovative MPTs including vaginal gel, vaginal ring, vaginal insert, diaphragm, microarray patch, rectal gel, rectal insert, long-acting injectable, an implant, and an intrauterine device. However, it will be several years before one is available.

Also underway is investigation of PC-1005 gel, a combination of the investigational NNRTI (MIV-150) plus zinc acetate and carrageenan. This is the only product designed for vaginal and rectal use targeting HIV, human papillomavirus, and herpes simplex virus simultaneously that has undergone a phase 1 study to date. Other early-phase explorations of MPTs include a microarray patch using cabotegravir and norelgestromin and a vaginal insert containing elvitegravir and tenofovir alafenamide.

A MPT that prevents HIV and sexually transmitted infections and simultaneously prevents unintended pregnancy would significantly help overcome barriers to negotiating condom use as well as adherence issues related to stigma and gender dynamics that have been seen in microbicide and PrEP trials.

Microbicide products have been or will be investigated, including vaginal dosage forms (gel, film, tablet, ring, and insert) and rectal dosage forms (gel, douche, enema, suppository, and insert). Tenofovir 1% vaginal gel is furthest along in development, with a completed phase 3 study (FACTS 001, NCT01386294). However, results revealed that the gel didn’t protect from HIV and adherence was a crucial factor in the unfavorable trial results.

Daranavi, maraviroc, raltegravir, and rilpivirine are also being investigated preclinically for utilization in HIV prevention as various microbicide topical products. Even though microbicides would fill an important HIV prevention need, it is imperative that any such product is safe and effective.

**IMMUNOPROPHYLAXIS**

Immunologic approaches have been studied, include active immunization with vaccines and passive immunization with broadly neutralizing antibodies (bNAb). VRC01 is the first of the bNAb to be found safe and to advance to efficacy trials for HIV-1 prevention, with final results expected by 2021. Additionally, five sizeable clinical efficacy trials are underway to evaluate vaccination strategies for PrEP. Even with high manufacturing costs, bNAb are expected to have favorable safety and PK profiles, potentially allowing for longer intervals between administrations. However, these immuno-prophylaxis products require intravenous administration, which may not be widely acceptable for patients.

**OTHER PRECLINICAL FORMULATIONS**

A number of other delivery methods are in preclinical trials. Products using microneedles, fibers, enemas, mucoadhesive intravaginal tablets, thin-film polymer devices, foams, sponges, diaphragms, and nanotechnology are being investigated for PrEP. Early-phase studies of PK and tolerability are encouraging, but few additional data are available.

**CONCLUSIONS**

HIV prevention does not happen in isolation and there is not an ideal PrEP formulation as one size does not fit all. However, the investigational products described above address some challenges in HIV prevention by employing a mix of delivery systems that account for different transmission circumstances, discreet on-demand methods, and offer a consistent use routine that’s available at every high-risk encounter or lack of adherence situation. On the contrary, these investigation therapies will not address the need for improved provider and public health education to ultimately employ positive attitudes related to HIV prevention strategies. Nonetheless, cost and overall feasibility will be additional considerations upon implementing these technologies.

References are available at ContagionLive.com.
Early Experience With the BioFire Pneumonia Panel

A balance between antimicrobial stewardship and the search for multidrug-resistant organisms.

BY MOLLY M. MILLER, PHARM.D, HANNAH M. CREAGER, PHD, ANDREW B. WATKINS, PHARM.D, ERICA J. STOHNS, MD, TREVOR C. VAN SCHOONEVELD, MD, SCOTT J. BERGMAN, PHARM.D

The past decade has seen the introduction and increased use of multiplex polymerase chain reaction (PCR) panels by clinical microbiology laboratories for rapid detection of pathogens in blood cultures, cerebrospinal fluid (CSF), stool, and respiratory tract specimens. Adoption of rapid PCR panels for positive blood cultures has been particularly widespread, and antimicrobial stewardship programs at many institutions perform audit and feedback based upon the results of such panels as a basis for interventions with providers.1 In addition to blood culture and meningitis/encephalitis panels, the Nebraska Medicine Antimicrobial Stewardship Program now reviews results of a new pneumonia panel produced by BioFire Diagnostics.

Unlike previously available respiratory panels, which detect almost exclusively viral pathogens, the Pneumonia Panel tests specimens from the lower respiratory tract (sputum, endotracheal aspirate, and bronchoalveolar lavage) and detects a number of bacterial targets and associated antibiotic resistance genes in addition to viral pathogens (Table 1). As such, it provides additional opportunities for stewardship interventions but also poses some unique challenges. Many of these challenges stem from the fact that the respiratory tract, unlike the blood and CSF, is not a sterile site, meaning that not every organism detected is clinically significant, and the relative abundance of different species is an important part of the microbiological work-up. Results for the bacterial targets on the Pneumonia Panel are semiquantitative; copy number is reported as being not detected, 103, 104, 105, or greater than or equal to 106. This imitates the semiquantitative reporting used by most laboratories for cultures, but the results are not generally concordant, and copies of DNA detected are not well correlated with bacterial colonies per mL. In polymicrobial specimens, the relative abundance does seem to correlate, with the highest copy numbers usually corresponding to the most common organism found. In our experience, organisms for which fewer than 103 copies are detected are often not found by culture. Results with low copy numbers may represent colonization rather than infection, or the presence of nonviable organisms after exposure to antimicrobial therapy. We recommend that the panel only be performed once on each type of sample, so we have little experience with interpreting results from subsequent tests while on or off therapy.

The increased sensitivity of this PCR diagnostic tool over standard culture creates several difficulties related to interpretation, which have been noted in the literature.2-5 These difficulties include increased likelihood of identifying colonizing organisms present in low numbers that are not causing infection; detection of multiple organisms or organisms that are not identified on culture; and semiquantitative results that are higher than what would be detected on culture and therefore difficult to interpret. Despite these difficulties, the pneumonia panel has shown potential for facilitating rapid identification of organisms and resistance genes, providing results in approximately 75 minutes.6 This may lead to earlier initiation of appropriate therapy, prompt discontinuation of broad-spectrum empiric therapy, or rapid deescalation to targeted therapy.2-4 Our experience thus far with the pneumonia panel is discussed here.

The pneumonia panel was implemented at Nebraska Medicine in May 2020, in the midst of the coronavirus disease 2019 (COVID-19) pandemic. It does not currently have SARS-CoV-2 as a target, although the respiratory pathogen panel does now include it. Ordering has been restricted to the intensive care unit and the pulmonary/critical care or infectious diseases teams. An institutional guidance document with information regarding the panel’s use and interpretation, as well as empiric therapeutic recommendations based on panel results and the antibiogram (Table 2), was published on the Nebraska Medicine Antimicrobial Stewardship website (www.unmc.edu/asp). The Antimicrobial Stewardship Program reviews pneumonia panel results during business hours 5 days per week and makes treatment recommendations in order to optimize therapy. Most often, we communicate recommendations to deescalate to therapy that targets the detected organism, or to discontinue antibiotics on the basis of a negative panel result; these recommendations are communicated to providers or pharmacists rounding with the primary team.

Table 1. Polymerase Chain Reaction Pneumonia Panel Pathogen and Bacterial Resistance Gene Targets

<table>
<thead>
<tr>
<th>Semiquantitative targets</th>
<th>Gram-positive organisms</th>
<th>Gram-negative organisms</th>
<th>Qualitative targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semiquantitative targets</td>
<td>Staphylococcus aureus</td>
<td>Acinetobacter calcoaceticus-baumannii complex</td>
<td>Atypical organisms</td>
</tr>
<tr>
<td></td>
<td>Streptococcus agalactiae</td>
<td>Enterobacter cloacae complex</td>
<td>Legionella pneumophila</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae</td>
<td>Escherichia coli</td>
<td>Mycoplasma pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pyogenes</td>
<td>Haemophilus influenzae</td>
<td>Viral pathogens</td>
</tr>
<tr>
<td></td>
<td>Klebsiella aerogenes</td>
<td>Klebsiella oxytoca</td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td>Moraxella catarrhalis</td>
<td>Coronavirus</td>
</tr>
<tr>
<td></td>
<td>Proteus spp</td>
<td>Moraxella catarrhalis</td>
<td>Human metapneumovirus</td>
</tr>
<tr>
<td></td>
<td>aeruginosa</td>
<td></td>
<td>Influenza A</td>
</tr>
<tr>
<td></td>
<td>Serratia marcescens</td>
<td></td>
<td>Influenza B</td>
</tr>
</tbody>
</table>

Table 2. Resistance genes

<table>
<thead>
<tr>
<th>Resistance genes</th>
<th>$S\ aureus$</th>
<th>CTX-M</th>
<th>IMP</th>
<th>KPC</th>
<th>NDM</th>
<th>VIM</th>
</tr>
</thead>
</table>

These members are active members of the Society of Infectious Diseases Pharmacists.
In our experience, community-acquired pathogens are commonly identified, likely due to the relatively large proportion of Pneumonia Panels ordered for patients with COVID-19 near the time of admission. Similar to the staffs of other facilities that have studied the panel, we have found that *Staphylococcus aureus* and *Haemophilus influenzae* are the most commonly identified organisms, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Given the timing of our implementation and potentially ongoing COVID-19 prevention efforts, few respiratory viruses have been identified to date, with positive results consisting exclusively of rhinovirus/enterovirus. Several positive panels have detected 3 to 5 bacterial targets; however, in these situations, most organisms are detected at low quantities with 1 species predominating. A handful of exceptions have occurred, with 1 notable case in which 5 organisms (*H influenzae, M catarrhalis, S aureus* (mecA+), *S pneumoniae*, and *S agalactiae*) were detected in quantities exceeding $10^8$ copies/mL in a patient previously treated with steroids. All of these organisms were subsequently isolated on culture and the patient was treated with antimicrobial therapy active against all identified organisms.

The pneumonia panel also qualitatively reports detection of resistance genes found in organisms typically causing pneumonia (Table 1); however, resistant organisms are not always identified by culture of specimens in which the pneumonia panel detected the presence of a resistance gene, suggesting that the resistance gene may have been present in the panel in a nonpathogen or low-abundance organism. Thus far, only *mecA/C* and *CTX-M* have been identified at our institution. In these instances, we recommended antimicrobial therapy to target MRSA or ESBL organisms. Whether this is always appropriate is uncertain: If the organisms carrying the resistance gene are not isolated on culture, patients may be exposed to unnecessarily broad antimicrobial therapy based on the PCR finding. When a resistance gene is detected on the pneumonia panel but does not grow on culture, we believe this warrants consideration of deescalation to therapy that targets only the organisms detected by culture.

Net effects of the pneumonia panel on antimicrobial stewardship at our institution are thus far unknown, although research is forthcoming. The increased sensitivity of the panel sometimes leads to specific organism detection despite growth of only normal respiratory flora on culture. For antimicrobial stewardship, this could be a detriment (eg, team decides to treat an organism when they ordinarily would have stopped antibiotics) or a benefit (eg, team narrows therapy to target the organism when they ordinarily would have continued broad coverage), and only time and experience with the panel will tell. At Nebraska Medicine, the Pneumonia Panel has been recommended only for use in patients with severe community-acquired pneumonia (CAP) or patients with CAP on expanded-spectrum therapy, patients with hospital-acquired or ventilator-associated pneumonia, or patients who are not improving despite receiving typical empiric therapy. By targeting these populations, we anticipate a reduction in broad-spectrum therapy based on pneumonia panel results. We are particularly hopeful that implementation of the PCR Pneumonia Panel will facilitate a reduction in vancomycin and anti-*Pseudomonas* agent use. It also has the potential to allow rapid expansion of therapy to antibiotics that better target resistant organisms when resistance genes are detected (eg, *KPC*), or to prevent escalation of therapy that might have otherwise been prescribed, based on the fear of resistant organisms, when resistance genes are not detected.

During the COVID-19 pandemic, many providers order the pneumonia panel on patients positive for SARS-CoV-2 to detect secondary bacterial pneumonia and prescribe antibiotics accordingly. In patients with severe COVID-19 pneumonia, it has been more difficult to convince treatment teams to discontinue antibiotics based on negative PCR results, even when culture results are concordant, because of the prolonged respiratory failure and clinical instability common in this population. However, positive pneumonia panel results have been helpful for providing a basis to narrow therapy and decrease exposure to broad-spectrum antimicrobials.

The implications of the pneumonia panel on antimicrobial stewardship, resource utilization, and clinical outcomes have not yet been determined. As provider experience with interpretation of pneumonia panel results grows, we are hopeful that it will be a valuable tool to help optimize antimicrobial therapy for hospitalized patients with severe pneumonia.

References are available at ContagionLive.com.
Varicella Zoster Virus and Human Papillomavirus Vaccination in Immunocompromised Patients

Vaccination for VZV and HPV requires special consideration in immunocompromised patients. They are at risk for more severe viral illnesses if not immune, but they may also have decreased response to, and increased adverse effects from, vaccines.

BY CATHERINE DEVOE, MD, AND PETER CHIN-HONG, MD

(continued from cover page)

The presence of immunocompromise requires special attention to several aspects of vaccination. The first is safety: Live attenuated vaccines are “weakened” but potentially have viable virus. This may cause disseminated infection in severely immunocompromised patients, and live vaccines are therefore generally avoided.

Inactivated vaccines do not contain live virus and cannot cause disseminated infection; therefore, they are safer. However, many inactivated vaccines contain adjuvants, which might theoretically increase the risk of rejection and/or graft-versus-host disease (GVHD) in solid organ transplant (SOT) and allogeneic hematopoietic stem cell transplant (HSCT) recipients, respectively. The second consideration is efficacy: Immunocompromised patients may not mount the expected immune response to a vaccine and may therefore derive less benefit.

As a general principle, vaccines should be administered prior to initiation of immunosuppression whenever feasible (eg, patients being listed for SOT should be vaccinated prior to transplant). Live vaccines should be administered 4 weeks or more prior to initiation of immunosuppression, and they should especially be avoided within 2 weeks prior to immunosuppression given the risk of developing disseminated disease. Inactivated vaccines should be given at least 2 weeks prior to immunosuppression to allow time for an adequate immune response.

In this article, we will discuss the specifics of VZV and HPV in immunocompromised patients, with a specific focus on vaccine safety and efficacy in this population.

The Table gives a summary of recommendations by type of immunosuppression.

PRIMARY VARICELLA VACCINE

Immunocompromised patients who contract primary varicella infection are at risk for disseminated disease, and they have a several-fold increased risk of death compared with their immunocompetent counterparts.

The first varicella vaccine was approved in 1995 for the prevention of primary VZV infection in susceptible children and adults. It is available in 2 formulations, both of which are live attenuated: a single-antigen formulation (VAR; Varivax), licensed for use in patients 12 months or older, and a combination formulation with measles, mumps, and rubella (MMRV; ProQuad), licensed only for use in patients aged 12 months to 12 years.

MMRV contains a 7-fold higher dose of varicella antigen than the single-antigen formulation, and it is not recommended for use in any immunocompromised population. VAR is given as 2 doses at ages 12 to 15 months and age 4 to 6 years for children, and 2 doses at least 4 weeks apart for patients 13 years and older.

VAR is recommended prior to immunosuppression for patients without evidence of varicella immunity, as long as it can be given ≥4 weeks prior to starting immunosuppression. It is also recommended for patients with HIV and CD4 greater than 200 cells/mm³, and for patients with primary immune deficiencies without defects in T-cell–mediated immunity. It can be considered for patients on long-term low-level immunosuppression (ie, patients receiving steroids equivalent to ≤ 20 mg of prednisone daily; patients on low-dose methotrexate or azathioprine).

As a live vaccine, it is contraindicated in patients who are highly immunosuppressed, including SOT and HSCT recipients. There have been reports of disseminated varicella due to the vaccine in this population.

VAR has been shown to be safe, effective, and immunogenic in children with HIV and CD4 percentages of at least 15%, Data on the immunogenicity of the vaccine in the other immunocompromised populations who can safely receive it are lacking.

ZOSTER VACCINES

Immunosuppressed patients are similarly at increased risk of disseminated infection and complications of herpes zoster. Two zoster vaccines exist but only 1 remains available in the United States. No longer available is the older of these, known as zoster vaccine live (ZVL; Zostavax), which was approved in 2006. A live attenuated vaccine, ZVL contains 13 to 44 times as much VZV antigen as VAR.

The newer zoster vaccine, available since 2017, is called recombinant zoster vaccine (RZV; Shingrix) and is a recombinant glycoprotein E vaccine. Systematic reviews suggested that RZV is more effective than ZVL in reducing the incidence of herpes zoster, and RZV is now preferred in most clinical contexts. Zoster vaccination is indicated for immunocompetent patients 50 years and older. There is no evidence for earlier vaccination in immunocompromised populations, with the exception of patients who have undergone autologous HSCT: autologous HSCT recipients 18 years and older may receive the RZV series starting 50 to 70 days post transplant, on the strength of a 2019 randomized controlled trial (RCT) showing RZV vaccination to be both safe and effective in reducing the incidence of herpes zoster in this population. Like other live vaccines, ZVL is contraindicated in many immunocompromised patients; it can be considered for patients with anticipated or low-level immunosuppression and for patients with HIV and CD4 200 cells/mm³ or greater. In the latter group, it has been shown to be safe and immunogenic.

For patients with higher-level immunosuppression, RZV is generally considered relatively safe, although for SOT and allogeneic HSCT recipients, there is a theoretical risk that the immune activation generated by the vaccine adjuvant could increase the risk of organ rejection or GVHD. A recent
RCT enrolling renal transplant recipients 4 to 18 months post transplant found that RZV induced an immunologic response without increasing the incidence of adverse events, including rejection; a similar study in lung transplant recipients is ongoing.15

For now, the current recommendation of the American Society of Transplantation and Infectious Diseases Community of Practice is that RZV use for posttransplant patients be determined on an individual basis using clinical judgment.16 Data for RZV use in allogeneic HSCT recipients are lacking. RZV has been shown to be safe and immunogenic in patients with HIV,17 and it is the preferred zoster vaccine for this population (although an official recommendation from the US Department of Health & Human Services is pending).

**HPV VACCINE**

The HPV vaccine has been available since 2006 for the prevention of HPV-related cancers (eg, cervical, anal, vulvar, vaginal, and oropharyngeal cancers) and genital warts.

Previous iterations have included a quadrivalent and a bivalent formulation; the formulation currently available in the United States is a 9-valent vaccine (Gardasil 9) and is recommended for unvaccinated immunocompetent females and males starting when aged 11 to 12 years, through 26 years.

<table>
<thead>
<tr>
<th>Table. Recommendations for VZV and HPV Vaccination by Type of Immunosuppression 3,4,11,16,24, 25</th>
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<tbody>
<tr>
<td><strong>VAR</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
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<td><strong>Schedule</strong></td>
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<tr>
<td><strong>Prior to planned IS</strong></td>
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<tr>
<td><strong>SOT recipients</strong></td>
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<td><strong>HCV recipients</strong></td>
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<tr>
<td><strong>HIV</strong></td>
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<tr>
<td>CD4&lt;sub&gt;+&lt;/sub&gt; 200 cells/mm³</td>
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<tr>
<td><strong>Chemotherapy</strong></td>
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<tr>
<td><strong>Primary immunodeficiency</strong></td>
</tr>
<tr>
<td><strong>Long-term low-level IS1</strong></td>
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</tbody>
</table>

*Patients who have previously received ZVL should still get RZV if no contraindications.

8 Acceptable evidence of varicella immunity is: documentation of 2 doses of varicella-containing vaccine ≥ 4 weeks apart; diagnosis or verification of history of varicella or herpes zoster by a health care provider; laboratory evidence of immunity or disease. Although having been US-born before 1980 is considered evidence of immunity in immunocompetent persons, this is not true for immunocompromised populations.1

9 Consider for auto-SCT recipients 18 years or older.

10 Give 2-dose series 24 months post transplant if neither GVHD nor ongoing immunosuppression is present, and 8-11 months after last dose of IV Ig. Recommended only for patients without ongoing GVHD, who are off immunosuppression, at least 8-11 months after last dose of IV Ig. Some data support giving at 50-70 days post transplant for auto-SCT recipients only.12

11 Although official recommendation from HHS is pending, many clinicians are administering RZV to patients with HIV. Can give 3 months post chemotherapy and 6 months post anti-B-cell biologics.11

12 Recommended only for patients without ongoing GVHD, who are off immunosuppression, at least 8-11 months after last dose of IV Ig. Some data support giving at 50-70 days post transplant for auto-SCT recipients only.12

13 Defined as steroids ≤ equivalent 20 mg prednisone/day, methotrexate ≤ 0.4 mg/kg/week, azathioprine ≤ 3 mg/kg/day, or 6-mercaptopurine ≤ 1.5 mg/kg/day.1

14 Acceptable evidence of varicella immunity is: documentation of 2 doses of varicella-containing vaccine ≥ 4 weeks apart; diagnosis or verification of history of varicella or herpes zoster by a health care provider; laboratory evidence of immunity or disease. Although being US-born before 1980 is considered evidence of immunity in immunocompetent persons, this is not true for immunocompromised populations.1

15 RZV use for posttransplant patients be determined on an individual basis using clinical judgment.16

16 Data for RZV use in allogeneic HSCT recipients are lacking. RZV has been shown to be safe and immunogenic in patients with HIV,17 and it is the preferred zoster vaccine for this population (although an official recommendation from the US Department of Health & Human Services is pending).

The vaccine is FDA approved for use through 45 years, and the Advisory Committee on Immunization Practices recommends shared decision-making for patients aged 26 to 45 years.18 For immunocompetent patients 11 years or older, and for all immunocompromised patients, it is given as a 3-dose series, at 0, 1 to 2, and 6 months. Immunocompromised patients are at significantly elevated risk of HPV-related cancers,19 and because the vaccine is considered safe, immunocompromised patients should be vaccinated according to the usual age guidelines.

In patients with HIV, the quadrivalent vaccine is well tolerated and produces high rates of seroconversion in patients both on and off antiretroviral therapy.20,21

Although immunogenicity is lower in patients with CD4 < 200 cells/mm³, seroconversion rates are still in the 70% to 90% range, depending on the serotype.22

Data for immunogenicity in patients with immunocompromising conditions other than HIV are more limited. A study of the quadrivalent HPV vaccine in 50 SOT recipients found that the vaccine series produced seroconversion in 53% to 68% of subjects, in contrast to 97% to 99% of immunocompetent patients in prior studies.23

**CONCLUSIONS**

Immunocompromised patients have a higher burden of VZV- and HPV-associated disease. As such, immunization becomes a key strategy to prevent the occurrence of disease. Guiding principles for the administration of vaccines include as follows:

- Administer vaccines 2 to 4 weeks before solid organ transplantation.
- If this is not possible, give vaccines (or missed doses) 3 to 6 months following solid organ transplantation to maximize productive antibody response.
- In general, do not use live vaccines (such as ZVL) in immunocompromised patients.

For VZV, we recommend RZV whenever possible as it is safe (inactivated virus) and effective. For autologous HSCT patients, we recommend RZV for recipients 18 years and older. For all other immunocompromised patients, we recommend RZV for those 50 years or older, administered prior to solid organ transplant if possible.

Fewer data exist for patients who have received solid organ transplants and for autologous HSCT recipients, so we recommend RZV vaccination on an individual basis (Table). For HPV, we recommend offering the 9-valent vaccine to all immunocompromised patients aged 11 to 26 years. ▲

References are available at ContagionLive.com.
Antiretroviral Therapy for HIV Infection

BY GINA BATTAGLIA, PHD

The efficacy of antiretroviral therapy (ART) has improved in recent years, but metabolic adverse effects (AEs), cost, and adherence remain key barriers to treating individuals living with HIV infection, according to participants in a Contagion® Peer Exchange panel, moderated by Joseph Eron, MD. During the discussion, participants considered the importance of rapid initiation of HIV treatment, factors to consider when choosing an ART regimen, ART’s safety profile and costs, relevant issues when switching ART regimens in asymptomatic patients, virologic failure or rebound, and resistance or intolerance to ART.

RAPID INITIATION OF HIV TREATMENT WITH ART

Allison Agwu, MD, ScM, said that the primary goal of ART is to get the virus to undetectable levels (<20 copies per mL) to preserve the patient’s immune system, prevent immune suppression and its sequelae, and decrease the risk for transmission. However, she added that the psychological benefit of starting therapy should not be overlooked. Colleen Kelley, MD, MPH, said that the undetectable equals untransmissible (U=U) message has been “life-changing” for patients in terms of reducing concerns about transmission and removing the stigma around HIV prevention and care, and Agwu added that this feeling of empowerment can be particularly helpful for the patients who feel unempowered in other areas of their lives.

“People feel better that they’re doing something to actually take control of their health, that U=U,” Agwu said. “It’s really a powerful message for themselves and empowering for individuals. It should be part of the equation when we think about what the benefits are in getting people started as soon as possible.”

Kelley also emphasized the importance of starting ART as soon as possible to improve likelihood of adherence. “People who receive antiretroviral therapy as soon as they are diagnosed are able to stay on antiretroviral therapy and adhere to the regimen a little bit better than folks who are told, ‘Come back in 2 weeks, and we’ll start your medicines then,’” she said.

However, Kelley added that implementation of rapid-start programs is resource-intensive, which presents a major practical challenge in many settings. “We don’t necessarily have the financial support to get the medications. Plus, we often have folks who are dealing with many other hardships in their lives, like housing and substance use, and childcare and jobs, and lack thereof,” said Kelley. “Having to deal with that whole person before they’re even ready to get on this new medication and deal with this new diagnosis is challenging.”

While Ian Frank, MD, agreed that the rapid start is ideal from a physiologic perspective, he added that some patients may not be ready to commit to starting ART. “We’ve got to convey the message that once they start, they’ve got to continue, and they’ve got to be ready for that,” he said. “Because of the complexities of the lives of people living with HIV infection, sometimes their priority is not their disease. Other factors are higher priorities—their partners, their housing stability, their kids—and we’ve got to respect that.”

FACTORS CONSIDERED IN CHOOSING AN INITIAL HIV THERAPEUTIC REGIMEN

The US Department of Health and Human Services (HHS) and the International Antiviral Society–USA guidelines recommend starting with an integrase inhibitor, such as dolutegravir, bictegravir, or raltegravir, plus 2 nucleoside reverse transcriptase inhibitors.2 The IHS guidelines have also added fixed-dose dolutegravir/abacavir/lamivudine as an option for initial treatment, and the phase 3 TANGO trial showed that switching to this...
A 2-drug combination was noninferior in maintaining virologic suppression for patients who reached virologic suppression (<50 copies/mL) on a tenofovir alafenamide (TAF)-based regimen of 3 or 4 drugs.3 “Almost everybody who takes these drugs consistently gets their viral load to an undetectable level,” said Frank. “We have safe, potent combinations that will work effectively as long as people take them.”

Agwu said that consideration of the long-term sequelae when choosing a treatment regimen is particularly important for adolescent patients (to reduce the risks of long-term effects on bone density and kidney function) and for women of childbearing age (because of concerns about neural tube defects associated with dolutegravir). Although treatment resistance is less common than it has been in the past, Agwu also said that adherence is an important consideration and may guide the decision to choose a less complicated regimen.

SAFETY PROFILE AND COSTS OF INITIAL HIV THERAPEUTIC REGIMEN
Kelley said that while metabolic alterations and weight gain have been observed historically with ART, some of the new integrase inhibitors promote notably rapid and substantial weight gain that has prompted her to switch some individuals off regimens that include these agents. “I do believe it is an issue for a minority of patients, but you will see it if you treat enough people with the integrase inhibitors,” she said. “It doesn’t necessarily change what I’m going to do to start, but my awareness is heightened.”

These clinical observations are also supported by data from the ADVANCE trial, which showed that weight gain was higher with TAF- and tenofovir disoproxil fumarate (TDF)-based regimens than with the standard regimen (TDF, emtricitabine, and efavirenz) and was also higher among female patients than male patients who received the same regimen.4 “I tell my patients this: Now that their body is not fighting HIV and burning more calories in the immunologic battle to control their infection, they’ve got to cut down the amount of food that they’re eating in order to be metabolically at equilibrium,” said Frank. “Occasionally you do need to switch people off and use an alternative regimen.”

Drug costs are also important to consider when treating individuals and reducing transmission, according to the panelists. “There’s a federal initiative to end the HIV epidemic, and the key pillars of that initiative are treatment for everyone who needs it and preexposure prophylaxis (PrEP),” said Julia Marcus, PhD. “Antiretroviral medications are really the solution all around, but they’re incredibly expensive. And the estimates of the costs that it would take to end the epidemic are potentially beyond what society can withstand.”

Marcus noted that the United States Preventive Services Task Force has recommended that private payers waive cost-sharing for all PrEP medications. According to Marcus and Eron, this may encourage use of PrEP among individuals at high risk for exposure who struggle with motivation to figure out the complexities of coverage. “Especially with PrEP, small barriers can be a huge disincentive,” said Eron.

SWITCHING THERAPIES IN PATIENTS WHO ARE SUCCESSFULLY TREATED
When switching therapies, Frank said that he aims to make the regimen more convenient and flexible and tries to switch asymptomatic patients to a preferred regimen if they are not currently on one. He added that resistance testing is also available to test for archived mutations in HIV DNA for patients who have failed to respond to a prior therapy or have an unclear history, with the goal to detect baseline resistance prior to switching therapy.

Kelley said that once patients have adequate viral suppression, she typically uses 2-drug combinations to reduce the pill burden and to eliminate drugs with long-term AEs or interactions with the patient’s other medications. “My mantra has been, ‘[Prescribe] the simplest, safest regimen that fits in a person’s life,’” concluded Eron.

Virological Failure or Rebound to HIV Therapies
Agwu said that rates of biological or virological rebound seem to have gone down with the use of new regimens, and she noted that failure or rebound likely indicates pragmatic issues (such as failure to get insurance coverage for the drug or to receive it from the pharmacy), drug interactions, or difficulty with adherence to daily dosing. She added that a team approach (one that includes pharmacists, nurses, and specialists) and ensuring the patient’s emotional comfort is important when trying to identify the source of virologic failure or rebound and addressing barriers in obtaining or taking their medication.

Kelley added that the need to test for drug resistance can be assessed based on conversations with the patient. “If they’ve just been off [their regimen], I’m less concerned about resistance [than with] someone who really does sound as though they’ve been trying to take it, that they’ve been getting it in their body on a somewhat consistent basis,” she said.

Frank added that patients may be more willing to discuss adherence with a nurse practitioner or social worker than with their physician. “Patients don’t want to tell me that they’ve done something that they know I’ll be a little unhappy about,” he said. “They don’t want to disappoint me.”

Drug Resistance or Intolerance to HIV Therapy
Frank said that in his experience, the prevalence of drug resistance has been decreasing, with virological suppression rates of 90% even in individuals who use injectable drugs daily. He attributed this reduction to the higher barrier to resistance with many of the drugs most frequently used, such as boosted protease inhibitors and next-generation integrase inhibitors. However, he said that he does encounter patients with multidrug resistance, including some patients who were started on single nucleoside therapy in the past. “For some patients, I am wondering when I will use the next-generation drugs that are available to us, and how to time that [initiation] in a way that’s most likely to be successful, with a long-term strategy in mind,” he said.

“We’ve got to convey the message that once they start, they’ve got to continue, and they’ve got to be ready for that. Sometimes their priority is not their disease...and we’ve got to respect that.”

—Ian Frank, MD

Agwu added that she often considers resistance testing in 2 groups of patients: those who have received elvitegravir-based regimens, because she has observed an accumulation of integrase mutations that can affect the efficacy of cabotegravir; and patients who have immigrated from Africa or the Caribbean, where patients receive different regimens and are often not tested for resistance or viral load.

Kelley added that ibalizumab, a humanized immunoglobulin G4 monoclonal antibody that binds to the CD4 receptor to prevent entry of HIV into cells, has demonstrated efficacy for patients who have multidrug-resistant infection that has failed to respond to multiple antiviral therapies and have no other therapeutic options. However, she noted that a very small proportion of patients in her practice (fewer than 5 of approximately 6000 active patients) are eligible for the antibody, and Eron said that it is more likely to be effective with other medications than as monotherapy. ▲

References are available at ContagionLive.com.
GETTING YOUNGER PEOPLE ON PREP

In an interview with Contagion® during International AIDS Society (IAS) AIDS 2020 Virtual Sessions, Philip Peters, MD, medical officer of the California Department of Public Health, discusses why it's critical for the future of HIV prevention for programs like the California Preexposure Prophylaxis Assistance Program (PrEP-AP) to reach younger at-risk persons now.

contagionlive.com/link/2540

THE SOCIAL HURDLES OF HIV AWARENESS AND PREVENTION

Hugh Klein, PhD, of the Kensington Research Institute, explains how HIV, its sexual transmission, its at-risk populations, and the marketing of its treatment and prevention have been victim to it all being "an American stigma."

contagionlive.com/link/2541

HIV SCREENING: ARE PRIMARY CARE PHYSICIANS FOLLOWING CDC GUIDELINES?

Epidemiologist Marc Pitasi, MPH, with the US Centers for Disease Control and Prevention, talks about facilitators of routine HIV screening among primary care physicians after sharing results from an online panel of US health care providers at AIDS 2020.

contagionlive.com/link/2542
In Low-Income Nations, Pharmacies Can Play Important Role for Patients With HIV

BY JOHN PARKINSON

Adult patients living with HIV who were virologically suppressed remained virologically stable with optimal adherence and retention in care when they willingly chose to refill prescriptions in community pharmacies (co-pharm) after transitioning away from hospital settings, according to results of a new study.

An overwhelming majority (98%) of the participants were retained in care, and 85% had optimal adherence.

"Patients remained virologically stable with optimal adherence and retention in care," the investigators wrote.

These findings were presented at the International AIDS Society (IAS) AIDS 2020 Virtual Sessions in July.

In low-income countries with overcrowded hospitals, community pharmacies can relieve the burden and help patients adhere to their regimen, thus offering a viable alternative to patients who need to maintain their medication and keep stable.

This study was done in Southern Nigeria from January 2017 to June 2019. It included 2938 patients who had a viral load of less than 20 copies/mL, and were recruited and enrolled in a community-based program where patients refilled prescriptions in a registered co-pharm. Baseline log viral load (VL) was 3.7; no significant difference in median VL before and after participants devolved to the co-pharm. The before median VL = 2.9 log copies/mL versus after median VL = 2.9 log copies/mL.

Twenty-nine public hospitals and 64 registered community pharmacies were recruited. This was a nonrandomized intervention study.

Sociodemographic and treatment data (medication regimen, prescription refill, retention in care and viral load) were collected. Baseline virologic suppression data after 12 months of devolvement.

The World Health Organization has recommended using community-based models for scaling up HIV treatment.

This [study] suggests that patients who are already virologically suppressed may remain stable even if they are devolved from the hospitals to the co-pharm," the investigators concluded. 

Overdose Deaths Encroach on Life Expectancy Gains Among People Living With HIV

BY GRANT GALLAGHER

People living with HIV are disproportionately affected by social problems pertaining to criminalized substances, such as overdose and chemical dependence, and amid the opioid epidemic these baseline challenges compound enough to mitigate gains in treatment access.

Like so many places throughout the world, the Canadian province of British Columbia has been hard hit by overdose deaths in recent years, culminating in the declaration of a public health emergency there in 2016.

A team of experts from the University of California, the University of British Columbia, and the British Columbia Centre for Excellence in HIV/AIDS assessed the impact of drug overdoses on people living with HIV in British Columbia, identifying factors associated with mortality by using competing risk methodology.

Patients in the data set began treatment with antiretroviral therapy between April 1996 and December 2017, through the publicly funded drug treatment program.

Overall, the 10,362 people living with HIV in the analysis had a median age of 40 years and follow-up of 6.93 years. Of these individuals, 26% were identified as using criminalized injection substances. The largest statistical loss in life expectancy occurred during the 2014-2017 overdose wave. The life expectancy for the greater patient population was 55 years in this period; when overdose deaths are excluded, the life expectancy increases a full decade to 65 years of age. Results were presented in July at the International AIDS Society (IAS) AIDS 2020 Virtual Sessions.

Authors identified the “harm reduction era” of 2002-2007 as having a lower overdose hazard for people living with HIV than during the 2014-2017 overdose wave. The team concluded that survival gains for people living with HIV in British Columbia have been blunted by the overdose crisis, a conclusion that likely holds in other places plagued by the opioid epidemic. 

annette shaff/Adobe Stock
A Case of Influenza H1 2009 With Severe Rhabdomyolysis and Secondary Acute Renal Failure With Liver Involvement

Although the reason is unknown, viral illnesses can cause rhabdomyolysis. Here is an examination of this ailment with influenza.

BY MANI KHORSAND ASKARI, MD, CMQ; HODA SHABPIRAY, MD; AND CAYTLIN DEERING, DO, AAHIVS

FINAL DIAGNOSIS: H1 2009 INFLUENZA WITH MULTIPLE ORGAN INVOLVEMENT

HISTORY OF PRESENT ILLNESS
An African American man, aged 22 years, was admitted to the hospital with complaints of progressive weakness and hematuria. One week prior to admission, he had begun developing upper respiratory tract symptoms, including rhinorrhea and sore throat, as well as fever and chills. Four days before admission, he started experiencing muscle pain, mainly over his cervical and paraspinal muscles, as well as pain in bilateral legs. He did not take any medications, including over-the-counter pain relievers, for these symptoms.

PAST MEDICAL HISTORY
No significant past medical history.

KEY MEDICATIONS
None

EPIDEMIOLOGICAL HISTORY
He reported that his 4 children (aged 1, 2, 4, and 7 years) experienced similar symptoms preceding the onset of his illness. He denied alcohol or drug use, but he was an active smoker before this illness with 1.5 pack-year smoking history.

PHYSICAL EXAMINATION
Upon admission to the hospital he was found to be afebrile, with blood pressure of 140/88 mm Hg. He was in no distress, with a clear lung exam, but he was tachycardic, with a heart rate of 105 beats per minute.

STUDIES
Laboratory studies demonstrated white blood cell count 5.9, creatinine (Cr) 1.59 mg/dL (normal range, 0.6-1.3 mg/dL; all subsequent figures in parentheses are normal ranges), calcium ionized 3.3 mg/dL (4.5-5.3 mg/dL), creatine phosphokinase (CPK) 407,176 U/L (24-195 U/L), myoglobin 33,673 ng/mL (17.4-105.7 ng/mL), C-reactive protein (CRP) 7 mg/dL (<0.9 mg/dL). Urinalysis showed zero red blood cells with large hemoglobin and protein of 300 mg/dL. Rapid strep testing of throat culture collected on the day of admission was negative for group A streptococcal infection. Chest x-ray did not show any infiltrate or acute abnormality, and abdominal CT scan done in the emergency department for hematuria did not demonstrate nephrolithiasis or other abnormalities.

Liver function tests (LFTs) done 6 hours after admission showed aspartate aminotransferase (AST) 1540 U/L (0-41 U/L), alanine aminotransferase (ALT) 286 U/L (0-40 U/L), alkaline phosphatase (ALP) 50 U/L (39-130 U/L), albumin 3.3 g/dL (3.2-5.3 g/dL), and total bilirubin 0.6 mg/dL (0.3-1.2 mg/dL). As part of the workup for acute kidney injury (AKI) by nephrology, all of the following were checked and were negative: thyroid panel, antinuclear antibody, HIV, C and P ANCA, anti-JO-1, complement, and anti-GBM antibody. Uric acid was 10.1 mg/dL (2.6-7.2 mg/dL), and random urine protein was 6260 mg/L with protein (Pr)/Cr ratio of 9.2. Serum protein electrophoresis (SPEP) and urine protein electrophoresis both were negative. Blood cultures and urine culture remained negative. Kidney ultrasound showed normal kidney size and no signs of hydronephrosis. Respiratory culture from the date of admission turned positive for Streptococcus pneumoniae. Due to abnormal LFTs, with AST/ALT ratio more than 2, hepatitis panel was obtained; it reported negative other than positive immunoglobulin G for hepatitis A.

CLINICAL COURSE
On the day of admission (day 0 in Table 1 and Figure [online]), he noticed red discoloration of the urine along with worsening weakness and muscle pain. He was admitted to the general medical floor with the diagnosis of rhabdomyolysis.

On day 1 of admission, Cr was 2.05 and CPK was 670,516. Both values continued to rise, with hemodialysis initiated when levels were 4.89 (Figure) and 1,271,160 (Table 2), respectively. AST peak was 4100 and ALT peak was 1043, with highest total bilirubin of 0.8 and lowest albumin level of 2.9; ALP stayed within the range of 44 to 51 and gamma-glutamyl transferase was 15 U/L (9-64 U/L). CRP also increased to 17.1 mg/dL.

A respiratory pathogen panel showed positivity for influenza H1 2009, and infectious diseases consultation was obtained. The patient was started on oseltamivir, dose-adjusted based on kidney function. For the positive streptozyme, he received 1 dose of intramuscular benzathine penicillin to prevent complications of probable recent strep infection. The patient received 2 days of intravenous (IV) ceftriaxone for positive S pneumoniae in the sputum; however, this was discontinued as his examination and clinical picture were not consistent with bacterial pneumonia. Nephrology consultation was obtained, and
the patient received aggressive intravenous rehydration. The patient was continued on IV fluid therapy with bicarbonate, as well as febuxostat for hyperuricemia. A Foley catheter was placed due to difficulty with mobility secondary to severe muscle pain. Urine output was adequate for the first 3 days of admission. Due to rising Cr and development of dyspnea, the patient was transferred to the intensive care unit on day 4 of admission and was subsequently transferred to a facility with liver transplant capabilities. The patient required intermittent hemodialysis. His CPK and ALT/AST continued to trend downward after the transfer.

TREATMENT AND FOLLOW-UP
After 10 days of supportive care and intermittent hemodialysis (HD) for AKI, the patient was readmitted to our facility due to patient preference. He did not require liver transplantation. After return to our facility, CPK was 1433, Cr 6.5, AST 43, ALT 53, albumin 3.4, and total bilirubin 0.6. International normalized ratio (INR) stayed normal for the duration of admission. After 4 days, ALT and AST both returned to normal levels of 33 and 27, respectively.

The patient continued to require intermittent HD and was able to be discharged with follow-up with nephrology and daily labs to direct HD treatment. He did not need any further hemodialysis 20 days after his discharge, and his Cr normalized.

DISCUSSION
Although various viral illnesses can cause rhabdomyolysis, influenza is the most common. The exact mechanism is not known. Rhabdomyolysis is breakdown of muscle with release of CPK, aldolase, AST, and ALT into the bloodstream. In their study, Sellers et al reported 27 cases and a case series of influenza A and B with rhabdomyolysis. The onset of CPK rise was between 1 and 10 days (mean, 7 days); the highest reported CPK was greater than 100,000 U/L, and higher CPK was associated with worse outcomes. Of 27 reported cases, 4 were positive for the H1 2009 strain. Of the 27, 16 had renal failure and 12 required hemodialysis. Ten of the 12 experienced full renal recovery, 1 died, and 1 needed HD beyond hospitalization.

Our patient’s initial CPK was 407,176 U/L on the day of admission, which was about 5 days after onset of his upper respiratory symptoms. CPK peaked at 1,271,600 U/L on the fourth day of admission, approximately 9 days after symptom onset. Rumnstrom et al reported an association between fever spikes and rise in CPK. However, we did not observe any correlation between rise in CPK and fever spikes, as our patient stayed afebrile for the duration of the admission. Mortality is high in influenza-related rhabdomyolysis, especially in the presence of renal failure. In patients who require HD, mortality could approach 40%.

Acute kidney injury in severe influenza infection is multifactorial, and pigment-induced nephropathy secondary to rhabdomyolysis plays an important role. If AKI occurs, it is typically seen early in the disease course. In one study, 78.1% of patients with severe influenza infection developed AKI less than 72 hours after ICU admission. Observational studies reported that the incidence of AKI in such patients ranged from 18% to 66%, with up to 22% requiring HD.

Our patient developed nonoliguric AKI on the day of admission. Cr continued to rise, and due to the decrease in urine output with no response to diuretic therapy and ensuing volume overload, he was started on and remained on HD with slow but complete recovery of kidney function after discharge. Risk factors for developing AKI include obesity, presence of chronic kidney disease prior to illness, and older age. Our patient had a high BMI (31.82 kg/m²) as a risk factor for AKI in addition to influenza infection.

The underlying mechanism for liver injury in influenza infection is not fully understood. Hypoxia with oxygen saturation less than 95% has been reported as a strong risk factor for liver injury. In one study, 58% of patients with H1N1 had abnormal liver enzymes. Elevaton of liver enzymes is reported to be positively correlated with elevation of CRP. Zaroglouildis et al reported no difference regarding LFTs in subgroups of their patients with positive or negative H1N1 testing, and the rate of hypoxemia was the same between 2 subgroups. They also reported a 12% prevalence of abnormal LFTs in H1N1-positive patients, which was lower than reported in other studies.

Our patient had elevated liver enzymes since the day of admission, with AST higher than ALT and with AST peak of 4100 U/L and ALT 1043 U/L on fourth day of admission. Complete normalization occurred within 24 days. We did not observe any change in total bilirubin, INR, or ALP. There was mild decrease in albumin; the lowest level during admission was 2.9 g/dL. Our patient never showed any signs of hypoxemia and did not need oxygen therapy; oxygen saturation stayed greater than 95% during hospitalization.

In conclusion, H1 2009 influenza A can manifest with different extrapulmonary adverse effects and serious consequences. These include rhabdomyolysis, secondary AKI, and severe elevation in liver enzymes; all must be monitored closely and treated accordingly. Paying close attention to the potential development of these adverse effects can prevent further morbidity and mortality of influenza H1 2009.

References are available at ContagionLive.com.
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