In the News
Comparing the Accuracy of COVID-19 Tests During Omicron
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2022 ESPID Conference
Neutralizing Antibodies in Children a Year After COVID-19 Infection
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HIV/AIDS
Gender-Affirming Care in Persons Living With HIV
by Jenna E. Januszka, PharmD; Renata O. Smith, PharmD, AAHIVP; Melissa E. Badowski, PharmD, MPH, FCCP, FIDSA, BCIDP, BCPS, AAHIVP

Gender-affirming care consists of comprehensive services including medical, surgical, mental health, and social services to support and affirm an individual’s gender identity. Gender identity refers to a person’s individual experience of gender.1,2 A transgender, gender nonconforming, gender nonbinary, or genderqueer person’s gender identity differs from the sex they were assigned at birth.3

In 2019, approximately 1 million individuals living in the United States identified as transgender or gender nonconforming.4 Transgender individuals made up approximately 2% of all new HIV diagnoses that year.5 Transgender persons are at high risk for acquiring HIV, with approximately 14% of trans women and 3% of trans men already living with HIV and even higher rates among racial minority transgender

Acute Infections
Invasive Nontyphoidal Salmonellosis: An Antimicrobial-Resistant Foe
by Mackenzie Keintz, MD, and Jasmine R. Marcelin, MD, FACP, FIDSA

Salmonella enterica subspecies enterica is a motile, Gram-negative bacteria divided into typhoidal serotypes (Salmonella Typhi and Paratyphi) and nontyphoidal serotypes (NTS). Although there are more than 2500 known NTS, approximately 100

Emerging & Re-Emerging Infections
A Viral Colonial Legacy: HIV, Monkeypox Emerged Due to Ongoing Colonial Viral Neglect
by Ngofeen Mputubwele and Joseph Osmundson, PhD

In mid June, one of our good friends was sick with monkeypox (MPX) but was unable to get tested. He was in immense pain and couldn’t sleep, but only had proctitis and internal lesions.

Multidrug-Resistant Infections
Will We Ever See Oral Carbapenems for ESBL Urinary Tract Infections?
by Theodore S. Rader IV, MD, MS

Following the publication of the ADAPT-PO trial (NCT03788967), which demonstrated noninferiority of oral tebipenem pivoxil hydrobromide (tebipenem HBr) to intravenous (IV) ertapenem, the FDA announced that the reviewed data were insufficient for approval of oral

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Gender-affirming hormone therapy (GAHT) consists of administration of exogenous hormones and suppression of endogenous hormone production, with the goal of obtaining characteristics more congruent with an individual’s gender identity.

(continued on page 16)
The Work Is Never Done

Whether it is investigators creating vaccines and therapies, public health officials trying to prevent the next outbreak (or dealing with a current one), or clinicians trying to provide quality care and good outcomes for their patients—all these health workers do tireless and sometimes thankless work that is never done.

After 2.5 years of COVID-19, a recent declaration of the monkeypox national emergency, and polio in New York, anyone involved in infectious diseases has been inundated to say the least. And this does not include the ongoing work of curing, treating, and preventing bacterial and fungal infections that are becoming increasingly more multidrug resistant. Although these infections may not be front-page daily news, they remain of the utmost importance, and in some cases, a matter of life and death.

Clinicians, public health officials, and investigators can never be afforded complacency when it comes to infectious disease. We are grateful to have these professionals doing what they do to keep us safe and care for us.

I’m reminded of that in the pages of Contagion®. Authors Joseph Osmundson, PhD, and Ngofeen Mputubwele discuss the origins of monkeypox and some of the connotations associated with it in its African origins, as well as the difficulties in trying to treat the current outbreak here in the United States. On the other end of the spectrum, Theodore S. Rader IV, MD, MS, writes about the difficulties of developing oral carbapenem-based antibiotics in urinary tract infection care. The ongoing medical challenges remain, whether health workers dealing with a new threat or an existing one—the work is never done.

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Mike Hennessy Jr
President and CEO
MJH Life Sciences®
EDITOR-IN-CHIEF LETTER

Paxlovid Prescribing by Pharmacists: A New Paradigm

It happened. Months after the Biden administration introduced its “test to treat” program, the US FDA authorized pharmacists to prescribe Paxlovid (nirmatrelvir/ritonavir) for patients with COVID-19 infection.1 This move helps to realize the promise of the test-to-treat program, allowing patients to couple rapid testing with prompt treatment. It is particularly important in areas where access to other health care providers is limited. As with all new programs, this will be a work in progress that will take time to refine, but I think it is a potentially significant step forward.

Some might argue that my perspective is obvious, but from that perspective I can say pharmacists are among our country’s most underused health care resources. US pharmacy education transformed in the early 2000s with the requirement that all schools of pharmacy offer the doctor of pharmacy (PharmD) degree as the sole entry-level degree. This accelerated changes in pharmacy curricula that were already in progress, moving programs based in basic sciences to those that emphasize clinical practice. This move has continued with augmented experiential education, increasingly transitioning students from the classroom to the clinic earlier to prepare pharmacists for less dispensing-focused roles. However, the move to the “all PharmD” degree has not been fully successful in advancing the profession. Clinical positions for pharmacists have indeed proliferated and become common, but these are most established within health systems, and many require additional residency training. Although outpatient clinical pharmacist positions have increased, many community pharmacies have not become the centers of advanced practice that were once envisioned.

The COVID-19 pandemic has highlighted the important roles that pharmacists play in US health care. Pharmacists administered large proportions of vaccinations for COVID-19, and as vaccinations have shifted from primary series to boosters, an increasing proportion of COVID-19 vaccines are given by community pharmacists. Pharmacies have been testing sites throughout the pandemic, offering polymerase chain reaction–based tests before rapid antigen tests (RATs) became widely available, and they serve as points of sale, insurance billing partners, and interpreters of RATs now. Because almost 90% of the US population lives within 5 miles of a community pharmacy,2 expanding access to COVID-19 therapeutics by allowing pharmacists to prescribe can help improve health equity in areas without sufficient other health care practitioners.

The move by the FDA comes with appropriate restrictions, however. Pharmacists must have access to laboratory values to assess patients for liver and renal function and a list of the medications that patients are taking, to screen for drug interactions.1 Of course, pharmacists must be state licensed, but because they cannot practice without a license, this is not a true restriction. More important, any patient whose medical history is too complex for pharmacist management should be referred to another health care provider, and patients with decreased oxygenation or labored breathing should be referred to acute care settings.

Widespread implementation of pharmacist prescribing for Paxlovid is unlikely, and it should not replace prescribing from primary care providers as the primary route of care for COVID-19. For one, pharmacist shortages are occurring throughout the country, and this new role has increased, many community pharmacies have not become the centers of advanced practice that were once envisioned.

As with all new programs, this will be a work in progress that will take time to refine, but I think it is a potentially significant step forward.

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Widespread implementation of pharmacist prescribing for Paxlovid is unlikely, and it should not replace prescribing from primary care providers as the primary route of care for COVID-19. For one, pharmacist shortages are occurring throughout the country, and this new role is not coming with increased reimbursement or relief from traditional pharmacist roles, such as dispensing and providing vaccination. Pharmacists are already busy. However, Paxlovid prescribing is 1 more tool that I am happy to see the FDA deploy to allow antiviral therapy for COVID-19 to reach more patients. Slowly but consistently, we continue to move forward. ▲

References are available at ContagionLive.com.

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

Active member of the Society of Infectious Diseases Pharmacists.
Reduced-Dose Trimethoprim-Sulfamethoxazole Effective in Treating Mild to Moderate Pneumocystis jirovecii Pneumonia

KYLE CROOKER, MD; ELEANOR STEDMAN, MD; SEAN BULLIS, MD; AND ANDREW J. HALE, MD

Pneumocystis jirovecii is a ubiquitous fungus that can cause severe respiratory infection in the immunocompromised host. Patients at risk for Pneumocystis jirovecii pneumonia (PJP) include those on immunosuppressive therapies or those living with HIV/AIDS, organ transplantation, or hematologic malignancy. In areas with a low prevalence of uncontrolled HIV/AIDS, patients with hematologic malignancies constitute the largest group at risk of PJP.

Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for PJP prophylaxis in many patients with hematologic malignancy. TMP-SMX is also the treatment of choice for mild, moderate, and severe PJP. The CDC guidelines recommend a standard dose of 15 to 20 mg/kg daily of the TMP component for adults with PJP but this recommendation is based on weak data extrapolated from pediatric literature. Moreover, adverse events from TMP-SMX are dose dependent, thus the standard doses of TMP-SMX typically used in PJP are frequently associated with significant adverse effects.

A recent meta-analysis of more than 300 patients compared reduced dose (10 mg/kg/d or less of TMP) with the standard dose (15-20 mg/kg/d of TMP) of TMP-SMX in the treatment of mild to severe PJP and revealed no statistically significant difference in mortality (absolute risk difference, −9%; 95% CI, −27% to 8%) but a significant reduction in adverse events with the reduced dose (absolute risk reduction of 18%; 95% CI, −31% to −5%). However, as this analysis included only 63 (14%) patients with hematologic malignancies, the results may not be generalizable to this population. Thus, questions remain regarding the ideal dosing of TMP-SMX in the treatment of PJP among patients with hematologic malignancies.

Hammarström et al examined this issue in their recent manuscript “Treatment With Reduced Dose Trimethoprim-Sulfamethoxazole Is Effective in Mild to Moderate Pneumocystis jirovecii Pneumonia in Patients with Hematologic Malignancies.” The authors completed a retrospective study of adult patients with hematologic malignancies who were treated for probable or proven PJP with TMP-SMX at 6 Swedish university hospitals between 2013 and 2017. Patients were included if they had (1) a hematologic malignancy or prior allogeneic hematologic stem cell transplant, (2) positive immunofluorescence or polymerase chain reaction for Pneumocystis jirovecii in a sputum or bronchoalveolar lavage sample, (3) both typical radiograph findings (ie, diffuse interstitial infiltrates or ground glass opacity) and respiratory symptoms (ie, dyspnea, cough, or hypoxia < 95% oxygen saturation of arterial blood without oxygen therapy), and (4) were treated with TMP-SMX, with an initial dose of 7.5 to 20 mg/kg/day of the TMP component. The reduced-dose cohort was defined as those who received 7.5 to 15 mg/kg/d of the TMP component, and the standard-dose cohort as those who received more than 15 to 20 mg/kg/d of the same, with doses adjusted for renal function. The primary outcome assessed a change in objective respiratory function, measured as the difference in partial pressure arterial oxygen and fraction of inspired oxygen ratio (PaO₂/FiO₂) between baseline and day 8 of TMP-SMX treatment. The secondary outcomes included clinical failure (failure to improve or worsening respiratory status as determined by clinical judgement) or death at day 8, 30-day mortality, and the frequency of adverse events.

A total of 113 patients were included in the study, with 80 patients in the reduced-dose cohort and 33 patients in the standard-dose cohort. Of the 33 patients receiving standard-dose TMP-SMX, 19 (53%) were transitioned to reduced-dose therapy between days 3 and 7 of treatment. The study population was predominantly men (80/113, 71%), older (median age 68 years, range 22-88), had normal or mildly reduced renal function (106/113, 95%) with a creatinine clearance of greater than 50, and hypoalbuminemia less than 30 g/L (77/113, 83%). The 2 study groups were comparable, aside from the standard-dose group having an ECOG performance status of greater than 3 in 27% (9/33) compared with 10% (8/80) in the reduced-dose group (P = .04).

For the primary outcome, the change in PaO₂/FiO₂ by day 8 was a mean (SD) of +70.2 (+104.2) mm Hg in the reduced-dose group compared with a mean (SD) of +83.8 (+107.5) mm Hg in the standard-dose group, which was not a statistically significant difference (P = .5). The secondary outcomes also did not reveal a statistically significant difference between the reduced-dose and standard-dose groups regarding clinical failure or death at day 8 (18% vs 21%, P = .8), overall 30-day mortality (14% vs 15%, P > .9), or adverse events (25% vs 33%, P = .4).

The study had several limitations, including a small sample size and its retrospective nature. Although there were no significant differences in mortality between the 2 treatment groups regarding severe PJP, the authors advise caution that a relevant difference cannot be ruled out. There is also concern for selection bias, as patients with a worse baseline prognosis were more likely to have standard-dose TMP-SMX.

Despite the limitations, this study included a well-defined cohort of patients from numerous institutions and was the first of its kind to analyze reduced-dose TMP-SMX for treatment of PJP in patients with hematologic malignancies. The authors demonstrated that reduced-dose TMP-SMX can be effective in mild to moderate PJP within the study population. Ultimately, this important study revealed the need for prospective, randomized investigations to establish updated guidelines for the treatment of PJP.

References are available at ContagionLive.com.

Highlighted Study
Is Eravacycline Ready for Prime Time Against CRAB Pneumonia?

by J. Drew Zimmer, PharmD, BCPS

A cinetobacter baumannii is a nonfermenting, oxidase-negative, Gram-negative coccolidus that has been associated with health-care–acquired infections, including pneumonia. One of the challenges for clinicians is that A baumannii employs multiple antibiotic-resistance mechanisms, making selection of antimicrobial therapy difficult.1 Compounding this, carbapenem-resistant A baumannii (CRAB) infections result in disproportionately increased mortality compared with other carbapenem-resistant pathogens.2 In a 2019 meta-analysis that evaluated 27 studies, including patients with multidrug-resistant A baumannii pneumonia, there was an overall mortality of 42.6%.3 The CDC has classified CRAB as an urgent public health threat.4 Currently, there are no consensus guidelines on the preferred antimicrobial therapy for CRAB infections. Both the Society of Infectious Diseases Pharmacists5 and the Infectious Diseases Society of America6 have offered guidance and reviews of the literature in treating CRAB. Some current recommended agents include β-lactams, polymyxins, aminoglycosides, and tetracyclines. There are currently a few agents in the antibiotic pipeline, but these agents are possibly years away from clinical use, so efficacy data are needed on available agents.

Eradavicycline is a synthetic tetracycline antibiotic that exerts its antimicrobial effect by inhibition of the 30S ribosomal subunit. It is structurally similar to tigecycline but has 2 modifications to the D-ring of its tetracycline core.6 Eravacycline retains activity against both Gram-positive and Gram-negative bacteria, including those that express tetracycline efflux pump and ribosomal protection mechanisms.7 Because of this, eravacycline is an antibiotic that has been touted for possible treatment of difficult-to-treat resistant (DTR) Gram-negative infections.

Scott et al completed a retrospective study evaluating the efficacy of eravacycline in hospitalized patients with pneumonia caused by DTR A baumannii within a 6 hospital health system in Las Vegas and Henderson, Nevada.8 Eravacycline treatment was compared with those receiving best previously available therapy (TABLE) between January 2017 and January 2021. Eravacycline was added to the health system formulary in February 2020. The primary outcome was 30-day in-hospital mortality. Secondary outcomes included clinical cure at day 14, hospital and intensive care unit length of stay, microbiologic cure, and readmission within 90 days with a positive A baumannii respiratory culture. Inclusion criteria included adults (> 18 years old) with a respiratory culture positive for DTR A baumannii who were admitted for pneumonia. DTR was defined as A baumannii that was nonsusceptible to all β-lactams and fluoroquinolones on automated susceptibility testing.9 Of 420 patients who were identified with infection, 93 met inclusion criteria and were included in the statistical evaluation. The primary outcome of in-hospital 30-day mortality was 33% for eravacycline-based therapy and 15% for best available therapy (P = .048). The eravacycline-based therapy group also had lower rates of microbiological cure (17% vs 59%; P = .004) and longer median durations of mechanical ventilation (10.5 days vs 6.5 days; P = .016). The other secondary outcomes also trended toward worse outcomes with eravacycline, although statistical significance was not achieved. A post hoc evaluation identified bacteremia and positivity for SARS-CoV-2 as negatively associated with the primary outcome. When patients with bacteremia were excluded, there were similar 30-day mortality rates (22% vs 16%; P = .506). When patients with both bacteremia and SARS-CoV-2 were excluded, there were no significant differences between the 2 groups in any primary or secondary outcome.

Limitations of the study include its retrospective nature, so the confirmation of a true bacterial pneumonia vs colonization can be very difficult. To hopefully restrict some of this limitation, patients were required to receive antibiotics for greater than or equal to 72 hours prior to inclusion. A small sample size is also a limitation, but the authors concluded that even with this, it was relatively robust because of the inclusion of DTR A baumannii in these patients. A further limitation is that the infection was limited to pneumonia and cannot be extrapolated to other sources of infection.

Results from this study should not necessarily lead to eravacycline-based therapy being utilized as a primary antibiotic selection. It does reaffirm that eravacycline could be considered in DTR A baumannii pneumonia without accompanying bacteremia, but careful consideration must be taken prior to initiating this therapy. This study will hopefully lead to further evaluations of currently available antibiotics to treat CRAB in pneumonia and other infections. ▲

TABLE. Eravacycline treatment as compared to best previously available therapy

<table>
<thead>
<tr>
<th>Eravacycline-based therapy</th>
<th>Best available therapies (n = 66)</th>
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</thead>
<tbody>
<tr>
<td>Eravacycline monotherapy</td>
<td>Tetracycline-based therapy (n = 20)</td>
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<tr>
<td>Eravacycline + β-lactam + colistin</td>
<td>Minocycline/tigecycline + β-lactam + colistin</td>
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<tr>
<td>Eravacycline + β-lactam + aminoglycoside</td>
<td>Minocycline/tigecycline + β-lactam + colistin</td>
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<tr>
<td>Eravacycline + β-lactam + TMP/SMX</td>
<td>Minocycline/tigecycline + β-lactam + quinolone + aminoglycoside</td>
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<tr>
<td>Eravacycline + aminoglycoside</td>
<td>Minocycline + aminoglycoside + colistin</td>
</tr>
<tr>
<td>Eravacycline + colistin</td>
<td>Colistin (IV) + colistin (inhaled)</td>
</tr>
<tr>
<td>Eravacycline + fluoroquinolone</td>
<td>TMP/SMX + colistin (inhaled)</td>
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IV, intravenously; TMP/SMX, trimethoprim-sulfamethoxazole.

References are available at ContagionLive.com.

Highlighted Study

Active member of the Society of Infectious Diseases Pharmacists
Communication Gaps Remain Between Primary Care Physicians, Specialists

By RICHARD PAYERCHIN

Communication gaps remain between primary care physicians (PCPs) and specialists who share patients, despite potential connections through improved electronic health records (EHRs). Lack of communication could affect a large number of patients across the country, according to a new study published in Annals of Family Medicine that examined connections between PCPs and specialists.

The 2008 study “found sizeable gaps in communication among physicians caring for mutual patients,” with potential effects on patients such as delayed diagnoses, unnecessary testing, and patient and physician dissatisfaction. With widespread use of EHRs, it appeared physician communication might have improved since then but wasn’t much better in 2019. Investigators examined responses from 4754 PCPs who used the Comprehensive Primary Care Plus (CPC+) payment model through the federal Centers for Medicare & Medicaid Services, along with other data such as Medicare claims and enrollment.

The survey asked 2 questions:
• When you refer a patient to a specialist, how often do you send the specialist notification of the patient’s history and reason for the consultation?
• How often do you receive useful information about your referred patients from a specialist?

Reply options included:
• Always or most of the time
• Sometimes
• Seldom or never

A total of 22% of PCPs reported they “sometimes” or “seldom or never” sent clinical information to specialists at the time of referral, and up to 35% reported they “sometimes” or “seldom or never” received information back from specialists after consultations, the study said. Physicians participating in the CPC+ survey were highly motivated with sophisticated EHR use, so “actual communication behaviors nationwide are likely worse than what we found,” according to the study.

“Because these are physician-level proportions, the number of patients who are potentially affected is large,” the study said. “Further, the presence of any communication between providers does not guarantee that practitioners are sending or receiving the optimal information needed for clinical decision-making.”

More communication measurement is needed because it is not enough to assume EHR systems will improve connections between physicians, the study said.

EARLY DIAGNOSIS OF COVID-19 IS ESSENTIAL TO PREVENT FURTHER INFECTIONS AND THE DEGRADATION TO SEVERE DISEASE. REVERSE TRANSCRIPTASE–POLYMERASE CHAIN REACTION (RT-PCR) TESTS ARE THE STANDARD COVID-19 DIAGNOSTIC, BUT THE RELATIVELY LONG TURNAROUND TIME FOR THE LAB ASSAY MAY HINDER TIMELY QUARANTINE AND CONTAINMENT OF THE VIRUS.

RAPID ANTIGEN TESTS (RATS) HAVE RECENTLY BECOME MORE PREVALENT AND CAN BE PERFORMED BY INDIVIDUALS FROM THE SAFETY OF THEIR OWN HOMES. HOWEVER, THE RISE OF THE HIGHLY INFECTIOUS AND EVASIVEOMICRON AND ITS SUBVARIANTS HAVE CALLED INTO QUESTION THE ACCURACY OF RATs.

Visit www.medicaleconomics.com to read more. This story was originally published in our sister publication, Medical Economics®.

Comparing the Accuracy of COVID-19 Tests During Omicron

By NINA COSDON

Early diagnosis of COVID-19 is essential to prevent further infections and the degradation to severe disease. Reverse transcriptase-polymerase chain reaction (RT-PCR) tests are the standard COVID-19 diagnostic, but the relatively long turnaround time for the lab assay may hinder timely quarantine and containment of the virus.

Rapid antigen tests (RATs) have recently become more prevalent and can be performed by individuals from the safety of their own homes. However, the rise of the highly infectious and evasive Omicron and its subvariants have called into question the accuracy of RATs.

Visit www.medicaleconomics.com to read more. This story was originally published in our sister publication, Medical Economics®.
Rapid, Reliable Diagnostic and PoC Tests Are Requisite for “Test to Treat”

Progress in rapid diagnostic and point-of-care testing propelled by the pandemic can improve timeliness and precision of anti-infective treatment.

By KENNETH BENDER, PHARMD, MA

The value of rapid diagnostic tests, point-of-care (PoC) tests not tethered to centralized laboratories, and self-administered home tests became widely appreciated in the waves of the COVID-19 pandemic for hastening identification, isolation, and treatment that interrupted the geometrically increasing rate of infection.

However, in the early stages of the pandemic, it was also widely acknowledged that SARS-CoV-2 was spreading faster than testing resources could provide timely and accurate results across communities. The disparity between transmission and testing was well characterized by Elisabeth Rosenthal, MD, editor-in-chief of Kaiser Health News, in a New York Times opinion piece published in July 2020, “When Is a Coronavirus Test Not a Coronavirus Test?”

“One canon of medical practice is that you order a test only if you can act on the result. And with a turnaround time of a week or 2, you cannot. What we have now is often not testing—its test theatre,” Rosenthal wrote.

Even before the COVID-19 pandemic, advances in testing technologies were welcomed for providing faster turnaround of actionable results with increased specificity and sensitivity for a range of medical conditions.

For infectious diseases, rapid identification of pathogens and their susceptibility provides opportunity for more precise treatment, with better patient outcomes and less antimicrobial resistance. Rapid diagnostic tests are enabling earlier differentiation of viral and bacterial infections. PoC tests are used to detect pathogens such as Group A Streptococcus for outpatients with a sore throat. In hospital settings, rapid diagnostic tests are coupled with artificial intelligence analysis of multiple clinical measures to detect early signals of sepsis and increase the opportunity for lifesaving intervention.

PANDEMIC PUSHES TECHNOLOGY

The availability of rapid antigen tests (RATs) for SARS-CoV-2 in hospital emergency departments enabled better triage and patient flow, with reduced transmission to other patients and staff. Widely accessible RATs facilitated safer gatherings and the reopening of commerce and travel. Refinements in molecular testing provided verification of RAT screening, confirmed effectiveness of treatments, revealed COVID-19 variants, and guided development of targeted vaccines.

Telehealth is among the technologies that quickly evolved under pressure of the COVID-19 pandemic, providing an alternative to travel and in-person consultations for many, as well as reducing risk of exposure to the contagion for both patients and practitioners.

A particular synergy from coupling telehealth with in-home self tests for influenza was evaluated by Mark Ebell, MD, MS, a professor in the Department of Epidemiology and Biostatistics in the College of Public Health at the University of Georgia in Athens, and colleagues. “We’ve all learned to recognize the potential for telehealth [and] its limitations,” Ebell told Contagion. “The need for in-person evaluation is generally driven by the severity of symptoms and the presence of red flags such as dyspnea. Oxygen saturation monitors are increasingly in the homes of patients, which may help identify patients who need in-person evaluation.”

Ebell and colleagues provided clinical case vignettes simulating telehealth consults of patients experiencing 24 hours of a flu-like illness to approximately 200 physicians. They then ascertained how the availability of a home influenza test result would affect their decision to treat empirically, have the patient come to the clinic for further evaluation, or to neither test nor treat.

“We found that once they got the test result, only half as many wanted the patient to come into their office,” Ebell said. “This is important because keeping patients out of the office can reduce the likelihood of transmission to others while lowering costs and increasing convenience for patients.”

The accuracy of a home self-test for influenza (Ellume) was recently evaluated in 87 patients with positive home test results by retesting with reverse transcription–polymerase chain reaction (RT-PCR). The investigators reported that the overall specificity and sensitivity of the home test compared with the PCR reference were 61% (95% CI, 50%-71%) and 95% (93%-97%), respectively.

Although progress in testing technologies has facilitated identification of pathogens and supported antibiotic stewardship efforts, the pandemic set back the success of those efforts, according to a 2022 Special Report from the CDC, "COVID-19 US Impact on Antimicrobial Resistance.”

In her forward to that report, Rochelle Walensky, MD, MPH, director of the CDC, wrote, “As the pandemic pushed health care facilities, departments, and communities near their breaking points in 2020, we saw a significant increase in antimicrobial use, difficulty in following infection prevention and control guidance, and a resulting increase in health care–associated, antimicrobial-resistant infection in US hospitals.”

Among the actions called for in the report is a merging of strategies to respond to COVID-19 and antimicrobial resistance, including using telehealth for contact tracing and to support specimen self-collection. The report also recommends additional investments into clinical laboratory programs such as the Antimicrobial Resistance Laboratory Network, as well as its evaluations of bacterial whole genome sequence submissions.

RAPID RESULTS WHEN AND WHERE NEEDED

The number and types of nucleic acid amplification tests that have received emergency use authorization from the FDA increased substantially during the pandemic to meet the urgent need to detect SARS-CoV-2. These include RT-PCR systems, loop-mediated isothermal amplification (LAMP), and clustered regularly interspaced short palindromic repeats.

Although most of these remain benchtop systems, a recent review describes some that have been miniaturized, automated, and linked to portable digital platforms as PoC tests for on-site rapid diagnosis of viral respiratory tract and other infections. These more nimble PCR-based systems can complete identification of genetic material—either RNA or DNA nucleic acid sequences—in between 20 and 100 minutes. The LAMP system for DNA amplification is credited for using a DNA polymerase that acts at a constant temperature of 60 to
“In recent years, we have seen broader acceptance of decentralized testing models and a dramatic increase in the adoption of molecular point-of-care and immunoassay at-home testing solutions... These developments have supported societies in their fight against the COVID-19 pandemic.”

— Alison Kuchta, MD, PhD
Invasive Nontyphoidal Salmonellosis: An Antimicrobial-Resistant Foe

By Mackenzie Keintz, MD; and Jasmine R. Marcelin, MD, FACP, FIDSA

(continued from cover page)

are reported to cause human disease.

The primary serotypes isolated in the United States are Enteritidis (20%), Typhimurium (16%), Newport (11%), 4, [5], 12i− (4%), and Heidelberg (4%). The global burden of typhoidal Salmonella is high, causing approximately 22 million infections and more than 200,000 deaths annually. However, the impact within the United States is limited, causing only approximately 400 infections and 1 death in 2016. NTS are estimated to cause 1.35 million annual cases in the United States, predominantly manifesting isolated, self-limited gastrointestinal illness; however, a subset progresses to severe invasive disease. The global burden of invasive nontyphoidal salmonellosis (iNTS) was estimated to be 535,000 cases, resulting in 77,500 deaths in 2017. Transmission can occur through foodborne exposures or direct animal contact, but human-to-human transmission is rare. iNTS can occasionally manifest as serious, life-threatening illnesses requiring antimicrobial intervention. Over the past several decades, the rates of antimicrobial-resistant NTS have continued to increase as agricultural antibiotic use increases, subsequently limiting empiric antimicrobial choices in serious illness.

MANIFESTATIONS AND DIAGNOSIS

The primary manifestation of NTS is gastroenteritis, which can be more severe than other types of infectious gastroenteritis. In some cases, Salmonella can cause systemic dissemination, resulting in bacteremia and metastatic foci of infection, including meningitis, arthritis, and osteomyelitis. The CDC estimates approximately 8% of NTS are invasive in the United States, which is similar to a global estimate of 6%, although this likely represents an underestimation because of inadequate sampling. Host factors and pathogen virulence can determine risk for translocation from the enteric system. Patients with diminished cell-mediated immunity are at higher risk of iNTS, including those with HIV or malignancies and those who are on glucocorticoids or immunosuppression. There may be an association between multidrug resistance and invasive infection, as one study found that NTS with multidrug resistance were more likely to cause bacteremia. It is unclear why there was an association between multidrug resistance and invasive infection. In patients without recent gastroenteritis presenting with NTS bacteremia, metastatic foci of infection should be investigated.

Endovascular foci of infection are a rare but serious complication of iNTS and are associated with a mortality of more than 50%. These infections can manifest as endocarditis or as mycotic aneurysms, which are more common in patients with a history of atherosclerosis. Endocarditis is frequently destructive and can be evaluated with an echocardiogram. Evaluating for mycotic aneurysm may be more challenging, as imaging alone may not necessarily be diagnostic of active infection; however, the presence of aneurysm and bacteremia is suggestive. Patients with gas or inflammation surrounding a previously known aneurysm in the setting of bacteremia should be suspected to be infection. A PET scan may also be useful in localizing infection. The primary mechanism of infection of the aorta is via hematogenous seeding, and blood cultures are positive in more than 50% of cases. However, contiguous spread of infection from vertebral osteomyelitis can also occur.

In adults, vertebral osteomyelitis is the most common osteoarticular manifestation. However, there are rare reports of prosthetic joint infections, as well. Cultures should be obtained from suspected sites of infection in bone and joint infections.

Meningitis is a rare manifestation of iNTS. Most infections occur in infants and neonates or those with other immunocompromising conditions. Diagnosis occurs with obtaining a cerebrospinal fluid sample and culture.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance in NTS is not uncommon. One study reported 12% of isolates demonstrating resistance to at least 1 antibiotic (ampicillin, ceftriaxone, or ciprofloxacin) between 2004 and 2012. Resistance to ampicillin was most common (6.5%), whereas ceftriaxone resistance was detected in 3.5% of isolates, and ciprofloxacin nonsusceptibility was isolated in 2.4%. Only 0.2% of isolates were nonsusceptible to all 3 antibiotics. In contrast, isolates reported to the National Antimicrobial Resistance Monitoring System between 2016 and 2018, 8.7% were resistant to ampicillin, 3.2% were resistant to both ceftriaxone and ampicillin, and 7.1% were nonsusceptible to ciprofloxacin. The percentage of isolates resistant to all 3 remained low, at 1.1% (FIGURE 1).

FIGURE 1. All nontyphoidal Salmonella serotype antimicrobial resistance rates from 2000-2018

- Ciprofloxacin nonsusceptible
- Ampicillin resistant
- Ceftriaxone resistant
- Multidrug resistant
The evolution of antimicrobial resistance in NTS has varied by serotype. Enteritidis had the largest increase in resistance to ciprofloxacin. In 2000, 2.2% of isolates were nonsusceptible to ciprofloxacin vs 22.5% in 2018 (FIGURE 2A). All other serotypes have had increased ciprofloxacin nonsusceptibility over the same time frame (FIGURE 2A). Trends of ceftriaxone resistance have been more variable (FIGURE 2B). Overall, ampicillin resistance has trended down but remains high (FIGURE 2C). The percentage of multidrug resistant isolates of all serotypes remains low but has been increasing in recent years, with Salmonella Heidelberg having the highest rate of multidrug resistance (FIGURE 2D). Once identification of serotype has been obtained, this can be used to predict sensitivity to antibiotics.\(^9\)

NTS are associated with foodborne illness and animal exposure, and it is intuitive that part of the reason antimicrobial resistance is increasing in this organism is associated with the use of antimicrobials in the animal husbandry population. Consequently, as the use of cephalosporins has been decreasing as of 2012, isolation of cephalosporin-resistant NTS in animals (while still significantly higher than found in humans) has also decreased.\(^9\) This may account for the decrease in ceftriaxone resistance that has been observed in human clinical isolates. Although fluoroquinolone use was discontinued in poultry in 2005, it is still widely used in cattle to treat respiratory infections.\(^9\) It is difficult to determine whether the relationship between the use of fluoroquinolone in agriculture is associated with the increase in fluoroquinolone nonsusceptibility in humans, as fluoroquinolone nonsusceptibility is not frequently assessed in animal husbandry populations.\(^8\)

TREATMENT
In patients with disease limited to the gastrointestinal tract, routine administration of antibiotics is not recommended, as it does not decrease the length of diarrheal illness and increases the risk of progression to asymptomatic carriage of NTS.\(^11\) Antimicrobial therapy should be considered in patients whose progression to invasive disease is more likely, including neonates, patients with HIV, patients older than 50 with atherosclerosis, cardiovascular disease, significant joint pathology, and those on immunosuppression.\(^7\)

Patients who progress to iNTS should be treated with antibiotics. The recommended empiric antibiotic treatment has evolved over the past decade, as antimicrobial resistance has increased. Although no formal recommendations exist, combination therapy with ceftriaxone and fluoroquinolone is reasonable in severe infection until susceptibilities are determined to confirm which agent will be effective, as multidrug resistance is rare.\(^12\) Ampicillin, ceftriaxone, and fluoroquinolones remain cornerstones of treatment when susceptibilities are known.

Patients with mycotic aneurysms should be treated with effective antibiotics and assessed for surgical intervention. A study by Soravia-Dunand et al showed that mortality of mycotic aneurysm treated with medical management alone was 96% compared with 40% with combined surgical and medical management.\(^13\) Previously, patients with Salmonella mycotic aneurysms were treated with open repair, but endovascular aneurysm repair (EVAR) has been more recently with some success.\(^1\) A meta-analysis evaluating all causes of mycotic aortic aneurysms did not find evidence to support either approach and recommend evaluating individuals on a case-by-case basis. Antibiotic pretreatment was associated with improved outcomes regardless of approach. Consideration for long-term suppression must also be made after EVAR, as there is prosthetic material implanted directly into an infected field.\(^14\)

Early osteomyelitis can be cured with antimicrobial therapy alone. In a meta-analysis, 45% of patients reviewed were treated with antimicrobial therapy alone, of which 80% were successfully cured. Of the patients treated with a combination of surgical intervention and antimicrobial therapy, 75% were cured. The mean duration of antimicrobial therapy was 11 weeks.\(^15\) Limited data on prophylactic joint infection and septic arthritis secondary to Salmonella exists. These infections are managed with a combination of antimicrobial therapy and surgical intervention. Best practices in prosthetic joint infection management frequently include 2-stage device revision; however, this management should be performed in consultation with appropriate surgical teams.\(^16\)

Most literature regarding antibiotic choice and duration of therapy for Salmonella meningitis has been in pediatric populations, as central nervous system involvement most frequently manifests in infants and neonates. The American Academy of Pediatrics recommends a third-generation cephalosporin for a duration of 4 to 6 weeks due to high rates of treatment failure. Repeating lumbar punctures may be indicated after 48 hours to ensure clearance and, if persistently positive, consideration of dual therapy with a fluoroquinolone should be pursued.\(^17\)

CONCLUSIONS
Nontyphoidal Salmonella infections have a wide array of clinical presentations, including gastroenteritis requiring no antimicrobial intervention, invasive NTS disease necessitating systemic antibiotics at a minimum, and in some cases, requiring surgical debridement and possible lifelong suppressive therapy. Increasing antimicrobial resistance of NTS has complicated empiric antimicrobial choice while awaiting isolation and susceptibility. Antibiotic overuse in the treatment of human disease and in agriculture has contributed to the continued escalation of antimicrobial resistance in NTS. Ongoing antimicrobial stewardship practices in both populations can help slow the trajectory of antibiotic resistance, thereby improving empiric options available for treatment of invasive nontyphoidal Salmonella infections. ▲

References are available at ContagionLive.com.
We wonder whether a test could detect the virus in his saliva, and a friend who was a clinician sent us a research paper. In this paper, one figure showed that it could, whereas another figure showed a lesion-pocked, bloody placenta and explained that the child who had just been born had died.1

For the second time this decade, a virus is spreading in novel ways around the world. Viruses emerge from animal reservoirs on every continent, including the hantavirus in Southwest desert areas in the United States and the swine flu in 2009.2 However, novel viruses or old viruses that are spreading in new ways are often narrativized, using heart-of-darkness imagery that imply these infections are foreign and the human populations they arose in are backward.

We argue that both the current MPX outbreak and the ongoing HIV pandemic proceed from the same flawed premise, in which we can separate the health of Black African individuals in the Democratic Republic of the Congo or Nigeria from the health of the communities we consider closer to home. This flawed premise incorporates an ugly reality, in which we view untreated pustules on Black individuals who live in Africa as unfortunate—but normal or expected—occurrences in that part of the world, even when effective vaccines and treatments exist. However, an outbreak of pus-filled boils on White individuals who live in London or New York City, for example, are a galvanizing tragedy, requiring immediate intervention.

We examine scientific data alongside social and political realities surrounding the emergence of 2 viruses: HIV and MPX. These viruses are fundamentally different: one is an RNA retrovirus that causes lifelong infections and the other is a DNA poxvirus that causes an acute infection. The reasons for their emergence include a global biomedical infrastructure that doesn’t respond to crises until they belong to White individuals in the Global North. Importantly, continuing these patterns of research and health care resources allocation is a choice that can be undone.

CASE STUDY 1: HIV

HIV is a retrovirus that infects T cells, an essential component of the adaptive immune system. In the Western imagination, HIV emerged in the 1980s and initially impacted homosexual individuals, persons with hemophilia, individuals who use heroin drug, and Haitians (or known as the 4 Hs).3 Even when HIV had arrived in the United States, its impact was immediately othered.

Of course, this pattern of infection would not last. Today, HIV among those with hemophilia is essentially nonexistent; structural factors render HIV still a crisis among queer and Black individuals, especially in the rural South, because of poor health care access.4

However, HIV did not emerge in the United States in the 1980s. It emerged in the region between Cameroon and the Congo and was first transmitted in an urban population under colonial rule in the Belgian Congo.

Viral molecular phylogenetics tell this story plainly, one that maps in synergistic ways with the cultural and political story of the Congo. Viral sequencing shows the date HIV arrives in New York City, which was around 1969 from Haiti.5 HIV emerged in the Congo under Belgian rule between the 1920s and 1940s as a virus that largely impacted rural communities until the infrastructure and labor needs put in place by the Belgian led to wider spread, especially in Kinshasa.6

This viral spread, which certainly included the deaths of many young individuals who were otherwise healthy, was entirely unnoticed by the biomedical infrastructure such as it was under Belgian rule. We may not have had the scientific understanding to isolate a novel retrovirus in the 1940s, as this was at the beginning of modern virology research, but a country with access to health care would notice rising unexpected deaths due to rare cancers and pathogens.

In 1960, the Congo liberated itself from Belgian rule. At independence, the Congo had exactly 0 Congolese doctors, engineers, or lawyers, according to the New York Times.7 Under explicitly racist colonial rule, Belgium forbade the Congolese from getting an education beyond the fifth grade. The extremely stringent exceptions included those adolescents intending to join the priesthood. Again, this is the context in which HIV spread without detection for so many decades—a nation of 15 million people and no doctors.

A nation cannot build itself with no professional class, so to fill that void,
the United Nations developed a program for many French-speaking Haitians to immigrate temporarily to the Congo to help train its first professional class.6 Regardless of the mode of viral transmission, wherever people move, an infectious disease will move as well. It is via this travel to and from Haiti that HIV permanently left the African context. HIV then traveled from Haiti to New York City around 1969, and from there to the world.5

Molecular biological analyses on HIV-positive samples found in various hospitals decades later show us this pattern, but the science alone does not explain it. The colonial and postcolonial history is fundamental to the biology of this ongoing pandemic.

CASE STUDY 2: MPX

MPX is an orthopoxvirus, similar to smallpox, that causes a painful rash. Its animal reservoir is not monkeys but various rodent species in the previously endemic regions of Central and West Africa, including the Congo. Spillover in these regions is common, but human-to-human transmission has remained low for decades.9

In the Western imagination, MPX emerged as a serious problem sometime in mid-2022. Even then, as cases rose in US cities in early summer, many still wondered whether MPX was something we needed to worry about. The “we” in that sentence meaning ordinary US citizens.

MPX was identified in 1958, and its human infection was characterized in 1970 in the Congo (then Zaire).8 According to our imperfect epidemiology, it killed mostly children in the Congo and spread to Nigeria throughout the 1970s.10 In 2003, there was an outbreak in the United States, affecting at least 47 patients.11 Yet most deaths have occurred in Africa, where since 2017, Nigeria has faced another outbreak that includes consistent human-to-human spread for the first time on record.12

Because of the similarity between MPX and smallpox, effective vaccines existed even before MPX was discovered in humans in 1970. However, once smallpox was eradicated in 1980, vaccination ceased worldwide, even where it helped limit MPX spread.13

Similar to HIV, the colonial and postcolonial history is fundamental to the biology of this MPX outbreak. When the first human MPX case was discovered in 1970, the Congo’s national health infrastructure was barely 10 years old. At the time, a US-supported dictatorship ruled and steered the national economy into the ground over the next 26 years. By the mid-1990s, dysfunctional medical infrastructures left millions without realistic options for treatment during illness.

At the same time, travel between Congo (the colonized country) and Belgium (the former colonial power) has been common for decades. The same goes for travel between Nigeria and the United Kingdom. Hundreds of thousands of Congolese and Nigerians live in Belgium, France, and the United Kingdom, and multiple commercial flights serve this colonized-colonizer corridor every day, through which people regularly visit family, vacation, and conduct business.

Under these circumstances—absent targeted research and intervention—widespread transmission of MPX into Europe was only a matter of time. Despite these obvious connections, the research and categorization of MPX was relegated to “neglected” tropical diseases, which receive less research funding. Fifty-two years after its discovery in humans, we still don’t know basic information about MPX’s epidemiology, diagnostics, and virology. Is the virus systemic (eg, in saliva and blood) or just on skin lesions? Is the virus found in semen or vaginal fluids? What is the actual seroprevalence of the virus in various regions? How long does the virus live on surfaces, and what types of cleaning supplies are needed to remove it? The answer to these questions is simple: We don’t know.

A Nigerian doctor noticed the change in transmission through sexual encounters in 2017, and he “tried to warn health officials and scientists repeatedly,” he later told reporters from NPR.14 All the while, the US federal government let 20 million doses of its vaccine expire in a warehouse15; none of those doses were considered for use in the endemic region. It’s unclear whether this could have stopped enough transmission to prevent our current global catastrophe, but it’s possible.

At present, Nigeria has no countermeasures to the virus, including vaccines and antiviral treatment.16 Nigerian queer activists remind us that queer individuals exist in every country, even where queerness is outlawed.17 The emergence of MPX into new social and sexual networks in Europe—largely but not exclusively queer sexual and social networks—has shocked many. Given our expertise in molecular microbiology and our knowledge of colonial history, we were not shocked. We argue that this situation must never be allowed to shock again.

CONCLUSION

Viruses emerge everywhere. The pattern of viral emergence in Africa and the spread among queer social and sexual networks is not biological. This pattern is because of centuries of systemic disregard for urgency in stemming all viral spread everywhere.

Both HIV and MPX spread in queer sexual networks after their emergence in the Global North. That US society marginalized all 4 of the Hs we described above, which played a clear role in the slow US response to HIV. The US government has been reluctant to respond to MPX, even as cases in queer individuals rose precipitously, deciding to activate only a small portion of MPX vaccines in response to this actual threat out of fear for a theoretical smallpox bioterrorism event.18 The World Health Organization panel recommended against labeling MPX a public health emergency because the virus was “only” spreading in men who have sex with men.19 Ignoring the suffering of a marginalized community dehumanizes them and normalizes their pain. As HIV taught us, these viruses will ultimately impact everyone.

We continue to envision health threats to Africa as marginally related to health threats in the rest of the world. This belief proceeds from the notion that African lives are marginally related to Western lives. This belief is not logical, humane, nor scientific.20 We argue that the lens of who is considered like or among “us” must change. Not only does narrowing that lens lead to our own peril because our social and sexual networks are interconnected, but it is also inhumane to imagine that individuals in certain parts of the world populated by people of color may suffer from preventable illnesses, whereas the West, which is populated by a White majority, ought not. We propose the first step toward change: As scientists begin to advocate for more research on MPX and more access to vaccines, they should explicitly include the endemic regions in that advocacy. Research capacity in all regions of the world, including African countries, is essential for self-determination and global public health. This is the first step toward shifting the imagined “us” in science and health policy to the “us” that exists in objective reality.21

References are available at ContagionLive.com.
Gender-Affirming Care in Persons Living With HIV

by Jenna E. Januszka, PharmD; Renata O. Smith, PharmD, AAHIVP; and Melissa E. Badowski, PharmD, MPH, FCCP, FIDSA, BCIDP, BCPS, AAHIVP
persons. Transgender individuals may prioritize gender-affirming hormone therapy (GAHT) over antiretroviral therapy (ART) if they perceive ART to decrease efficacy of GAHT. Previous literature suggests provision of gender-affirming care to persons living with HIV improves quality of life as well as engagement and retention in care. 

GENDER-AFFIRMING HORMONE THERAPY

GAHT therapy consists of administration of exogenous hormones and suppression of endogenous hormone production, with the goal of obtaining characteristics more congruent with an individual’s gender identity. Currently, there are several clinical practice guidelines to inform gender-affirming care, but it is important to note that data to guide treatment decisions in persons living with HIV specifically are scarce. 

In general, goals of GAHT should be individualized to each patient and target acquisition of secondary sex characteristics that better align with the patient’s gender identity. Some may prefer limiting hormonal effects or maintaining a mix of feminine and masculine characteristics. Therefore, recommendations for specific serum level monitoring targets herein are based on cisgender adult normal ranges to avoid long-term complications of supratherapeutic levels, with the goal of total feminization or masculinization.

FEMINIZING HORMONE THERAPY

Estrogen is the cornerstone of feminizing hormone therapy (FHT). However, because estrogen therapy alone is not enough to suppress testosterone levels, FHT also typically consists of an antiandrogen and sometimes progestogen and/or gonadotropin-releasing hormone (GnRH) agonist.

Estrogen Therapy

There are several preparations of estrogen available: oral conjugated estrogens, ethinyl estradiol (EE), and oral or sublingual, injectable, or transdermal 17β-estradiol. 17β-Estradiol is biochemically identical to the estrogen released from the ovary and is preferred to EE and oral conjugated estrogens because of its more favorable safety profile. EE is commonly formulated into oral contraceptives and increases risk for venous thromboembolism. In addition to venous thromboembolism risk, conjugated estrogens also increase cardiovascular (CV) risk. The transdermal formulation is thought to have the least thromboembolic risk of all preparations.

Sublingual administration of micronized tablets and the injectable formulations have been found to have variable pharmacokinetics and higher serum concentrations, as they bypass first-pass metabolism. Injectable estradiol can result in peak levels of 250 pg/mL and troughs of 50 pg/mL; decreasing the dosing interval between injections may decrease these fluctuations in levels. The most common adverse effects of 17β-estradiol preparations are mood swings, migraines, hot flashes, and weight gain. Dosing and considerations for monitoring can be found in TABLE 1. Studies comparing the efficacy of the agents look primarily at postmenopausal women, with no 1 formulation more efficacious than the others for all outcomes. Moreover, the desired effects in the study population differ from the desires of transgender persons. Therefore treatment decisions should be based on patient preference.

Monitoring parameters for 17β-estradiol therapy include maintenance of serum estradiol levels between 100 and 200 pg/mL and serum testosterone less than 50 ng/dL. Timing of monitoring is further described below in TABLE 2. Conjugated and synthetic estrogens cannot be evaluated via blood testing and are not recommended for use as GAHT.

Estrogen therapy is also associated with increased triglycerides (TG) without significant effects on high- and low-density lipoproteins (HDL and LDL). Ritonavir- and cobicistat-boosted ART, efavirenz, and tenofovir alafenamide (TAF) are also associated with dyslipidemias. Prior to initiating estrogen therapy in individuals taking these antiretrovirals (ARV), providers should discuss interventions tailored to decrease CV risks, such as smoking cessation and lifestyle modifications. Currently, there is conflicting evidence regarding the risk of CV events with abacavir. Nonetheless, abacavir should be used with caution in patients taking estrogen, especially those with CV risk.

Ritonavir-boosted protease inhibitors, efavirenz, etravirine, and nevirapine are expected to decrease serum concentrations of estradiol. Therefore, the US Department of Health and Human Services recommends patients taking these antiretrovirals maintain methadone dosing to avoid CV risk.
TABLE 1. Common Estrogen and Testosterone Preparations for GAHT Therapy

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSING</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17β-Estradiol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral/sublingual (micronized</td>
<td>1-6 mg/day</td>
<td>• Doses &gt; 2 mg/day should be given in 2 divided doses</td>
</tr>
<tr>
<td>estradiol)</td>
<td>MAX: 8 mg/day</td>
<td>• Sublingual administration/dosing with variable PK and higher</td>
</tr>
<tr>
<td>Transdermal</td>
<td>50-200 mcg/day</td>
<td>• Can monitor levels at any time</td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>5-30 mg every 2 weeks</td>
<td>• Inexpensive</td>
</tr>
<tr>
<td>Estradiol cypionate</td>
<td>2-5 mg every 2 weeks</td>
<td>• May require multiple patches</td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral testosterone</td>
<td>100-200 mg SC/IM every 2 weeks, or 50% of</td>
<td>• Fluctuations in serum concentration cause cyclic changes in mood</td>
</tr>
<tr>
<td>cypionate</td>
<td>the dose SC every week</td>
<td></td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>750 mg IM once, then repeat 4 weeks later,</td>
<td>• Monitored through REMS program</td>
</tr>
<tr>
<td></td>
<td>then 750 mg IM every 10 weeks</td>
<td>• Less variation in serum concentration</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>2-8 mg/day</td>
<td>• Applied at bedtime to mimic diurnal testosterone release</td>
</tr>
<tr>
<td>Gel (1%)</td>
<td>12.5-50.0 mg/day</td>
<td>• Applied in morning to axillary area</td>
</tr>
<tr>
<td>(1.6%) 20.25-60.75 mg/day</td>
<td>MAX: 100 mg/day</td>
<td></td>
</tr>
<tr>
<td>Axillary gel (2%)</td>
<td>30-60 mg/day/SC/IM</td>
<td>• Unaffected by axillary hair and antiperspirants</td>
</tr>
</tbody>
</table>

GAHT, gender-affirming hormone therapy; IM, intramuscular; PK, pharmacokinetic; REMS, Risk Evaluation and Mitigation Strategy; SC, subcutaneous.

Services (DHHS) guidelines recommend increasing the dose of estradiol in patients taking these medications concomitantly to achieve desired clinical effects. These ARVs are no longer commonly prescribed in the United States but may still be used in other countries. Because of conflicting information provided in the DHHS guidelines, it is unclear the effect of cobicistat-boosted regimens may have on estradiol concentrations. Current evidence has investigated only the impact of these regimens on EE exposure, showing decreased EE exposure with boosted darunavir and elvitegravir but no difference with boosted atazanavir. Close monitoring of serum estradiol levels may be required to achieve desired clinical effects.

**Antiandrogens**

Antiandrogens suppress production of testosterone and suppress male characteristics. These medications include spironolactone, GnRH agonists, and 5-α reductase inhibitors.

Spironolactone is a potassium-sparing diuretic with androgen receptor-blocking properties at high doses as well as dose-dependent gynecomastia. Doses of 200 to 400 mg daily have been reported without negative effects. Total daily doses greater than 50 mg should be divided into 2 doses. Hyperkalemia rarely occurs and is more likely in patients with impaired renal function or concomitant use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or sulfamethoxazole-trimethoprim. Because of its diuretic effect, hyponatremia can occur and patients may experience self-limiting polyuria and polydipsia and polyuria.

GnRH agonists, such as histrelin and leuprolide, block the release of follicle-stimulating and luteinizing hormones, leading to full gonadal blockade. Histrelin is a surgically inserted implant that lasts 12 to 36 months, whereas leuprolide requires injections ranging from daily to every 3 to 4 months. Although more commonly used to delay puberty in adolescents, these medications may be used in combination with estrogen to lower testosterone levels. Redistribution of body fat toward the affirmed gender can occur; however, most studies simply report an increase in body fat and decrease in muscle mass, which may or may not be desired. Effects of GnRH agonists on bone mineral density (BMD) have not been well studied but may be of less concern when used as an adjunct to estradiol. Exogenous estrogen therapy has been shown to be sufficient in maintaining normal BMD. Therefore, tenofovir disoproxil fumarate (TDF) has been associated with a decrease in BMD. It should be used with caution in transgender patients who are at higher risk for osteopenia and osteoporosis, including those on GnRH agonists in the absence of hormone therapy. Hypertension has also been reported with GnRH agonists.

Lastly, 5-α reductase inhibitors block the conversion of testosterone to dihydrotestosterone. Because they do not suppress testosterone production or activity, these inhibitors have less of an antiandrogen effect when compared with GnRH agonists. Dutasteride is more selective of the pilosebaceous unit compared with finasteride and therefore may have more feminizing effects. These agents are a good option for patients seeking only partial feminization or experiencing hair loss after total androgen blockade. Normal dosing in gender-affirming care is finasteride 1 to 5 mg daily and dutasteride 0.5 mg daily. Both are associated with decreased libido and ejaculation disorders.
TABLE 2. Guidance for Monitoring GAHT

<table>
<thead>
<tr>
<th>TEST</th>
<th>TARGET LEVELS</th>
<th>BASELINE</th>
<th>3 MONTHS a</th>
<th>6 MONTHS a</th>
<th>12 MONTHS a</th>
<th>ANNUALLY AS NEEDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium (K+) and renal function b</td>
<td>K+ &lt; 5.0 mmol/L</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Estradiol</td>
<td>FHT: 100-200 pg/mL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>MHT: 320-1000 ng/dL; FHT: &lt; 50 ng/dL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sex hormone binding globulin b</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

FHT, feminizing hormone therapy; GAHT, gender-affirming hormone therapy; MHT, masculinizing hormone therapy. Adapted from 2016 University of California, San Francisco clinical practice guidelines.

a During initial year of therapy only
b For spironolactone use
c Used to calculate bioavailable testosterone

Boosted ART is expected to increase concentrations of these agents. Conversely, efavirenz, etravirine, and nevirapine may result in decreased 5α-reductase inhibitor concentrations; therefore, increased doses may be required to achieve desired clinical effects.13

Progestogens
To date, evidence from well-designed trials for progestogens as FHT is lacking. Nevertheless, progestogens are thought to improve breast development, mood, and libido without evidence to suggest harm.14,15 Commonly used progestogens include micronized progesterone 100 to 200 mg at bedtime or medroxyprogesterone 2.5 to 10 mg at bedtime.16 Depot medroxyprogesterone acetate is less common in transgender women but may be used in transgender men to induce amenorrhea.17

Physical changes with FHT can be expected between 3 and 12 months after treatment initiation. Decreased sexual desire and spontaneous erection may occur within 1 to 3 months of starting hormone therapy. Within 3 to 6 months, redistribution of body fat, decrease in muscle mass, skin softening, breast growth, and decrease in testicular volume can be expected. Finally, after 6 to 12 months, terminal hair growth declines.

MASCULINIZING HORMONE THERAPY
The general approach to masculinizing hormone therapy (MHT) is the administration of exogenous testosterone, with the goal of developing male secondary sex characteristics and suppression or minimization of female sex characteristics.

Testosterone
Testosterone is available in injectable and transdermal formulations, which are all thought to be equally efficacious. Dosing is summarized in Table 1. Adverse effects of injectable formulations include acne, polycythemia, sleep apnea, and dyslipidemia, whereas transdermal formulations (including the patch) may also cause skin irritation and hypersensitivity.18

According to the Endocrine Society guidelines, the normal male range for total testosterone levels is between 320 and 1000 ng/dL, but reference values may vary by assay.9 If patients experience decreased libido and mood, testosterone should be uptitrated to target midrange values. Further uptitration to the upper end of the reference range is unlikely to produce further masculinizing results and is not recommended.9 Depot medroxyprogesterone acetate 150 mg every 3 months may be used in transgender men to induce amenorrhea until full effects of testosterone are seen.9,11

Physical changes with MHT expected to occur within 1 to 6 months of the initiation include the cessation of menstruation, increased libido, increased body and facial hair, increased muscle mass, and redistribution of body fat. Deepening of the voice, clitoromegaly, and sometimes male pattern baldness can be expected within 12 months of testosterone therapy.9

Testosterone therapy has a similar drug interaction profile to that of 5α-reductase inhibitors regarding ART. Boosted ARVs are expected to increase concentrations of testosterone, whereas efavirenz, etravirine, and nevirapine may result in decreased concentrations; therefore, increased doses of testosterone may be required. Exogenous testosterone also increases LDL and TG while decreasing HDL in transgender men. Therefore, caution should be used when initiating boosted ART, efavirenz, abacavir, and TAF.13

CONSIDERATIONS FOR PRE-EXPOSURE PROPHYLAXIS
The CDC and the United States Preventive Services Task Force recommend use of preexposure prophylaxis (PrEP) in all high-risk individuals, including transgender persons.18 Small pharmacokinetic studies have found lower serum concentrations of emtricitabine (F)/TDF and F/TAF in transgender women. However, these lower concentrations were still within the expected ranges for patients taking these medications and above the levels necessary to confer 90% protection from HIV infection.20 F/TDF has no effect on serum levels of gender-affirming hormones, more specifically testosterone and estradiol.21 Long-acting injectable cabotegravir (CAB) is not expected to have any drug-drug interactions (DDIs) with GAHT and was found to be superior to oral PrEP for prevention of HIV infection.22,23 Therefore, F/TDF and CAB can each be safely used as PrEP in the setting of GAHT. F/TAF is expected to remain efficacious in transgender women on FHT, but it is currently not approved for transgender men.19,22

CONCLUSIONS
Modern ARV regimens have few, if any, expected DDIs with GAHT, including agents used for PrEP. Clinicians should discuss the benefits of adherence to agents used for HIV treatment and prevention, as well as the minimal risk for DDIs with GAHT. ▲

References are available at ContagionLive.com.
Will We Ever See Oral Carbapenems for ESBL Urinary Tract Infections?

Recent issues surrounding the ADAPT-PO and SURE-2 trials place the spotlight on the difficulties in developing oral carbapenem-based antibiotics and cast their future into doubt.

By Theodore S. Rader IV, MD, MS

(continued from cover page) tebipenem HBr. Specifically, the FDA cited concerns about improper classification of trial participants that, when properly classified, resulted in tebipenem HBr no longer meeting noninferiority criteria. Spero Therapeutics, Inc, the manufacturer of tebipenem HBr, has announced a corporate restructuring while it prepares to meet with the FDA to address these concerns. These announcements are the most recent in a series of disappointing outcomes in the development of oral carbapenem therapy for urinary tract infections (UTIs). Although the future development of oral carbapenems is not entirely clear, there are reasons for concern that the class may not help support a growing clinical need.

WHAT IS THE CLINICAL NEED FOR AN ORAL CARBAPENEML-BASED ANTIBIOTIC?

A 2019 Centers for Disease Control and Prevention report identified extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae as a serious threat in antimicrobial resistance. That same report estimated there were nearly 200,000 ESBL infections in the United States during 2017, causing approximately 9100 deaths. In addition, between 2012 and 2017, the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococcus* (VRE), and carbapenem-resistant Enterobacteriaceae infections decreased, whereas the rate of ESBL infection increased from 37.55 to 57.12 cases per 10,000 hospitalizations (a 55% increase). Most of these cases (> 80%) were classified as community onset. The most common ESBL-producing organism is *Escherichia coli*, which underscores the need for oral antibiotics that can effectively treat ESBL infections. Rates of ESBL-producing *E coli* vary by region in the United States, with significantly higher rates along each coastline. Rates range from 10.5% in the West North Central region (Minnesota, North and South Dakota, Nebraska, Kansas, Iowa, Missouri) to 29.6% in the Mid-Atlantic region (New York, Pennsylvania, Delaware, New Jersey). Fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX) are the recommended oral options for complicated UTI (cUTI) and pyelonephritis caused by ESBL-producing

Enterobacteriaceae is a causative agent of different infections.
infections, according to recent guidelines published by the Infectious Diseases Society of America. Alarmingly, the rate of fluoroquinolone and TMP-SMX resistance against ESBL E coli in the United States is nearly 70% and 60%, respectively. Unfortunately, other oral antibiotics, such as nitrofurantoin and fosfomycin, are not recommended in cases of cUTI or pyelonephritis because of low concentrations in the upper renal tract. Considering these factors, at least 60% of patients with cUTI or acute pyelonephritis caused by ESBL-producing bacteria have no viable oral antibiotics for treatment.

EXISTING CARBAPENEM ANTIBIOTICS
This is the niche that is supposed to be filled by the oral carbapenem class, a quest that has been progressing for the past 30 years. The first successful oral carbapenem, faropenem medoxomil, was approved for pediatric use in Japan in the early 2000s. It has broad activity against many gram-positive and gram-negative aerobes and anaerobes, and it is resistant to degradation by ESBLs and AmpC ß-lactamases. It has no activity against Pseudomonas aeruginosa, Stenotrophomonas maltophilia, VRE, or MRSA. Approved indications in Japan include acute bacterial sinusitis, community-acquired pneumonia, acute exacerbation of chronic bronchitis, cUTI, and uncomplicated skin and soft tissue infections. Postmarketing surveillance of faropenem medoxomil showed sustained clinical effectiveness for assessed clinical conditions. Importantly, there was no appreciable change in the resistance patterns observed in common isolates. Despite multiple phase 1 and 2 trials, the FDA issued a nonapproval letter for faropenem medoxomil in 2006, citing concerns about validity of study populations and inability to verify diseases being treated, including community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial sinusitis, and uncomplicated skin and soft tissue infections. License holder Replidyne, Inc, ultimately abandoned the US market for faropenem medoxomil, with no current signs of revival.

Sulopenem, an oral and IV carbapenem-class antibiotic, as well as tebipenem, an oral carbapenem, have also been in preclinical development pathways. Sulopenem is an IV and oral option to treat ESBL organisms, although it has limited activity against Pseudomonas and Burkholderia species. However, clinical data are notably limited. Iterum Therapeutics plc has released some conference abstracts, but there has not been a full peer-reviewed publication on the clinical efficacy of sulopenem in phase 2 or 3 trials. Data from the SURE-1 trial (NCT03357614) were presented in a late breaker session at IDWeek 2020. In the trial, adult women with pyuria, bacteriuria, and signs and symptoms of UTI were randomly assigned to sulopenem etzadroxil/probenecid or ciprofloxacin. In the combined primary analysis, sulopenem was noninferior to ciprofloxacin, but these findings appear to be related to superiority in quinolone nonsusceptible isolates (62% of whom still had a clinical response to ciprofloxacin compared with 83% of the sulopenem group). Recently presented data on the SURE-2 trial (NCT03357614) of oral stepdown sulopenem vs IV ertapenem did not demonstrate noninferiority. Iterum Therapeutics submitted a new drug application, but the FDA has requested at least 1 more well-designed clinical trial against a different comparator drug and further nonclinical data to determine an optimal dosing regimen.

Regarding tebipenem, the recently published results of the ADAPT-PO trial, a successful noninferiority trial comparing tebipenem HBr with IV ertapenem for cUTI and pyelonephritis, warrant deeper examination. There was significant microbiologic failure in both groups, although this did not impact the overall study results. The FDA requested additional clarifications, citing discrepancies in the classification of patients. When reclassified, tebipenem did not meet the criteria for noninferiority. As outlined above, Sero Therapeutics is currently working with the FDA to address these concerns but is restructuring to focus on other therapeutic products.

CURRENT BARRIERS TO ORAL CARBAPENEM THERAPY
What, then, are the barriers to an oral carbapenem-based antibiotic? Neither sulopenem nor tebipenem has demonstrated noninferiority compared with IV ertapenem. One barrier to approval may be in the definitions of cure recommended by the FDA in clinical trials for UTI. This includes both a clinical and microbiologic cure. To meet this requirement, a late test of cure in needed at least 5 days after completion of therapy and then 21 to 28 days post randomization, both showing less than 1000 colony-forming units of the pathogen in urine cultures to meet the end point. Both sulopenem and tebipenem struggled to get above 60% microbiologic cure at the late test-of-cure visit despite high early clearance rates, which are equivalent to or worse than comparator drugs at the late test-of-cure visit.

Other barriers also involve the pharmacokinetic properties of these agents. Under ideal conditions, sulopenem is 20.1% to 33.6% orally bioavailable, which can be boosted by administration with food and the inclusion of probenecid to the formulation (as sulopenem etzadroxil/probenecid). Urine concentrations are variable, with 35.5% of unchanged dose recovered in healthy volunteers without the addition of probenecid, which increases the renal tubular secretion. Tebipenem HBr is more orally bioavailable at an estimated 50% to 60%, with active metabolites excreted mostly through the kidneys. Tebipenem concentrations in urine range from 38% to 64% of the administered dose, and in patients with renal impairments, it has a longer elimination half-life and higher area under the curve (AUC). However, in patients with worse renal function, less of the drug is eliminated over time, decreasing overall AUC. In patients with severe renal function, only 38% was eliminated vs 55% to 64% of patients with moderately impaired renal function.

Additionally, there are limitations regarding the effectiveness of some of these carbapenem antibiotics. Faropenem and sulopenem have broad activity, but some pathogens, including P aeruginosa and Burkholderia cepacia demonstrate high intrinsic resistance to the carbapenem class, despite lacking a carbapenem-hydrolyzing ß-lactamase. In general, sulopenem is less potent against gram-negative organisms (4- to 32-fold increased minimum inhibitory concentration, 50% compared with IV ertapenem and meropenem), although it may be better against Enterobacter species. It is not active against P aeruginosa. Tebipenem HBr fairs better against P aeruginosa, but in vitro and in vivo studies of the activity of tebipenem HBr have demonstrated minimum inhibitory concentrations of greater than or equal to 4 μg/mL, which calls into question the effectiveness in clinical models, as the necessary doses may not be well tolerated.

WHERE DO WE GO FROM HERE?
With these limitations in mind, where do we stand on ESBL UTI treatment? We may still see either sulopenem or tebipenem make it to market in some form, but both have had issues clearing the clinical trial barriers to FDA approval and require additional clinical data. If they are not available, several potential agents are currently in development. OMNIVance (QPX7728), ETX0032CPDD, and VNRX-7145 are oral ß-lactamase inhibitors that, when paired with a ß-lactam, can greatly restore the antimicrobial activity against ESBLs and other resistant pathogens. Unfortunately, these agents and others are still within early phase 1 and 2 clinical trials and will take time to be approved. Until then, our oral treatment options for ESBL cUTI and pyelonephritis will remain quite limited.

References are available at ContagionLive.com.
The Role of Pharmacists in the World of Pediatric Antimicrobial Stewardship

Antimicrobial misuse carries a heavy price tag, contributing to over 2.8 million infections of antimicrobial resistance each year in the United States alone. Children are not spared from antimicrobial resistance, with recent and dramatic increases in prevalence, including extended-spectrum \( \beta \)-lactamase–producing Enterobacterales. The complexity of antimicrobial use in children is higher due to individualization of dose regimens and limited pediatric data for guiding appropriate use of antimicrobials, which necessitates assessment by a pharmacist.

Pharmacists are essential to navigate the intricacies of incorporating pharmacokinetics (PK), pharmacodynamics (PD), and clinical outcomes data to determine the best antimicrobial therapy for children. As highlighted by the Centers for Disease Control and Prevention and the Infectious Diseases Society of America, pharmacy expertise strengthens antimicrobial stewardship (ASP) in any clinical setting. Although ASP and infectious diseases (ID) pharmacists focus their roles and responsibilities on judicious and appropriate use of antimicrobials, all pharmacists play a role in ASP and reducing the rate of antimicrobial resistance.

In this article, we will focus on the role and impact of pediatric ASP pharmacists, touching on the applicable skills, training, and potential barriers to highlight opportunities for all pharmacists’ involvement in pediatric ASP.

PHARMACIST TRAINING

A pharmacist’s scope and accessibility to patients span across inpatient and outpatient settings of all age groups, enabling them to play a pivotal role in ASP and therapeutic decision-making in the pediatric population.
training in ID at a pediatric institution in the United States, limiting the number of pediatric-specific ASP/ID training positions available each year. Possible alternative training paths include completion of a PGY2 program in adult ID, but pediatric skills specific to medication selection and administration feasibility will require additional learning. In contrast, a PGY2 in pediatrics may include a rotation in ID but the opportunity for a robust, longitudinal experience in ID will be absent. Despite the differences in settings and experiences, given the standard objectives for accredited residency programs, there are common skills developed that cross all disciplines, including coordination of patient care, drug information and literature evaluation, practice improvement, and teaching. Each year of residency training is estimated to equal 3 years of experience; hence, these skills can be developed through work experience and additional education opportunities.

Learning opportunities for all pharmacists are readily available and important to expand their knowledge and skills to steward antimicrobials. Several certificate programs, live didactic sessions during professional conferences, and self-study materials from numerous organizations, such as the Society of Infectious Diseases Pharmacists, Making a Difference in Infectious Diseases, and the American Society of Health-System Pharmacists, are available. However, these trainings have limited pediatric ID content to differentiate between the approach to children and adult diagnostics and treatments of infection. Pediatric-specific learning opportunities from the Pediatric Infectious Diseases Society (PIDS) include attending the annual IDWeek conference, with PIDS-endorsed programming, to obtain continuing pharmacy education credit, as well as numerous resources online such as the Pediatric ASP Toolkit. This tool kit is a compilation of countless references to contextualize the importance of pediatric ASP and guide the implementation of both outpatient and inpatient ASP, and many more settings pertinent to stewardship.

The track to becoming a pediatric ASP/ID pharmacist includes a variety of options and combinations of residency training, professional organization–offered programs, and work experiences. Given the overlap in skills attained through residency and work experience, all pharmacists have the potential to further develop their stewardship skills and support stewardship initiatives to improve antimicrobial prescribing.

**THE PHARMACIST’S ROLE IN PEDIATRIC ASP**

Pharmacist involvement with ASP is not a novel idea; on the contrary, studies have shown both the financial and clinical impact on antimicrobial prescribing in pediatric populations. The role of an ASP pharmacist typically includes administrative-, clinical-, educational-, and research-related responsibilities. The limitation in the number of pediatric-specific guidelines by professional organizations, and results from large randomized clinical trials, may place an additional emphasis on literature evaluation skills for pediatric ASP pharmacists. Pediatric ASP pharmacists often utilize data extrapolated from adult studies and guidelines, along with their PK and PD expertise, to determine patient-specific therapy plans and indication-specific guidelines for antimicrobial use. Similar to adult ASP pharmacists, common strategies to steward antimicrobials and improve clinical outcomes include prospective audit and feedback and antimicrobial restriction in the inpatient setting. 

**FUTURE DIRECTIONS**

Barriers to non-ASP or ID pharmacists supporting stewardship activities may include “lack of clinical knowledge, experience, and empowerment to contribute actively to physicians’ antimicrobial-prescribing decisions,” but also competing work demands. As previously discussed, the lack of readily available pediatric ASP/ID pharmacy training programs serves as one of the primary limitations to the availability of pharmacists specifically trained in pediatric ASP/ID. Therefore, non-ASP pharmacists being placed in pediatric ASP roles can benefit from institutional support, both financially and culturally, to complete educational programs outside of residency training and attend conferences for the opportunity to collaborate with pediatric ASP pharmacists from other institutions.

**CONCLUSION**

All pharmacists play a role in ASP, regardless of title, and can be leveraged to support initiatives led by pediatric ASP pharmacists. Furthermore, pharmacists seeking additional knowledge and skills to steward antimicrobials have numerous opportunities available, but pediatric-specific options are limited. Pediatric ASP pharmacists can serve as collaborative partners with other institutions to support outreach and ASP initiatives to reduce the development of antimicrobial resistance.

References are available at ContagionLive.com.
COVID-19 vaccine boosters appear to have a similar safety profile as the initial series and appear to reduce the risk for severe disease, hospitalization, and mortality related to COVID-19 infection. However, the rare adverse reactions tend to be overrepresented in the media. In a recent Contagion® Peer Exchange, moderated by Peter L. Salgo, MD, infectious disease experts discussed the safety and efficacy of COVID-19 boosters and strategies to improve uptake among individuals who are vaccine hesitant.

SAFETY AND EFFICACY OF COVID-19 BOOSTERS

Adverse effects from the booster shots appear to be similar to those with the initial doses or series, although the reactions vary among individuals, and a serious adverse event could occur with any of the vaccines, Donald Alcendor, PhD, said. However, Salgo noted that unlike past rollouts of vaccines, a single adverse reaction can become front-page news without the context of the actual incidence of severe reactions. "Whether it’s clots, neurologic complications, [or] myocarditis, [the general public doesn’t] necessarily have the statistical background to evaluate this is 1 in 1,000,000, 1 in 10,000,000, 1 in 100,000," Salgo said.

Alcendor said that explaining to potential vaccine recipients about the safety of other vaccines and the rigorous process they go through to obtain approval is important to provide context for the overall safety of the COVID-19 vaccine. "I explain to parents their experience with vaccines, and they have quite a bit. I ask them, 'Do you have a child that goes to public school?' They tell me yes, [so] I say, 'To go to public school, there [are] state-mandated vaccinations they have to have, and they [must] be updated every year.' I [also] ask them, 'How many of your children come back after receiving a vaccine and complain of an adverse event?' I don’t hear anything. The reason being is that vaccines have been safe and effective for decades," he said.

Alcendor added that vaccines also go through an extensive process to obtain approval. In the United States, this includes an investigational new drug application, 3 phases of clinical trials, a biologics license application, inspection of the manufacturing facility, presentation of the results to the FDA Vaccines and Related Biological Products Advisory Committee, usability testing of product labeling, and pharmacovigilance trials after approval to ensure safety.

"Vaccines are the most highly scrutinized public health interventions we know," Alcendor said.

“Vaccines are the most highly scrutinized public health interventions we know.”

— Donald Alcendor, PhD

Jeff Goad, PharmD, MPH, added that information about vaccine adverse effects is often obtained from anecdotal reports on social media, where adverse reactions tend to be overrepresented. “One of the things we must do is [encourage] patients who took their 5 [or] 6 year old [and] didn’t say anything—their arm didn’t even hurt—to [post that experience on] social media. Because guess what’s showing up there? ‘My arm hurt. I got some weird reaction that people associate with vaccine.’ That’s all [people are] seeing. Therefore, we must encourage our patients [to] post this stuff on social media: ‘My kid got vaccinated, it was fine.’

Salgo and Angela Rasmussen, PhD, also added that individuals were more likely to accept a higher level of risk and adverse events from polio and smallpox vaccines several decades ago because they had observed the harmful effects of the diseases caused by the viruses. "When you don’t grow up seeing your friends paralyzed, seeing your friends in an iron lung, or seeing children all over the place getting sick and sometimes dying from a preventable illness, you start to get a little complacent," Rasmussen said.

The novelty of the SARS-CoV-2 virus, which was initially transmitted zoonotically to the human immune system, has resulted in a high level of mortality from COVID-19, Alcendor explained. "We look at the Spanish flu, where young people had not seen that virus, and [it] had a tremendous amount of mortality in younger folks [but] not in younger folks [who] had seen that virus prior. It has to do with your immune recognition of something. If your immune system has something to go on, then it's
going to be better equipped to fight it. We had nothing to go on with [COVID-19]," he said.

**RISKS OF COVID-19 BOOSTER SHOTS**

The efficacy and safety are essentially similar across the 3 manufacturers of COVID-19 booster shots (Pfizer-BioNTech, Moderna, and Johnson & Johnson), according to Alcendor. "[When] we think [about] what a vaccine should do—prevent severe disease, hospitalizations, and death in [individuals who] receive it—there’s no difference between those 3 vaccines," he said.

Goad said the adverse event profile for Pfizer’s booster appears similar to that of the second dose of the initial series, which had more reported adverse events than the first dose, and he expects these findings to be similar with the other vaccines based on anecdotal reports.

Individuals who are pregnant are a highly undervaccinated population and have a high risk for complications related to COVID-19, so ensuring this population is up-to-date on COVID-19 vaccinations is important, Jason Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS explained. "Some of the worst outcomes I’ve seen personally have been in pregnant women, and they’re heartbreaking," he said.

Alcendor added that data from the Moderna trial (NCT04958304) of women who became pregnant after receiving the COVID-19 vaccine showed no adverse effects, and Moderna studies of a rat animal model found no changes in fertility, number of pups birthed, or changes in pregnancy, further supporting that the vaccine was safe in this population. Rasmussen added that no increase in miscarriage or stillbirth was found among those who were pregnant and vaccinated compared with unvaccinated counterparts. Alcendor also added that the American College of Obstetricians and Gynecologists and all other governmental bodies for health and wellness of women have approved vaccination in those who are pregnant and breastfeeding.

**COVID-19 BOOSTERS: POPULATION TRENDS**

Goad noted that the CDC is tracking the number of individuals who have received at least 1 dose, are fully vaccinated (defined as completion of the primary series), and have received a booster dose. Gallagher added that reducing the proportion of individuals who have not received any vaccines is considerably more important than widespread uptake of booster shots among those who received an initial vaccine series.

Goad said that a key shortcoming of the current surveillance system is that vaccination status, hospitalization, and severe disease are not evaluated prospectively and tend to exist in separate silos. However, data are promising regarding the ability of vaccine boosters to reduce severe disease in certain populations and possibly infection rate, according to Gallagher. Early data from Israel in 2021 found that compared with those who received only the initial vaccine series, patients 16 years or older who received a booster dose of the BNT162b2 (Pfizer-BioNTech) messenger RNA vaccine at least 5 months after their initial series had a lower rate of confirmed infection by a factor of approximately 10 across 5 age groups (range among age groups, 9.0-17.2). Boosting also lowered the rate of severe illness by a factor of 17.9 (95% CI, 15.1-21.2) in the age group of 60 years and older and 21.7 (95% CI, 10.6-44.2) in the 40- to 59-year age group. Gallagher noted that severe disease is the "true end point of concern" and should be studied further, with respect to booster efficacy.

References are available at ContagionLive.com

Access the videos

Scan the QR code by hovering the camera from your smartphone to watch the full videos at ContagionLive.com.
New research that was presented at the 32nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) identified what is believed to be the longest known COVID-19 infection. A patient in London tested positive for COVID-19 with a polymerase chain reaction (PCR) test for 505 days before their subsequent death.

The investigators, from King’s College London and Guy’s and St Thomas’ NHS Foundation Trust, studied 9 patients with COVID-19 to evaluate how the virus changes over time in immunocompromised individuals. When presenting their research at ECCMID in Lisbon, Portugal, from April 23-26, 2022, they detailed one of the first occult COVID-19 infections.

Occult infection is classified as a patient believed to be cleared of the virus, seemingly confirmed by negative COVID-19 tests, but who is later found to have an ongoing infection. “The patient was symptomatic and tested positive for COVID-19 before recovering,” the investigators said. “They then tested negative several times before developing COVID-19 symptoms again several months later. A PCR test was positive and genome sequencing of the virus, at this point, showed the infection was caused by the Alpha variant, which had been eliminated from the United Kingdom by then, suggesting the virus had been present in the body ever since the initial infection but remained undetected.”

The investigators recruited immunocompromised patients with COVID-19 from March 2020 to December 2021. The patients had weakened immune systems due to solid organ transplantation, HIV, cancer, or medical therapies for comorbidities. The 9 study participants tested positive for COVID-19 for at least 8 weeks. The average infection length was 73 days, but 2 of the patients had persistent infections for over 1 year.

“We wanted to investigate which mutations arise and [whether] variants evolve in these [individuals] with persistent infection,” said first author, Luke Blagdon Snell, MD, MRCP, of Guy’s and St Thomas’ NHS Foundation Trust. “Some of these variants transmit more easily between [individuals], cause more severe disease, or make the vaccines less effective.”

Neutralizing Antibodies in Children a Year After COVID-19 Infection

Although once erroneously believed to be incapable of contracting COVID-19, we now know children are infected at the same rate as adults. What remains unknown are the specific immune responses to COVID-19 in pediatric patients.

Prior research has suggested mildly symptomatic children produce more anti–COVID-19 neutralizing antibodies (NAbs) than adults. One study, presented at the 40th Annual Meeting of the European Society for Pediatric Infectious Diseases (ESPID), examined COVID-19 NAbs in children 1 year after infection.

The investigators conducted a multicenter prospective analysis of clinical records and blood samples from children who contracted COVID-19. The children were admitted to the Luigi Sacco University Hospital and the Vittore Buzzi Children’s Hospital in Milan, Italy, between February 21 and May 1, 2020.

Using SARS-CoV-2 neutralization assay, the investigators evaluated the neutralizing activity of blood plasma collected 12 months after COVID-19 infection. The investigators also collected and characterized data about COVID-19 infection severity and vaccination status.

A total of 17 children were included in the analysis, 10 of whom were boys. The children were split into 3 different age categories: preschooler children (0-5 years), school-aged children (6-12 years), and adolescents (12 years and older). The average age of the cohort was 8 years. Of the children, 5 had a COVID-19 infection characterized as severe or critical, including respiratory failure or myocardial dysfunction. Only 3 of the children were vaccinated against COVID-19 at the time of blood sample collection.

Maximum neutralizing activity (1280) was found in the vaccinated children; among the unvaccinated children, maximum neutralizing activity was 320. The average neutralizing activity of the cohort was 330 overall and 90.3 if the vaccinated children were excluded from consideration. The children who were vaccinated against COVID-19, all 3 of whom had also recovered from infection a year earlier, had an increased humoral response after receiving the vaccine.

The investigators noted there were no significant differences in COVID-19 neutralizing activity across different ages. Activity did increase with age, but this trend was not maintained if the vaccinated children were excluded.

Additionally, if the vaccinated children were excluded from analysis, there were no significant differences among COVID-19 neutralizing activity between children with a prior paucisymptomatic or moderate infection and those with a severe or critical infection.

The investigators concluded that NAbs in children a year after COVID-19 infection differed most significantly by vaccination status. They recommended further study into differences in neutralizing activity by age with a larger cohort.
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CASE STUDY

Disseminated Gonococcal Infection Complicated by Suspected Osteomyelitis of Humeral Head

by STEVEN MUDROCH, MD, and LAYA MANO

FINAL DIAGNOSIS:
Gonococcal septic polyarthritis

HISTORY OF PRESENT ILLNESS:
A 33-year-old man presented to the emergency department with a chief complaint of pain in the right wrist and left shoulder that began 3 weeks prior to presentation. The pain in both joints began at the same time and had been preceded by an intense workout. It was persistent, severe, and refractory to nonsteroid anti-inflammatory drug use. The right wrist had associated swelling and erythema, whereas the left shoulder had no associated findings on presentation. Subsequently, the patient developed similar pain in the left ankle, with associated swelling, erythema, and decreased range of motion. The patient denied any trauma to the joints, history of autoimmune disease, and recent upper respiratory or systemic symptoms. Notably, the patient also denied any history of urinary frequency, urgency, or skin findings of the genitals.

The patient was previously seen in our emergency department 3 days earlier with a similar presentation. At that time, urine Chlamydia trachomatis/Neisseria gonorrhoeae amplification testing, syphilis antibody cascading reflex, HIV fourth-generation antigen/antibody screen, and hepatitis C virus antibody screening were negative. He was afebrile and his white blood cell (WBC) count was 10.1 k cells/mm$^3$ (normal, 4.0-11.0 k cells/mm$^3$). At that time, he was given intravenous (IV) ketorolac and IV fluids, then discharged to home.

PAST MEDICAL HISTORY:
He had a history of gunshot wound to the chest with residual foreign bodies, which did not require intervention.

EPIDEMIOLOGIC FACTORS:
The patient endorsed sexual activity with multiple male partners without use of barrier protection. He has a previous history of injection drug use with fentanyl and was placed in inpatient rehabilitation treatment 1 month prior to presentation. Methamphetamine use was also noted. The patient reported a past history of ethanol use, although none in the 6 weeks prior to admission. He denied any known family history of autoimmune disease.

PHYSICAL EXAMINATION:
On admission to the hospital, the patient was febrile to 101 °F and tachycardic with a pulse of 105 beats per minute; on exam, he was in no acute distress. Exam of the right wrist revealed tender swelling of the volar aspect of the wrist. Examination of the left shoulder revealed significant tenderness of the left deltoid and pain radiating to the biceps, as well as warmth and decreased range of motion. Examination of the left ankle demonstrated effusion, warmth, and limited range of motion secondary to pain.

STUDIES:
Initial studies from the emergency department were notable for elevated C-reactive protein at 12 mg/dL (normal 0.4 mg/dL), leukocytosis of 11.6 k cells/mm$^3$ (normal, 4.0-11.0 k cells/mm$^3$), and thrombocytosis of 959 k platelets/mm$^3$. A transverse section of the left upper extremity showing a large left joint effusion and evidence of diffuse synovitis. There is a deep contour deformity of the humeral head demonstrating cortex that is indistinct as well as possibly irregular, concerning for osteomyelitis.

FIGURE.
(normal, 150-450 k platelets/mm$^3$). The left ankle effusion was aspirated in the emergency department, and synovial fluid WBC count was found to be 150,000 white blood cells/mm$^3$, with 88% neutrophils.

X-ray imaging of the right wrist, left ankle, and left shoulder was largely unrevealing but demonstrated no fractures or traumatic injury. CT of the left upper extremity demonstrated a large left shoulder joint effusion with diffuse synovitis likely reflecting septic arthritis and multiple fluid collections adjacent to the effusion within the superior aspect of the subscapularis recess of the glenohumeral joint. It also revealed irregular cortex of the humeral head and small focal areas of erosion, concerning for humeral osteomyelitis (FIGURE).

**HOSPITAL COURSE:**
The patient was initially treated with vancomycin and piperacillin/tazobactam, and he underwent joint aspiration of the left ankle. His initial leukocytosis resolved within the first day of admission to 8.7 k cells/mm$^3$. By hospital day 4, the synovial fluid culture from the left ankle was growing Gram-negative rods, and the primary team narrowed coverage to piperacillin/tazobactam alone. On hospital day 5, the culture speculated to *N. gonorrhoeae* with resistance to ciprofloxacin and intermediate sensitivity to tetracycline. Treatment was switched to ceftriaxone for a planned course of 10 days.

Because of a lack of improvement in pain and range of motion in the left shoulder despite adequate antibiotic therapy, the infectious diseases service was consulted on hospital day 9 and recommended a CT scan of the left upper extremity to further evaluate. This test showed a joint effusion and findings concerning for osteomyelitis of the humerus, as indicated above. Orthopedic surgery was consulted, and they determined there was no need for acute surgical intervention, as the patient appeared to be improving clinically on antibiotics alone.

On hospital day 12, interventional radiology performed an ultrasound-guided drainage of the left shoulder effusion, a sample of which was sent for culture. Cell count of the synovial fluid from the left shoulder demonstrated 28,000 white blood cells/mm$^3$, with 77% neutrophils and 110,000 red blood cells/mm$^3$. The synovial fluid culture from the left shoulder did not grow any organisms. By the time of hospital discharge, the patient had received 1 week of appropriate IV antibiotic therapy. The infectious diseases service recommended oral cefixime to complete a total antibiotic course of 3 weeks for disseminated gonococcal infection, with a plan to reassess as an outpatient to determine an ultimate duration of therapy for possible osteomyelitis.

The patient followed with rheumatology as an outpatient 2 weeks after discharge and was noted to still have pain and decreased range of motion in the left shoulder despite ongoing antibiotic therapy. However, he was subsequently lost to follow-up with infectious diseases and orthopedics.

**DISCUSSION:**
We present the case of a 33-year-old man with disseminated gonococcal infection (DGI), with imaging findings concerning for osteomyelitis of the left humeral head. Our patient was suspected to have contiguous osteomyelitis of the left humeral head based on positive synovial fluid culture from the left ankle and imaging of the left shoulder that demonstrated a large joint effusion, with evidence of diffuse synovitis and possible osteomyelitis. Although possibly representative of trauma from a gunshot wound, without growth of other pathogens from culture of the left shoulder synovial fluid, an infection of the shoulder driven by *N. gonorrhoeae* was felt to be most likely.

DGI is an uncommon manifestation of an infection from *N. gonorrhoeae*. Studies from the 1970s found an incidence rate of 0.5% to 3.0%, although this is currently suspected to be lower because of the decrease in prevalence of the implicated strain and overall decline in gonorrheal infection rates in the interim. DGI has historically been more common in women (particularly those who were pregnant or within 7 days of menses), but there may be a shift within the past 20 years to more equal distribution between genders or even male predominance. Bone involvement had been previously described in studies dating back to at least the 1920s; however, in the current era of antibiotics, osteomyelitis due to *N. gonorrhoeae* appears to be quite rare, with 2 reviews of the literature yielding less than 20 case reports.

There are 2 common presentations for DGI: (1) a syndrome of polyarticular arthritis, dermatitis, tenosynovitis and (2) monoarticular or pauciarticular supplicative arthritis. As in the case with our patient, there are often minimal genitourinary symptoms. Interestingly, prior studies had noted that culture growth of *N. gonorrhoeae* from blood and synovial fluid cultures was nearly exclusive in those with primarily dermatitis and tenosynovitis were much more likely to have positive blood cultures, and those with a demonstrable joint effusion on physical exam were more likely to have only a positive synovial fluid culture. The pathogenesis of DGI and osteomyelitis due to *N. gonorrhoeae* remains uncertain, although delay in time of diagnosis may be an important factor.

Treatment for gonococcal osteomyelitis is not well defined. Duration and selection of antibiotics are varied, from 1 week of IV ceftriaxone to 12 months of therapy with unresolved symptoms. Recent literature, including the OVIVA trial (NCT00974493), has suggested that an oral regimen may have similar failure rates as compared with IV antibiotics for orthopedic infections at 1 year. In our patient, it was not clear whether the imaging findings represented true osteomyelitis, so rather than expose the patient to potential adverse effects, our plan was to reassess and repeat imaging studies prior to completion of 3 weeks of therapy for DGI, but the patient was lost to follow-up.

Rates of gonorrhea infections have increased in the United States over the past 5 years; when adjusted for population, the incidence has increased by 40% from 2016 to 2020. There is also growing concern for the development of resistant strains of this pathogen. Based on these factors, it is reasonable to anticipate an increase in the number of cases of DGI. Thus, when developing a differential for polyarticular joint pain, medical providers should be familiar with less common clinical manifestations of infection from *N. gonorrhoeae*, including musculoskeletal presentations such as osteomyelitis. ▲

References are available at ContagionLive.com
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